Self-management of oral anticoagulation therapy - Methodological and clinical aspects

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PUBLICATIONS

This thesis is based on the following publications, which will be referred to in the text by their Roman numerals:

I. TD Christensen, NT Andersen, J Attermann, VE Hjortdal, M Maegaard, JM Hasenkam. Mechanical heart valve patients can manage oral anticoagulant therapy themselves. European Journal of Cardio - Thoracic Surgery 2003;23(3):292-298.

II. TD Christensen, NT Andersen, M Maegaard, OK Hansen, VE Hjortdal, JM Hasenkam. Oral anticoagulation therapy in children – successfully controlled by self-management. The Heart Surgery Forum 2004;7(4):221-225.

III. TD Christensen, M Maegaard, HT Sørensen, VE Hjortdal, JM Hasenkam. Self-management versus conventional management of oral anticoagulant therapy: a randomized controlled study. European Journal of Internal Medicine 2006;17(4):260-266.

IV. TD Christensen, M Maegaard, HT Sørensen, VE Hjortdal, JM Hasenkam. INR results and coumarin dose among patients self-managing their oral anticoagulation therapy: findings from a randomized, controlled trial. American Journal of Cardiovascular Drugs 2007;7(3):191-197.

V. TD Christensen, SP Johnsen, VE Hjortdal, JM Hasenkam. Self-management of oral anticoagulant therapy: a systematic review and meta-analysis. International Journal of Cardiology 2007;118(1):54–61.

VI. TD Christensen, TB Larsen, C Jensen, M Maegaard, B Sørensen. International normalized ratio (INR) measured on the CoaguChek S and XS compared with the laboratory for determination of precision and accuracy. Thrombosis and Haemostasis 2009;101(3):563-569.

VII. TD Christensen, C Jensen, TB Larsen, M Maegaard, K Christiansen, B Sørensen. International Normalized Ratio (INR), coagulation factor activities and calibrated automated thrombin generation - influence by 24 hours storage at ambient temperature. International Journal of Laboratory Hematology 2010;32(2):206-214.

VIII. TD Christensen, C Jensen, TB Larsen, K Christiansen, B Sørensen. Thrombin generation and coagulation factor activities: evaluation and comparison with the international normalized ratio. Blood Coagulation & Fibrinolysis 2009;20(5):358-365.

Publications I and II are based on results which form my Ph.D. thesis entitled: Self-management of oral anticoagulant therapy. Faculty of Health Sciences, Aarhus University, Denmark 2005. Publication III–VIII or any of the results herein have not earlier been submitted in order to achieve an academic degree.

INTRODUCTION

Oral anticoagulation therapy (OAT) with coumarins (vitamin K-antagonists) has been available for more than 60 years, and is prescribed for both prophylactic and therapeutic use to patients at increased risk of thromboembolism (1). OAT has a narrow therapeutic index, and monitoring is based on the International Normalized Ratio (INR) conventionally determined on citrated plasma obtained by venepuncture. Based on the INR measurements, health care providers determine the appropriate dose of coumarins (e.g. warfarin (Marevan®) and phenprocoumon (Marcoumar®)). Hence, the INR is used as guidance for the coumarin dose.

Despite this close monitoring of therapy, thromboembolism and bleeding are common concerns and accounts for a large proportion of the morbidity and mortality in these patients: major bleedings have an incidence ranging from 0.3 – 13.4 % per year and that of major thromboembolism ranging from 0.4 – 3.5 % per year (2-6), though highly dependent on selection of patients and definition of events.

In patients with mechanical heart valves, a low quality of OAT is the most important independent predictor of reduced survival (7) and is responsible for approximately 75 % of all postoperative complications observed in these patients (4).

Optimised management of OAT improves the quality of treatment (8-10). Different methods of managing OAT exist: routine care

(provided by the general practitioner), hospital outpatient clinic, highly specialised anticoagulation clinic, shared care, use of computer assessed dosage, patient self-testing (PST) and patient self-management (PSM) (1, 8, 11-13). PSM is a concept where the patient takes an active part or even a leading role in his or her own treatment. For many years it has been used as the standard treatment in diabetics, who measure their blood glucose using a portable apparatus and perform insulin dosage according to this (14-16). The concept of PSM has also been shown to be successful in other settings, e.g. in patients with hypertension and asthma (17, 18). PSM in OAT implies that the patient analyses a drop of blood using a portable coagulometer (INR-monitor). The coagulometer displays the INR, which the patient uses for coumarins dosage. PST merely implies that the patient performs blood sampling and analysis while a health care provider decides on dosage adjustment (13, 19).

Today patients with chronic diseases and on long-term treatment are increasingly engaged in their own treatment and have to take an active part in their treatment[1]. Therefore, PSM seems to be a natural step in terms of management.

However, the history of PSM begins many years ago; the first paper on this issue was published in 1974 by Erdman et al (20), who trained mechanical heart valve patients to manage their own OAT based on a standard Prothrombin Time (PT) test analysed at the laboratory. These initial results seemed promising, but for many years PSM did not gain much attention, until 1985 where a young German female student with a mechanical heart valve became frustrated by her OAT managed by her general practitioner (21). The patient purchased a coagulometer and began PSM on her own. After reporting her experience to the medical society, PSM was gradually launched as a therapeutic concept in Germany. PSM gained increased popularity, especially in Germany, and other countries followed this lead. However, it is still not clarified which subset of patients (in terms of indication for OAT, age, comorbidity etc.) that potentially will benefit from PSM, and how large this potential effect is.

A precondition for a correct dosage of coumarins is a correct estimation of the INR, and the method and apparatus used for providing the INR measurements is in this context essential. The coagulometers used for PSM have not been investigated adequately in terms of precision and agreement, so this is warranted. In this context, it is important to state that PSM is a concept including patient self dosing based on self testing of INR, whereas the evaluation of the coagulometer estimates the quality of INR measurements and not the quality of OAT.

INR has proven adequate for adjusting dosages. However, it is doubtful that the level of INR reflects the overall haemostatic capacity or thrombotic potential of individual patients (22, 23). Furthermore, the predictive value of the INR in estimating individual patients' risk of complications is questionable (24, 25).

Oake et al (25) found that nearly 50 % of all major complications occurred even when the INR was within therapeutic INR target range. Accordingly, it is important to obtain knowledge of parameters that can bring additional information in order to predict complications.

Measurement of continuous calibrated automated thrombin generation (CAT) may serve as a more sensitive and global haemostatic parameter and potentially with better performance in predicting risk of complications in patients on OAT. In addition, coumarins main effect is by depression of the coagulation factors II, VII, IX, and X. It may be speculated, that determination of the clotting activity of these coagulation factors could provide supplementary predictive information regarding risk of complications (22, 23, 26). However, in order to predict complications in the individual patient, it is important to further characterise these tests; to estimate the variability of these tests over time, to see if the results are associated with the INR, their practical and clinical application and whether or not these new methods will bring additional information regarding the overall coagulation activity.

The aims of this thesis were to:

- Estimate the variability of coagulation factors II, VII, IX and X and continuous calibrated automated thrombin generation in patients on stable oral anticoagulation therapy.
- Compare and evaluate coagulation factor activities (II, VII, IX and X) and continuous calibrated automated thrombin generation with the International Normalized Ratio (INR) in patients on stable oral anticoagulation therapy.
- To assess the variability of INR, coagulation factor activities, (II, VII, IX and X) and continuous calibrated automated thrombin generation during 24 hours of storage of blood samples at ambient temperature.
- Estimate the precision and accuracy of the coagulometers used for patient self-management of oral anticoagulation therapy.
- Determine the feasibility and quality of patient self-management of oral anticoagulation therapy prescribed to different patient categories such as mechanical heart valve patients and children.
- Compare patient self-management of oral anticoagulation therapy with conventional management in a randomised controlled trial.
- Evaluate the efficacy and safety of patient self-management of oral anticoagulation therapy in a systematic review and meta-analysis.

METHODOLOGICAL CONSIDERATIONS

Oral anticoagulation therapy, definition

OAT is a therapy that prevents coagulation; it reduces/stops the blood from clotting. Coumarins reduces the clotting activity and the effect is mediated via inhibition of gamma-carboxylation and thereby predominantly suppression of the activity of the vitamin K dependent coagulation factors in blood, namely coagulation factors II, VII, IX and X (1). The coumarins used are predominantly warfarin (Marevan®), phenprocoumon (Marcoumar®) and acenocoumarol (Sintrom Mitis®). OAT is indicated for both prophylactic and therapeutic use in patients at increased risk of thromboembolism, e.g. in patients with prosthetic heart valves, atrial fibrillation and thrombophilia. Careful adjustment of dosing based on the measurement unit INR is used to determine the clotting tendency of the blood, and it is required in order to reduce the risk of complications (1).

[1] The Patient with chronic disease. Self-monitoring, self-care and patient education. A catalogue of ideas. The National Board of Health, Denmark 2007 (http://www.sst.dk).

Monitoring oral anticoagulation therapy

INR, basic principles

INR is a calculated using this formula: $INR = \left(\frac{PT_{patient}}{MNPT} \right)^{ISI}$

MNPT is the Mean Normalized Prothrombin Time and ISI is the International Sensitivity Index.

Simplified, the INR is a calibrated estimate of the clotting time; normal individuals have an INR of approximately 1.0, so an INR of 2.0 implies a clotting time double as long as normal.

The INR system was launched in 1983 and is a standardisation of the PT (27); the latter being a clotting time of a plasma (or whole blood) sample in the presence of a preparation of thromboplastin (tissuefactor and phospholipids) and the appropriate amount of calcium ions. The time is reported in seconds.

MNPT represents the average normal PT, normally taken from 20 healthy individuals. ISI is calculated by calibrating the locally used thromboplastin with a reference thromboplastin, and the ISI reflects the responsiveness of a given thromboplastin to the reduction of the vitamin K dependent coagulation factors (1).

Calculation of the ISI has been done as shown by Van den Besselaar et al (28).

The INR is a mathematically adjusted PT (29), therefore the "objective true" INR is not known (30, 31). Differences in INR using the same test sample is observed, which is not to be regarded as an indictment of the INR system, but merely display the variables in PT testing (see below) (27).

Coagulation factor activities

Determination of the clotting activity of single coagulation factors II, VII, IX, and X may provide supplementary predictive information regarding individual patient's risk of complications (22, 23, 26). Casuistic observations by Sarode et al (32) found no correlation between INR and coagulation factor II and X in patients with supratherapeutic INR (> 5.0). Costa et al (33) found a weak relationship between coagulation factor II and X versus the level of INR, and advocated that coagulation factor II and X could be used for optimising monitoring. Furthermore, D'Angola et al (23) have stated that the activity of coagulation factor II better reflects the antithrombotic effect than the INR. Van Geest-Daalderop et al (34) found that the mean INR was inversely related to the suppression of coagulation factors, but the variability over time was not estimated. In contrast, Watala et al (35) found that coagulation factors II, VII and X were strong modulators of INR, explaining 90 % of the INR variability. Others have found a differentiated suppression of the function of coagulation factors II, VII, IX and X in patients with similar INR's (36-38). So far, systematic recording of the activity of single coagulation factors II, VII, IX, and X is not part of daily clinical practice and has never been evaluated and compared with the INR in a prospective clinical setting.

Christensen et al (VIII) found no significant variability of the activity of coagulation factors II, VII, IX, and X during a 6-week observation period in patients on stable OAT. The level of INR was significantly associated with the activity of coagulation factors II, VII, IX, and X, so the results of the two tests can be used concomitantly and/or interchangeably. Approximately 50 % of the total variability of the coagulation factor activities was reflected by the INR, whereas the remaining variability was within the subject (patient). Coagulation factor activities can therefore potentially be used to provide further information to the risk of bleeding and thromboembolism, since 50 % of the variability within the subject is not displayed in the INR value. This residual variability could therefore encompass additional information regarding the clotting activity within the individual patient. This is supported by the finding that a considerable variability of coagulation factor activity was observed between patients with the same INR values.

Larger clinical trials with a longer follow-up period, preferably using clinical endpoints, are needed in order to draw any firm conclusions regarding the clinical consequences. This could be done in "high risk" patients, e.g. patients with a high variability of the INR values, limited time within therapeutic INR target range or those patients who previously experienced a complication. However, since complications are relatively rare, a large number of patients are needed to be included. It could also be done as a case-control study where patients admitted to hospital with complications are cases, and controls are patients without complications.

Christensen et al (VII) found no influence on the results of coagulation factor activities, when samples were stored for up to 24 hours at ambient temperature, and this increases the practical adaptability of using this test in a clinical setting. However, it is a potential drawback that the analyses are expensive to perform. Based on the study by Christensen et al (VII, VIII), the premises for a larger study have therefore been given, since these tests were characterised and their potential application in patients on OAT was tested.

There was no difference between different methods used (laboratory, CoaguChek® S and CoaguChek® XS), so the INR for comparison to the coagulation factor activity can be measured using either of these methods (VIII).

Christensen et al (VIII) included a well-defined and closely monitored group of patients and used advanced statistical analysis, including assessment of both within- and between patient variability, making the internal validity of the study high. The study limitations include i) limited number of parameters of coagulation measured, e.g. differences in levels of natural anticoagulants, such as protein C and antithrombin could have added, ii) no measurements of other modifying factors such as polymorphisms and genotype (39), and iii) some patients had aspirin prescribed. Furthermore, a potential drawback compromising the external validity is that patients included were on stable OAT and with a therapeutic INR target range within 2 - 3. However, the presence of INR values ranging from 1.40 to 5.60 have likely limited this potential bias. Furthermore, the influence of the different levels of INR was accounted for in the statistical analysis. Additionally, nearly 50 % of all major complications occur even when the INR is within the therapeutic INR target range (25). A longer observation period and a larger number of patients combined with more frequent measurements than every third week (e.g. every week) would have strengthened the conclusion.

In conclusion, measurement of coagulation factor activities may improve measurement of coagulation activity in patients prescribed OAT beyond the parameters currently clinical available.

Global evaluation of haemostatic capacity using calibrated automated thrombin generation

INR has proven adequate for adjusting dosages. However, it is doubtful that the level of INR reflects the overall haemostatic capacity or thrombotic potential of individual patients (22, 23). Furthermore, the predictive value of the INR in estimating individual patient's risk of complications is questionable (24). Measurement of CAT may serve as a more sensitive and global haemo-

static parameter with better performance in predicting risk of complications in patients on OAT.

Measurements of CAT have been used to study the global haemostatic capacity in a variety of coagulopathies (40-42). The INR measures merely time to clot, whereas the CAT is portraying the full coagulation dynamic (43). In patients prescribed OAT, CAT has only been sparsely investigated; Gatt et al (26) have performed tests in patients on OAT with atrial fibrillation and found a close association between recordings of CAT and INR within the therapeutic INR target range, but a wide variability existed. However, the study used simplified statistical analysis, and therefore no firm conclusion can be drawn. In contrast, Brummel et al (22) have described profound variability in thrombin generation measured in minimally altered whole blood from patients on OAT despite similar and stable levels of INR. Brocal et al (44) found a high correlation between INR and thrombin generation, concluding that thrombin generation could potentially indentify patients with a high risk of complications, but additional studies are needed. Again, the study is flawed by the use of simplified statistics.

Christensen et al (VIII) found no significant variability of CAT during a 6-week observation period in patients on stable OAT. For the various parameters of CAT, 22 - 61 % of the variability was displayed in the INR measurement, and residual variability was found to be within the subject (patient). The level of INR was significantly associated with the various parameters of CAT, so the results of the two tests can be used concomitantly and/or interchangeably.

Only measurements analysed immediately after sampling was included, since the CAT parameters are influenced by storage time (VII). The practical use of CAT in a clinical setting is limited due to changes over time.

The significance regarding additional information, strengths and limitations are those mentioned above (coagulation factor activities), except that the study could be additionally berated for not adding corn trypsin inhibitor to the blood samples (45). Artificial spontaneous contact activation could potentially be abolished and thereby obtain a reduced variability, but others had questioned this assumption (46). Secondarily, relatively large standard deviations regarding the different parameters is concerning. However, this can be reduced by adhering to new international standards in terms of using standardised reagents and reference plasma (47).

In conclusion, measurement of CAT may improve measurement of coagulation activity in patients prescribed OAT beyond the parameters currently clinical available.

Other methods

Indentifying patients at an increased risk of complications are potentially possible; coagulation factor activities and CAT have been discussed above. Other methods include e.g. estimation of prothrombin fragment 1 + 2, thrombin-antithrombin complex (38, 48) and thrombelastography (49, 50). However their use awaits further studies regarding their precise association with the INR. Furthermore, it is beyond the scope of this thesis, and will therefore not be discussed further.

Methods of measuring INR

Precision and accuracy of INR, methodological aspects and definitions

In general, the terms precision and accuracy are used when estimating the quality of a method; accuracy is the degree of veracity while precision is the degree of reproducibility[2].

Precision is descriptive in general terms (e.g. acceptable and poor), whereas imprecision (the reciprocal of precision) is expressed by means of the standard deviation or coefficient of variation (CV) of the variability. The total variability of the INR can be divided into three parts: pre-analytical, biological and analytical variability. The term precision can be replaced by the terms repeatability and reproducibility. Repeatability is the agreement between the results of consecutive measurements (within the same measuring series), and reproducibility is the agreement between the results of discontinuous measurements of INR carried out under changing measuring conditions over time. The analytical variability deals with the apparatus used for INR measurements, and this should display a CV of less than 3 % (30).

Accuracy is the closeness of agreement between the result of one measurement and the true value. Accuracy can be divided into analytical accuracy (*"does the test give the same results estimated purely numerical as on the gold standard?"*), and diagnostic accuracy (*"does the test provide accurate information about diagnosis, prognosis, risk of disease, and other clinical issues as on the gold standard?"*) (51). The analytical accuracy should ideally be below +/- 0.2 INR within the therapeutic INR target range (for most purposes between 2 and 3) (30, 52, 53). The diagnostic accuracy can be defined as relevant (i.e. not resulting in a change of coumarin dosage) using different degrees of agreement (54, 55) or according to that defined by Poller et al (56), where a deviation of ≥ 15 % was defined as clinical relevant.

Laboratory, pre-analytical variability

There are several pre-analytical factors, which can cause erroneous INR: 1) sampling and blood collection problems, 2) evacuated tube effects, 3) sodium citrate concentration, 4) storage time, 5) storage temperature and 6) inadequate sample (27, 57). Item number 1, 2 and 6 can be substantially reduced, if the samples are taken correctly. However, it is likely, that they have a major impact in a clinical setting. Since both their impact and methods to eliminate them are known, they will not be discussed further. Item no. 3 can be eliminated by using tubes containing coagulation sodium citrate of 3.2 % instead of 3.8 % (28). The storage temperature has been found to be of minor importance (58).

However, regarding the storage time, dispute exists. In the daily clinical setting blood samples are frequently sent by mail, and INR analysis are delayed until the following day (59). Furthermore, laboratory INR measurements are used as an effect parameter in PSM trials (60, 61) (III, IV). Accordingly, this effect parameter has to be properly validated.

It has been shown that INR remains unchanged if analysed within 24 hours (62-68), whereas other studies have shown time dependent derangements of the measured INR (58, 59, 69) Unfortunately, the published studies (58, 59, 62-67, 70) suffer from various methodological shortcomings; e.g. small sample size (66, 67) or simplified and insufficient statistical analyses (63, 67, 70) resulting in non-conclusive results (71). Noteworthy, the studies report-

[2] http://en.wikipedia.org/wiki/Accuracy_and_precision

ing on no alteration of the INR following a 24 hour storage of blood samples mainly focus on the effect on the overall mean INR, and thereby potentially missing crucial and clinical important changes in each individual patients (58, 69).
Christensen et al (VII) found in a prospective case-series study no differences in INR measurements as a result of 24 hours storage. Advanced statistical analyses were used looking both at mean and individual INR measurements. The study group consisted of a well-defined and closely monitored group of patients with only a few different indications for OAT. However, high external validity of the study is assumingly maintained because the indications are not expected to influence the results.
A potential limitation of the study is that only patients on stable OAT with a therapeutic INR target range of 2 - 3 were included. A larger variability of the INR could potentially affect the results, e.g. it may be speculated that high INR values are more susceptible to 24 hours storage of blood samples. Yet, the problem is considered to be limited since a range of INR values from 1.70 to 5.60 were included. The conclusions could have been strengthened, if a larger group of patients had been included and/or a longer observation period had been applied. Furthermore, in order to document that samples are unaffected when send by mail, they should have been posted and not just stored, since the mechanical handling of the blood-samples is likely to have an impact on the INR measurements (58). Another potential shortcoming is the use of one type of thromboplastin and only one laboratory, and the original WHO method for INR analysis was not used (see below). However, the applied method used in the laboratory is in coherence with high international standards (see below) (29).
In conclusion, several potential correctable pre-analytical factors can affect the INR measurements. However, the INR result is unaffected during 24 hours of storage at ambient temperature.

Laboratory, biological variability

The biological variability comprise factors within the patient that influence the INR (e.g. vitamin K-dependent factors, calcium, magnesium), but also the interaction between patient factors and the PT measurement system (e.g. type of thromboplastin and reagent used) (30). The biological variability is therefore the within patient variability, and it is important to estimate and isolate the influence by this factor as a basis for evaluating a new method/apparatus for INR measurements. The biological variability is found to have a CV of approximately 9 % (53, 72). However, the pre-analytical and biological variability are often considered as one parameter (73).

Laboratory, analytical variability

The INR system of PT standardisation was originally based on manual tilt tube determination of PT's and envisaged the assignment of a single ISI value for each batch of thromboplastins reagent (27, 74). A minimum of 80 fresh plasma samples (20 healthy donors and 60 patients stabilised on vitamin K-antagonist) should be used (75). Today however, the manual PT technique has been almost universally replaced by coagulometers.
Numerous factors can influence the INR measurements (27). The ISI of thromboplastins reagents often differs according to the type of instruments used (28). The original reference thromboplastin was the International Reference Preparation of Thromboplastin, Human, Combined (coded 67/40) and was established by the WHO Expert Committee on Biological Standardization in 1976 (74). Subsequent generations of International Reference Preparation have been made, all calibrated against the original reference or latter generations, and this provides bias (75). Furthermore, the ISI value varies; highly sensitive thromboplastins (ISI of approximately 1) provide more accurate INR measurements than those with a higher ISI. The thromboplastin also varies in terms of origin; e.g. coming from rabbit brain, bovine or recombinant types (1, 75).
The PT can also be measured using different methods; Quick's and Owen's methods[3] (29, 76), the latter being predominantly used in the Nordic countries. Additionally, several other factors have impact on the INR measurement: e.g. haematocrit, whether whole blood or plasma analysis is used, matching of the used thromboplastin, instrument and the ISI, the applied statistics, and the stability of the patients OAT (29, 57, 63, 77-79).
As shown above, many factors influence the analysis of INR and it is not an easy task to optimise this and thereby achieving accurate and precise INR measurements in a laboratory setting. This has been approached by applying international guidelines to the laboratories (1).
ISI calibration in a normal laboratory setting is often not possible since standard thromboplastin reagents are difficult to assess and there is a requirement for large samples of plasma (28, 75).
In order to reduce the interlaboratory variability and the need for plasma, methods for local calibration have been developed in an international collaboration (27, 28, 75, 80).
Accordingly, laboratories can calibrate their own local system using certified plasma in two different ways:
1) A modification of the WHO method where plasma is assigned a manual PT value by a reference centre. In the local laboratory these PT's are plotted against the local coagulometer and thromboplastin combination. The ISI is calculated as described previously and INR can be determined from the local PT's and MNPT.
2) Assignment of INR values to a set of plasmas with the manual method and an international thromboplastin standard by a reference centre. The PT's of these plasma's are measured using the local coagulometer and thromboplastin combination. The latter PT's are plotted against the reference INR's, and the INR's of patients can be interpolated from local PT's using this line, and accordingly there is no need for ISI or MNPT determination (direct INR determination).
The latter is being widely used, e.g. in Denmark, where DEKS[4] delivers the PT's of the certified plasma's.
The interlaboratory variability has a CV in the ranges of 10 – 20 % if none of the above methods are applied (28, 75, 80, 81). However, by using either of these methods, this variability can be reduced to a CV of 5 – 6 %. The method using direct INR determination is probably superior in reducing the variability compared to the other technique (80).
INR determined in the laboratory using a standardised and quality controlled method (as using calibrated plasma (see above)) is often used as reference to which all other methods should be compared (82). However, this is a contentious statement, since the original method (gold standard) of estimating the INR in a laboratory is using the WHO reference thromboplastin and by applying the manual tilt-tube technique (74), not the INR analysed in a normal laboratory setting. This includes the above mentioned

[3] The Quick method (first described in 1935) measures the changes in coagulation factors II, VII and X, but is also dependent on the level of coagulation factor V and fibrinogen. The Owen method (developed in the 1950's) uses another dilution and measures merely the changes in coagulation factors II, VII and X.
[4] Danish Institute for External Quality Assurance for Laboratories in Health Care (http://www.deks.dk/index.html).

methods to reduce variability. The variability when using other methods than the original WHO method should therefore be stated when comparing INR measurements in the laboratory to other methods (e.g. coagulometers). However, the gold standard is rarely used.

The quality of day-to-day routine measurements (internal and external quality control) can be increased through participation in quality assurance programs, e.g. DEKS. In a scientific investigation, an increased quality validation is needed. The studies that have compared the laboratory to other methods (e.g. coagulometer) are flawed by lack of double measurements/estimations of the INR on the laboratory (61). Optimally, both within run analyses[5] and between run analyses[6] should be performed before comparison with other methods (e.g. coagulometer). In general, the precision of a method should be thoroughly estimated before methods are compared in terms of accuracy (83).

Christensen et al (VI) measured the INR using both non-frozen and frozen samples, finding a CV of 0.8 and 1.3 %, respectively. No statistically significant difference in agreement between frozen and non-frozen was found, hereby providing a basis for comparison between the laboratory and coagulometer. A drawback is that only one laboratory was included, and optimally it should have been a multicenter study, so the variability between laboratories would have been estimated. Otherwise, the INR should have been analysed using the original method (gold standard) as defined by the WHO (74). However, the CV's are below the required 3 % (30).

It has been brought forward (April 2009) that the calibrators delivered by DEKS in the period for the studies by Christensen et al (VI-VIII) have not been correct. The calibrator with the high INR value, which was estimated to be 3.92, was found to be closer to 3.62[7]. All the results published by Christensen (VI-VIII) were therefore recalculated accordingly, and it did not have a significant impact on the results. The conclusions of the published studies remain unchanged. However, the coagulometers investigated in study VI were slightly more accurate compared to the laboratory measurements than previously found[8], but also here the conclusion remains unchanged (see below). However, this issue clearly displays the difficulties in measuring a "correct" INR even when adhering to high international standards and underlines that estimating the INR should be done using the original WHO technique (gold standard).

In summary, various parameters affect the INR measurements. The correct and most accurate method of estimating the INR is the original WHO method, which is the gold standard. However, using certified plasma, the interlaboratory CV is in the range of 5 – 6 %. If this method is not applied by the laboratories their variability is even higher (minimum 10 %). It is important to have these considerations in mind when INR measured in a laboratory is compared to other methods.

Coagulometer (INR-monitor)

The first study using a fingerstick blood-sample and a portable coagulometer was published in 1987 (84).

Since then several types of coagulometers have been introduced on the market; e.g. CoaguChek® (Roche Diagnostics, Switzerland), INRatio® Monitor (HemoSense, Inc., USA), Pro-Time® (International Technidyne Corporation, USA) (13, 61, 85, 86). Other brands are likely to be introduced.

All the coagulometers work basically in the same way; a drop (10-30 µl) of capillary whole blood is released by a finger puncture device and applied on the test strip and inserted into the coagulometer. The clotting process is initiated by thromboplastin and clot formation is subsequently detected. However, the detection of the clot is different from one coagulometer to another and minor differences in terms of function exist. All the coagulometers are calibrated using lot-specific code chips or stored lot specific conversion equation. Furthermore, most of them can have both internal- and external quality control performed.

A more in depth presentation of the functionality and technical specifications of the coagulometers are discussed thoroughly in other papers, e.g. (85-87).

Some coagulometers are not included due to the following reasons: simplified versions (Hemochrom Jr and GEM PCL) of the ProTime®/ProTime® 3 coagulometers (88, 89), the predecessors to the CoaguChek® in terms of the Coumatrack (Dupont Pharmaceutical Co, Delaware, USA) (19, 90-93) and Biotrack 512 (Ciba-Corning, Massachusetts, USA) (88, 94, 95). Furthermore, the AvoSure™ PT-Pro (Avocet Medical Inc., California, USA) and Harmony (LifeScan Inc., Johnson & Johnson, California, USA) have been withdrawn from the market (96). Lastly, the Thrombolytic Assessment System (TAS)/RapidpointCoag™ (Pharmanetics Inc, North Carolina, USA) is not included since it does not analyse capillary blood (88, 97-100). The i-STAT® System (Abbott Point of Care Inc., New Jersey, USA) is a semi-professional system and accordingly not shown (101). Lastly, only coagulometers displaying the result in INR were included. The first introduced CoaguChek® models (CoaguChek® and CoaguChek® S) are no longer for sale. However, many patients still use them and they were used in the studies by Christensen et al (I – VIII) and are therefore included.

The CoaguChek® coagulometers (CoaguChek®, CoaguChek® S and CoaguChek® XS) have been intensively investigated both in terms of accuracy and precision and they are the most used coagulometers in clinical trials (4, 60, 102-104), and in the daily clinical setting (105). The other types of coagulometers have been applied in only a limited number of studies, and have not yet gained substantial impact in the clinical setting. Accordingly the main focus in this section will be on the CoaguChek®.

The variability of the INR measurements depends on the same pre-analytical, biological and analytical variables as described for the laboratory. The pre-analytical variability depends on various things; who (patient or health care provider) that takes the blood-sample, handling of the test-strips, temperature etc., but the precise influence of these factors has not been quantified. The biological part is also the same as mentioned for laboratory testing, except that concomitant use of low-molecular weight heparin, heamotocrit, fibrinogen level and presence of antiphospholipid antibodies has a relative large impact on the INR result (79, 106-108).

Studies including other types of coagulometers (INRatio® (Hemosense Inc., California, USA), Pro-Time®/Pro-Time® 3 (International Technidyne Coporation, New Jersey, USA and SmartCheck INR System (Unipath, Bedford, England)) (97, 98, 109-114) than the CoaguChek® are published. The studies are limited in numbers, and hence firm conclusions are difficult to obtain. However, the precision and accuracy are in the same range as the CoaguChek®

[5] The two samples analysed immediately after each other.

[6] The two samples analysed a certain time (e.g. 4 weeks) after the two first samples are analysed.

[7] DEKS newsletter (April 2009).

[8] After recalculation, the CoaguChek® S and CoaguChek® XS had 31 % and 21 % of all INR measurements deviating ≥15% from the non-frozen laboratory measurements, respectively.

and the CoaguChek® S, but inferior to the results obtained by the CoaguChek® XS. The studies including only children will be discussed in another section (see below).
Several studies has investigating the precision and accuracy for the CoaguChek® and CoaguChek® S coagulometers (52, 55, 56, 60, 88, 89, 93, 94, 101, 102, 105, 110, 112-152) (VI).
The CoaguChek® XS has a different detection system than its predecessors (105, 149, 152-157) (VI). The CoaguChek® XS has a smaller variability and is more accurate than the predecessor models.
In terms of precision, the CV should ideally be less than 3 % (30), but the CV is found to range from 1.4 - 8.5 %. In terms of accuracy, all the coagulometers, compared to the laboratory, tend to overestimate the INR when INR measurements are high, especially above 4.0 (55, 133, 154). A small tendency to underestimate INR is found when INR is within and below the therapeutic INR target range (105, 149, 156) (VI)
The dosage of coumarins would have to be changed in 8 - 25 % of the cases due to potential inaccuracy of the coagulometer (89, 110, 113, 125, 133).
Estimating the precision of a coagulometer provides problems, since it is not possible to perform ordinary within- or between runs. Methods to circumvent this have been suggested (30, 158, 159), but none of these methods have been entirely comparable to ordinary within- or between runs. It is not possible to store the blood without interfering with the coagulation process, and it is not possible to reuse the test strip. A feasible method of estimating the within run imprecision is to perform INR measurements in duplicates (e.g. using two different fingers), but no established method exists for between-run estimation.
In terms of estimating the variability, one has to be aware of the comparator used (laboratory). As stated above, the laboratory also displays variability, especially since the original WHO method is only used in a limited number of studies (56, 134). This has to be taken into account when comparison of accuracy is done, since it cannot a priori be stated which of the two methods is the most accurate (30). The interpretation of the results regarding the potential inaccuracy of the coagulometers has to seen in this context.
Many of the studies displayed have not used optimal designs, e.g. most studies used correlation coefficients for estimating accuracy, and not mean versus difference (Bland–Altman plot) assessing the mean/median difference (30, 83). Furthermore, by using single INR measurements comparison instead of multiple comparisons, the method being investigated is biased.
Other parameters regarding the comparator (laboratory) including the ISI value, type of quality control performed in the laboratory, use of calibrated plasma, the number of included laboratories and the use of automated versus manual detection of clotting time vary significantly between studies. This should be taken into account when comparison and interpretation is done. Furthermore, the definition and use of either analytical- or clinical accuracy varies, and many of the studies have been supported by the manufacture of the apparatus (coagulometer), which implies potential bias.
Some studies have concluded that the laboratories have an equal interlaboratory variability (CV of approximately 10 %) compared to that of the coagulometers (76, 160). However, these studies are potential flawed since they predominantly estimate the variability of the laboratory from an overall median, and it is not clear if certified plasma was used. If so, the CV of the interlaboratory variability is potentially reduced by 50 %.
Christensen et al (VI), found that the CoaguChek® S and CoaguChek® XS had a precision (CV) of 3.4 and 2.3 %, respectively. Applying analytical accuracy and comparing single measurements, the INR measurements tended to be lower (0.33 - 0.42 INR) on the coagulometers, compared to the laboratory. Regarding diagnostic accuracy, the CoaguChek® S and CoaguChek® XS deviated ≥ 15 % from the laboratory measurements in 43 and 40 % of the patients, respectively[9]. A deviation of 15 % with an INR of 2.5 will provide a range of 2.125 – 2.875 (± 0.375 INR), and whether this will increase the risk of thromboembolism and bleeding events is unsettled. However, any improvement in accuracy is of cause preferably. Optimally, the original WHO method should have been used as comparison, or secondary using several laboratories, so that the interlaboratory variability could have been estimated instead of merely using one laboratory. However, a laboratory using the "direct method" with calibrated plasma was used, and the external validity has probably not been severely compromised (28). The results found by Christensen et al (VI) are comparable to the results found by Poller et al (56, 134, 161), who used the original WHO method.
The study by Christensen et al (VI) included a well-defined and closely monitored group of patients combined with the use of appropriate and advanced statistical analysis making the internal validity of the study high, especially by using multiple comparisons. Furthermore, the precision of the methods were measured before calculation of agreement which strengthen the conclusions of the study (83). Lastly, patients made the measurements on the coagulometers themselves, thereby reducing the influence of letting a health care provider do the blood sampling and analysis. A drawback is that the patients had to be on stabile OAT and with a therapeutic INR target range within 2 – 3. However, the ranges of measurements were from 1.70 to 5.60, and extrapolation beyond this is not possible.
In the studies reporting the highest reduction of the interlaboratory variability, it is still in the order of a CV of 5 %. This figure should be compared to the inaccuracy found in the coagulometers, e.g. in the study by Christensen et al (VI), and the implication should be done in respect of this. Even a CV of 5 % of the laboratory measurement variability will also result in a less pronounced inaccuracy when comparing the coagulometer and the laboratory.
It is important to remember that differences in INR using the same test sample is observed, which is not to be regarded as an indictment of the INR system, but merely display the variables in PT testing (27).
In conclusion, several coagulometers are available on the marked and their precision has generally found to be adequate for clinical use in patients. Their performance in terms of accuracy has to be viewed in respect of the inherent inaccuracies of INR measurements. The coagulometers accuracy seems in this respect generally acceptable and they can be used in a clinical setting. However, external quality control is essential.

Quality control

Laboratory INR measurements have been standardised worldwide by extensive international work and has been adapted to excessive quality control (28, 29). This has not been the case with the coagulometers.

[9] After recalculation, the CoaguChek® S and CoaguChek® XS had 31 % and 21 % of all INR measurements deviating ≥15% from the non-frozen laboratory measurements, respectively.

The manufacturer of the coagulometers provides control-solutions with a known INR value (internal quality control). The frequency of performing this quality control varies between 1 - 12 times per year (61, 121, 122, 162, 163) (III, IV). It only estimates the functionality of the individual/single device, but does not test the accuracy (164). Therefore, as a sole quality control it is not sufficient. An external quality control checking the accuracy has been recommended (102, 121, 122, 164, 165) (VI), but has not yet been widely adapted.
This external quality control can be accomplished using different methods (31, 56, 162, 164, 166-168):

1. Comparing INR from venous samples analysed on the laboratory with that of the coagulometer
2. Comparing INR from a reference coagulometer with that of the coagulometer
3. Plasma (with a known INR value) sent from a central laboratory and compared with the result of the coagulometer
4. Comparing INR measured on a certified (calibrated) coagulometer with that of the patients coagulometer using 5 sets of plasma

Number 1 is generally named the split-sample method (168), but it is dependent on the quality of the INR measured on the laboratory, does neither account for imprecision nor accuracy, is time consuming and seems not suitable for external quality control. Method number 2 has the same obstacles as number 1.
Number 3 is the method developed by the UK NEQAS[10], which provides lyophilized plasma for external quality control to a number of centres using the coagulometers (166). One sample containing 2 sets of plasma (e.g. send every 3rd month) is provided, and patients are independently able to perform the control (164, 167). It does estimate imprecision by using two samples, but does not estimate inaccuracy, since the deviation is based on a deviation from an overall performance. Furthermore, since the reporting of results is done centrally, a time delay is present.
Number 4 is the method recommended by the European Action on Anticoagulation[11] (EAA), who recommends 5 samples at each time-setting (56, 169). The samples can be delivered by the ECAT (External quality Control of diagnostic Assays and Tests) Foundation.
The participation in external quality control cost money and is voluntary, and this contains obvious problems in terms of selection and uniformity. Obviously, the quality control has to be independent of the manufacturers of the coagulometers. The direct effect in terms of safety and increased quality and hence a reduced incidence of complications has not been documented. The recommendations are primarily based on general assumptions from different groups (e.g. EAA). Despite the lack of documentation, external quality control is mandatory (134, 161, 170) (VI). The method proposed by the EAA is superior, since it takes imprecision and inaccuracy into account (170, 171), and the result is instantly available for the patient, so no time delay is present. Yet, it has the drawback of demanding considerable resources. However, both the UK NEQAS and the EAA methods are applicable. Further trials will hopefully compare methods, optimally by using clinical endpoints.

[10] United Kingdom National External Quality Assessment Scheme for Blood Coagulation.
[11] Formerly named European Concerted Action of Anticoagulation (ECAA).

In summary, quality control is mandatory. Internal quality control is not adequate, so external quality control is needed. At present the EAA method seems to be the best method available.

Calibration
Regarding calibration of the coagulometers, it is merely the CoaguChek® that has been investigated, hitherto only this coagulometer is discussed. However, the general terms can be extrapolated to other types of coagulometers.
The manufacturer of the CoaguChek® coagulometer calibrates each lot (batch) of test strips and the corresponding code chip. The code chips carry the lot-specific information of the calibration. It is the ISI value, which can be calibrated. It has been advocated, that subsequent calibration of the coagulometers should and could be performed by the users/authorities (31, 172-174) in order to provide accurate INR measurements (134). It is possible to calibrate the CoaguChek® coagulometer using whole blood, fresh, citrated plasma (128, 172, 173) and even lyophilized plasma (175). Though possible, it is does not seem feasible. It requires an ISI calibration for parallel conventional manual PT testing with the local PT test system (instrument/thromboplastin combination) and an International Reference Preparation on plasma from the same whole blood samples used in tests on the coagulometer in order to comply with WHO guidelines (56). A calibration of each individual apparatus is therefore not a feasible option (134). Poller et al (175) has accordingly recommended calibration using lyophilized plasma for the manufacturers of the coagulometers and for centres involved in regulatory controls or clinical trials. Leichsenring et al (176) performed an ISI calibration on a master lot. This is an "overall" calibration of the thromboplastin generally used in the CoaguChek® XS coagulometers and not of the individual coagulometers. Others have argued that the CoaguChek® coagulometer with its test strips and code-chips is a local PT-system, and therefore, calibration can safely be done by the manufacturer, and no calibration should take place afterwards (158).
Christensen et al (VI) found it not possible to perform calibration of the coagulometers using the laboratory as reference, since the 95 % confidence intervals were wide and included zero. An external, independent, and thorough calibration is lacking and calibration is at present solely entrusted to the manufacturer. Since calibration is not feasible, the use of external quality control seems even more demanding (see above) and it should optimally be done as suggested by the EAA.

Type of management
In this section a brief overview of the different models of management will be provided with the emphasis on the published randomised controlled trials. There are numerous non-randomised trials and reviews, and only a brief overview of the main findings regarding these will be given.
In general, OAT management can be delivered by using one of the below mentioned methods:

- Routine care (provided by the general practitioner)
- Care provided by hospital outpatient clinics (provided by physicians working at a hospital, but not specialised in OAT)
- Care provided by highly specialised anticoagulation clinics (provided by a dedicated, specialised clinic where physicians, nurses and pharmacists are trained in the specialty of OAT)

- Shared care (a collaboration of conducting the OAT between the general practitioner and a hospital outpatient clinic (combining primary and secondary care))
- Use of computer assisted dosing (the dosage of coumarins is performed using a computer soft ware system)
- PST (the patient takes the blood-sample using a coagulometer, but the dosage of coumarins is done by a health care provider)
- PSM (the patient takes the blood-sample using a coagulometer and perform the dosage of coumarins themselves) (will be discussed in subsequent sections).

Routine care and care provided by hospital outpatient clinics are often referred to as conventional management.
However, this is a simplification of a more complex issue; e.g. computer assisted dosing can be utilised both in routine care, care by hospital outpatient clinics and PST. Highly specialised anticoagulation clinics can also be provided in both primary and secondary care, and this makes firm definitions and conclusions regarding the type of management difficult.
Some have advocated that more specialised treatment should be superior compared to routine care (177-180), while others have questioned it (181). This statement regarding superiority of specialised treatment has not been documented in a randomised controlled trial. However there are numerous non-randomised trials and they possess inevitable selection bias, so only randomised controlled trials will provide solid knowledge. Overall, an increased knowledge of OAT seems to increase the quality of treatment (182).
Only a few randomised controlled trials exist regarding management; PST was found to be superior compared to routine care (183-185) and to highly specialised anticoagulation clinic (186). Holm et al (187) found shared care superior compared to routine care. Poller et al (188, 189) tested different software systems[12] by comparing them to highly specialised anticoagulation clinics/conventional management in a randomised controlled trial. They found an overall non significant reduction in clinical events, but a significant improvement in time within therapeutic INR target ranges. Wilson et al (190) compared highly specialised anticoagulation clinics to routine care finding a significant improvement in time within therapeutic INR target ranges and patient satisfaction with OAT in the former group, but no differences regarding complications.
Claes et al (191) randomised patients into different settings, finding a better quality of treatment mainly as a result of an education and support programme, and this result is confirmed by Khan et al (192). Overall, the diversion in opinion is probably due to the extended use of non-randomised studies, a difference between countries in the precise definition and function of the type of management, performance bias in terms of differences in education of patients/doctors, and the extended use of surrogate endpoints. However, based on the available data from randomised controlled trials, the conclusion is that an increased knowledge of OAT (valid for both patients and health care providers) increases treatment quality. Furthermore, when comparing PSM to other types of management, it is important to be explicit on what precise type of model it is being compared against.

Patients
The studies included in this section are both non-randomised studies and randomised controlled trials.
PSM should only be offered to patients on long-term OAT (more than one year), since it requires training (see below) (162).
So far only a highly selected group of patients have been subjected to PSM. The patients have to be compliant and possess adequate mental and physical abilities to perform a finger stick in order to obtain a blood sample, operate the coagulometer, perform coumarin dosage based on the displayed INR, perform different quality control checks and know when to contact a health care provider for help or advice.
In a randomised controlled trial or cohort study, the control group has to be comparable with the PSM group, also with respect of being qualified for PSM. The number of patients excluded due to not fulfilling these criteria's should be documented, and the patients dropping out of the training should be accounted for by using an intention-to-treat analysis (61). Since PSM patients represent a highly selected group it is not possible to extrapolate the results to OAT patients in general. It is essential to be attentive regarding the external validity of the studies.
Heneghan et al (193) found that the drop-out was significantly higher in the PSM group compared with controls. This increases attrition bias, and thereby limits the external validity of trials. Most of the studies have included patients with various indications of OAT, which makes it difficult to extrapolate the results to a specific patient population (V).
The fraction of patients, who are both physically and mentally capable of PSM, is difficult to assess. The criteria's for assessing eligibility are seldom defined. An objective, uniform and validated method for assessing eligibility is needed, taking both physical and mental capabilities, expected compliance and interest in the OAT into account. In the ESCAT I-study (4) approximately 80 % of heart valve operated patients were considered eligible, while others (194-196) have estimated the fraction to vary between 20 – 60 %. Murray et al (197) found that approximately 16 % of patients having their OAT controlled by general practitioners were willing and able to perform PSM with 1 year of follow-up. Fitzmaurice et al (198) found that only 25 % of available patients could be included and thereby randomised, and only approximately 60 % of these patients completed the follow-up. Gardiner et al (199) found that 23 % of all patients referred for OAT could actually perform PSM. In a Cochrane review, it was found that PST or PSM was not feasible in almost 50 % of all patients (200).
Christensen et al (III) found 13 % unqualified for PSM and additionally 5 % dropped out during training for patients referred to PSM. The criteria's for assessing eligibility were clear and reproducible. Studies looking at individual patient characteristics are needed, and will hopefully clarify some of these aspects regarding selection of patients (201).
In conclusion, patients subjected to PSM are a highly selected group of patients. Based on the available data, at most 50 % of patients prescribed OAT are interested in and qualified for PSM.

Risk factors for complications
For patients prescribed OAT, the major risk factors of thromboembolism are: age > 70 year, peripheral/cerebral arterial disease and INR measurements < 1.5 (202-204). The major risk factors for bleeding are: age > 65 year, other diseases (heart, kidney, liver), other medication, poor compliance, alcohol abuse, long duration of OAT, a high therapeutic INR target range, INR meas-

[12] PARMA 5 and DAWN AC.

urements > 4.5, a large variability of INR measurements and former bleeding events (183, 203-210).
The indication for OAT and the quality of the treatment is related: patients with mechanical heart valves have relatively few clinical complications compared to that of patients with atrial fibrillation and prophylaxis for deep vein thrombosis (211, 212). The risk of complications is highest during the first 3 months after commencing OAT (4, 6, 13, 213), probably due to the increased variability of the INR measurements after commencement of treatment.
In general, higher median INR measurements are desirable, since the curve of a safe INR interval is skewed, with a higher risk of complications when the INR is low (214). Christensen et al (IV) found a higher median INR value and a higher dose of warfarin in patients performing PSM compared with conventionally managed patients. No difference was found in patients prescribed phenprocoumon. The long half-life of phenprocoumon leads to less frequent dose changes than in the case of warfarin and thereby requires a longer observation period than that applied in this study. An explanation for the higher median INR found among patients in the PSM group could be due to e.g. the inaccuracy of the coagulometer (used by patients to determine dose adjustments), an increased frequency of testing or an increased patient knowledge regarding the safe INR interval. Study limitations include the relatively small number of patients and the short observation period.
The coumarins are metabolized primarily by the enzyme CYP2C9[13] (1), which has a different activity in each patient. The enzyme exists in different polymorphisms, namely CYP2C9*1, CYP2C9*2 and CYP2C9*3. Patients with CYP2C9*2 and CYP2C9*3 have a slower metabolism of the coumarins compared to that of CYP2C9*1 (215, 216). This increases the risk for INR measurements outside therapeutic INR target range, an increased variability of INR measurements and an increased risk of bleeding complications (217-222). A test for this genetic risk factor has been proposed (223) and to use it for estimation of the warfarin dose (224). No studies exist regarding PSM and the genetic impact. The results found in conventional management can probably not be directly extrapolated to PSM, since the increased frequency of testing, selection of patients and increased knowledge of OAT could diminish the genetic impact on the variability of INR measurements. Numerous other factors also influence the dose of coumarins, such as VKORC1[14] genotype, diet, age, body mass index and medication (224-228).
In the last 20 years, six studies have compared the different types of coumarins. The ones with the longest half-life were superior, in terms of a more stable therapy, compared to the other; phenprocoumon vs. acenocoumarol (212, 229, 230), warfarin vs. phenprocoumon (231) and warfarin vs. acenocoumarol (232), and one study finding no difference in warfarin vs. acenocoumarol (233). All studies are biased by being non-randomised trials and the use of primarily surrogate endpoints. Only two studies (229, 231) included patients performing PSM. Jensen et al (231) found that despite phenprocoumon patients having a higher time within therapeutic INR target range and a smaller variability of INR, a tendency of fewer complications in the warfarin group was present, however not significant.
In conclusion, patients on OAT exhibit different risk of complications. An increased risk is found in patients with an indication for OAT in terms of thrombophilia and atrial fibrillation, a high comorbidity, old age, specific sets of genotype and potentially the use of coumains with a short half-life.

Type of training for PSM
In conventional management, training seems beneficial; trained patients on routine care perform better in terms of an increased time within therapeutic INR target range compared to untrained patients (192, 234, 235).
In PSM major differences exist regarding the duration and extent of the training. One study (236) reported that selected patients on long-term OAT did not need any specific training (apart from the function of the coagulometer) to be able to adjust their coumarins equally as well as done by a highly specialised anticoagulation clinic. However, the majority of centres have group sessions including 4 - 10 patients and consisting of 2 - 3 lectures, each lasting approximately 2 hours (60, 103, 104, 165, 197, 234). The teaching lessons deal with the function of the coagulometer and blood sampling, basic knowledge of the coagulation system and hence dosage of coumarins. In some centres, the patients commence PSM no later than 14 days after start of training (60, 103, 104, 165, 234). A training period of three teaching lessons, each two hours, with just one patient spread out on 27 weeks has also been used (102, 121, 122) (I-III). In this setting, the function of the coagulometer and blood sampling are trained initially, and the patient then gradually takes over the management of the OAT. This provides the basis for appropriate follow-up, and a thorough and individualised training. A drawback is that many resources from the centre are being allocated to training, is time-consuming and it maintains the patient in conventional management for a long time (27 weeks). No studies have compared group sessions versus individualised training in PSM.
A complete standardisation of a training program is not advisable, since older patients need significantly more training time in theoretical advising than younger patients (115). The education level of patients per se does not seem to influence the ability to learn PSM. However, there is a tendency that patients with a high education perform better in terms of an increased time within therapeutic INR target range compared to those with a lower education (237). Considering the increasing population of elderly patients with atrial fibrillation and the widespread use of OAT, a more flexible and individualised training program is reasonable.
Many centres supply the patients with a coumarin dosage algorithm (90, 104, 130, 238), since the use of algorithms as guidelines reflect experience/knowledge collected from many patients. Others have not used algorithms (60, 121, 122) (I-III), since the dosage adjustment differs from patient to patient. In diabetic patients a fixed algorithm for insulin dosage adjustment has been shown to have no or even harmful effect (239). The use of algorithms in OAT has not been tested and documented in the context of PSM. There is thus a substantial need for investigations looking at the impact of individualised training taking age, education level and the use of algorithms into considerations.
The drop-out rate during training varies between 2 - 40 % (60, 165, 197-199), but this figure is highly dependent of the eligibility criteria's. In some studies the patients have to pass an exam/evaluation before they are labelled as qualified to perform PSM (103, 121, 122, 240) (I-III). Intuitively, this seems reasonable, but the benefit of using such evaluations has not been documented.
A nationally approved, formalised training program named "The Association of Self Management of Anticoagulation" (ASA) has been established in Germany. They also provide training for train-

[13] A subgroup of the cytochrome P-450 system.
[14] Vitamin K epoxide reductase subunit 1.

ers (health care professionals) and they offer a peer review procedure where centres can be certified (85).
In Britain, guidelines have been published in order to standardise eligibility of patients, training etc. (162, 241). It is uncertain whether these models can be transferred to other countries, but some kind of international standardisation is advisable in order to increase overall quality (86). Wofford et al (242) performed a systematic review regarding the best strategies for patient education (including both PSM and conventional management), and concluded that patient education vary greatly in strategy, content and patient testing. The authors called for more standardisation.
In conclusion, training for PSM is necessary, since the management form requires both practical skills and theoretical knowledge. Different training programs can be used. Yet, international standards could potentially increase overall performance.

Quality assessment of oral anticoagulation therapy in trials

General considerations
The purpose of this section is to describe the different effect parameters used in trials regarding PSM and their potential advantages and disadvantages. Hereby, interpretations of the clinical consequences can be done in respect of these issues. The specific results of PSM trials will not be discussed in this section.

Complications
The incidence of major clinical complications; namely death, major thromboembolism and bleeding events are generally considered the best method for quality assessment, and it is used in large trials as clinical endpoints (4, 198, 202, 206, 243-245).
However, since the incidence of these complications is relatively rare, more than 1000 patients must often be included in order to get a statistically valid result. Thus, such studies are obviously time and resource demanding. Moreover, the definition of major complications is inconsistent (205, 243, 246-248) and the registration of all complications in a study population is often insufficient (249). It can therefore be difficult to perform comparisons between studies. Finally, patients included in a randomised controlled trial or a cohort study constitutes a highly selected group, treated and observed under ideal conditions. The quality of the treatment is therefore often overestimated compared to the "true" (daily life) picture regarding the incidence of complications in the target- and sample population (6, 178, 250), displaying the difference in efficacy versus effectiveness. The use of registers/databases to investigate the incidence in the whole target population, and not just in a selected group, is important when interpretation of the results of a randomised controlled trial or a cohort study is done.
Minor complications are from a methodological point of view even more complex to assess than major complications, and they will not be further discussed.

Variability of INR
The deviation/variability of the INR measurements correlates with the number of thromboembolism and bleedings events (6, 202, 206, 251, 252), and it has therefore been used as an indicator of the quality of OAT (60, 104). A high OAT variability (large fluctuations of INR values) significantly increases the risk of bleeding and thromboembolism (7, 203, 253). Like time within therapeutic INR target range (see below) it is merely a surrogate endpoint.
Comparison of the deviation using two different methods (coagulometer and laboratory) is an inappropriate effect measure (61) (V). The comparison of the deviation using two different methods is biased. Therefore, uniform control (external) INR samples should be applied. These INR samples should be taken on a regular basis; every 7^{th} - 14^{th} day seems optimal, although this has not been documented. Control INR samples in a trial should be send from various sites to a reference laboratory[15], which optimally should use the original WHO standard regarding INR analysis.

Time within therapeutic INR target range
Studies have demonstrated that the number of complications increases in parallel with the time patients spend outside therapeutic INR target range (247, 249, 252, 254). Although, time within therapeutic INR target range is a surrogate endpoint, it is often used for assessing the quality of the OAT (60, 202, 234, 255), since the required number of patients is low, and data is relatively easy to assess (249).
Time within therapeutic INR target range can be estimated with various methods giving different results (19, 247, 256-258). Five different methods have primarily been used, namely cumulative, cross-section, weeks within range, equidivision and linear interpolation (247, 256, 258). Today, the preferred method is linear interpolation[16], the so-called "Rosendaal-method" (257, 258). It is the most precise method and the most conservative, since it tends to underestimate time within therapeutic INR target range compared with the other methods (257). The use of different methods will make comparison between studies difficult.
The result of time within therapeutic INR target range is highly dependent on the therapeutic INR target range. All things being equal, a therapeutic INR target range of 2.0 - 4.0 will provide a higher time within therapeutic INR target range compared to a therapeutic INR target range of 2.0 - 3.0. This makes comparison between studies difficult, since different therapeutic INR target range are used for similar indications for OAT, both within- and between countries (4, 122, 255, 259). Time within therapeutic INR target range is also highly dependent on the frequency of testing (260). It is higher when the sampling rate is increased; up to two times per week has been shown to be the optimal sampling rate in order to increase time within therapeutic INR target range (260). Oake et al (25) found that nearly 50 % of all major complications occurred even when the INR was within therapeutic INR target range, and that time within therapeutic INR target range correlated with the incidence of thromboembolic events but not with that of bleeding events.
Wan et al (261) found a significant correlation between time within therapeutic INR target range and major complication in non-randomised trials, but a non significant correlation in randomised controlled trials. Wan et al (261) advocated for the use of time within therapeutic INR target range as an indicator of anticoagulation control. However, these findings merely confirm the potential bias using data from non-randomised trials.

Patient satisfaction/quality of life
The quality of treatment can also be measured in terms of patient satisfaction (quality of life), but it can merely be considered as a subjective statement and not as a clinical endpoint. If used in order to get a reliable and reproducible result, it has to be measured using standardised and validated methods (60, 103) such as

[15] The same laboratory should analyse all the blood samples, so that the "between laboratories" variability is eliminated.
[16] Divide the time between two measurements in days, and use small steps of 0.1 INR over the range of the time interval.

the SF-36[17] (262). A standardised scheme for assessing satisfaction/quality of life needs also to be adapted to the special conditions of PSM patients (263).

Children

Ten trials have tested PST and/or PSM in children (120, 121, 264-270) (II).

OAT in children entails many aspects, which are coincident with adults, but also aspects, which are uniquely related to this subgroup of patients. Despite the number of children on OAT being small they contribute with many 'treatment years', since the condition is often permanent and OAT is started early in life. The quality of OAT and patient compliance are major determinant factors for morbidity and mortality (271, 272). Fluctuating INR measurements entails the need for frequent blood specimens: up to 4 times a month, with adjustment of the dosage, if needed, once or twice a month (273). Hence, only 10 - 20 % of the children can be safely monitored using monthly samples (274). Other problems exist: concomitant medication, practical problems such as difficulties in performing venepuncture, interruption of attendance at school, interruption of parental professional engagements, problems when going abroad, and compliance (especially in puberty) (273, 275). OAT can be optimised in several ways: using paediatric OAT clinics, social support to the parents, determinations of the optimal therapeutic INR target range and a coagulometer for analysing INR at home (PST) (274-276). The quality of OAT in children has increased during the last decades, and the incidence of major complications is now comparable to those of adults (273). However, these estimations are based on a limited number of patients.

Estimation of time within therapeutic INR target range has been done in a limited number of studies; Spevak et al (277) found that only 64 % of the treated children maintained a PT within the desired range on at least 50 % of the measurements. Streif et al (278) found, in a paediatric OAT clinic including a total of 319 children, that the percentage of INR measurements within target range depends on age and therapeutic INR target range; under the age of 1 year time within therapeutic INR target range was 37 % +/- 16 (mean +/- 1 standard deviation) rising up to 53 % +/- 19 for patients between 13 and 18 years. When looking at the time within therapeutic INR target range, the figures were 49 % +/- 21, 47 % +/- 18 and 61 % +/- 20 for therapeutic INR target range being 1.4 - 1.8, 2.0- 3.0 and 2.5 - 3.5, respectively. These findings show that time within therapeutic INR target range is inversely related to the age of the child and the therapeutic INR target range. Twenty-eight of the children performed PST and here 68 % (mean) of the INR measurements were within therapeutic INR target range (278).

Seven studies (121, 265-267, 269, 270) (II) have assessed the feasibility of PSM in children. In one study (265), only 30 % (six patients) of the children performed PSM, and no results were reported for this subgroup. Christensen et al (121) used a case-series design and it was found that the median time within therapeutic INR target range was 65.5 % (range: 17.6 - 90.4 %). The study has limitations; no control group, lack of information regarding basic-, target- and sample population, no information about medication, number of patients not found suitable for PSM, drop-out rate during training, a small number of patients (14 in total) and a relative short follow-up time (547 days, range: 214 - 953 days). The mean age was 9.7 years (range: 2.2 - 15.6 years) and the therapeutic INR target range was 2.0 - 3.0 and 2.5 - 3.5. Taking into consideration the age of the patients and the therapeutic INR target range, a time within therapeutic INR target range of 65.5 % is not significantly superior compared to other types of management (278). Christensen et al (II) made a long-term follow-up (mean: 3.6 years) including more patients (N = 22) than in the previously study (121), finding an improvement in time within therapeutic INR target range to a median of 73.1 % (range: 30.3 - 91.0 %). This improvement could be due to a time-effect, but the result is promising in terms of persistence of treatment quality over time. Furthermore, Christensen et al (121) (II) published some of the first studies testing the feasibility of PSM in children, and hereby leading the way for making PSM a treatment option in this group of patients.

The paper by Mähönen et al (267) was also a case-series study (including 19 patients) with a mean follow-up of 28 months and the median time within therapeutic INR target range was 69 %. A major part of the patients found that PSM had major practical advantages compared with conventional management.

Bauman et al (270) published in 2010 a small randomised controlled trial, where 28 children with congenital heart diseases performing PST were randomised to either continue with PST or to commence PSM. Follow-up time was 1 year. No difference was found regarding time within therapeutic INR target range (83.9 and 83.0 % in the two groups, respectively). However, a higher quality of life was found in the PSM group. The authors called in their conclusion for clinical studies with a larger sample size. It is merely a small study with a highly selected group of children already performing PST, and the results cannot be extrapolated to vast majority of children on conventional managed OAT. However, it can be concluded that PSM is at least as good a treatment option as PST in selected children. Bauman et al (279) also conducted an observational study with the use of a standardised child focused educational intervention in order to provide the child and caregivers an understanding of the use of the coagulometer and of OAT in general. They found it feasible, providing an increased knowledge and an increase in time within therapeutic INR target range. It was concluded, that it could potentially lead to an optimised care and outcome in children on OAT. As in adults, it can be concluded that an increased knowledge of OAT increases treatment quality.

The different models of the CoaguChek® coagulometers have been used in paediatric settings (120, 121, 150, 156, 266, 280, 281). It was shown to function well and provide acceptable accurate results compared with the laboratory, and the small difference between the laboratory and CoaguChek® coagulometers had no clinical consequences. Yet, Nowatzke et al (266) concluded that the CoaguChek® coagulometer offered acceptable accurate and precise measurements, but the performance of the apparatus should be monitored with regular standard laboratory measurements. Furthermore, high and low INR measurements obtained by the coagulometer should be controlled by the laboratory, since agreement between the coagulometer and laboratory decreases with INR measurements outside the therapeutic INR target range (266). The new model of CoaguChek® coagulometer (CoaguChek® XS) was found to be more accurate than the predecessor CoaguChek® S (156, 280). Greenway et al (281) found that the CoaguChek® XS was more accurate compared to the original WHO method used in the laboratory than when compared to standard INR analysis in the laboratory. This finding underlines the importance of using the WHO method as comparison method.

[17] Short Form 36 Health Survey Questionnaire. A validated method of estimating quality of life.

PST has been investigated in four studies (120, 264, 268, 270), and it has been demonstrated that this is a feasible treatment option with good results.
These different objections make it difficult to compare the results of these studies directly with other studies regarding OAT in children. It can therefore merely be concluded that PSM is feasible in a highly selected group of paediatric patients, and the results seem very promising. Larger studies, preferably randomised controlled trials using clinical endpoints, are obviously needed in order to elucidate whether these new regimens of treatment are superior to conventional management of OAT.

Economics

The direct expenses related to PSM are purchase of the coagulometer, finger puncture device, test strips, resources for training of the patient, staff and equipment of a PSM centre and external quality control of the coagulometer.
The direct savings regarding PSM are no or a reduced number of laboratory INR controls and no consultation regarding dosage of coumarins is performed by the general practitioner/hospital outpatient clinic/highly specialised anticoagulation clinic. The expenses for PSM depend on the number of patients affiliated to the centre. The direct expenses related to PSM and other types of treatment modality have been studied, but controversies remain (103, 154, 240).
The indirect costs or savings are difficult to assess. It has been argued that PSM reduces complications and the overall cost would therefore be reduced (4, 282). This conclusion is based on many assumptions, estimates, and subjectivity in matters such as the definition of complications, clinical course of various complications, finding the patients with complications and costs of treatment (61).
Cost-effectiveness analyses including the estimated incidence of complications in the two groups found that PSM is cost-effective compared to general practitioner/hospital outpatient clinics/ highly specialised anticoagulation clinic (282-284). It is, as mentioned above, based on many theoretical assumptions, and only tested in one randomised controlled trial (285), finding PSM not to be cost-effective. It has not been investigated in a meta-analysis due to the inaccuracy and inconsistency of the available data (61) (V).
Furthermore, the result of this type of analyses can hardly be transferred from one country to another due to differences in terms of organisation of the health care system, rehabilitation of patients with complications, estimation of costs etc. Each country will have to perform a cost–effectiveness analysis, potentially done as a Health Technology Assessment, which only has been done in a few countries, England[18] and Denmark[19]. Both of these assessments did not find PSM cost-effective.

Societal costs are one thing; the individual costs for the patient is another issue. In some countries (e.g. Germany and Denmark) the patients have all expenses reimbursed (apparatus, test strips etc.). In other countries (e.g. Britain, Sweden and USA), patients will often have to pay for the instrument themselves, while the test strips are covered by the health care system. The patient saves money by avoiding transportation and work leave for blood sampling.
In summary, there exists no evidence regarding cost-effectiveness of PSM compared with conventional management.

Trials

General considerations

In this section, the results of the observational studies on PSM will be displayed and discussed. Regarding the randomised controlled trials, the baseline characteristics of these studies will be presented and the methodological problems regarding the studies will be discussed. Merely the results regarding INR variability and quality of life will be discussed, since the remaining of the effect parameters are incorporated in the section regarding systematic reviews and meta-analysis.

Observational studies

To date, 14 observational studies (non-randomised trials) have been published (90, 92, 102, 104, 122, 130, 194, 199, 236, 238, 286-288) (I).
The case-series studies (92, 194, 238, 286-288) (I) have generally been small size studies (ranging from 8 - 1375 patients (mean: 263 patients, median: 16 patients)) with a short follow-up time (range: 3 - 39 months, mean: 17 months, median: 11 months), primarily using surrogate endpoints (time within therapeutic INR target range). There are generally no obvious description concerning the basic-, target-, sample population and how the sampling of patients was done. It is a highly selected group, and due to the design no control group is included. This limits the conclusions that can be drawn from these studies, and interpretation must be done with caution. However, it can be concluded that highly selected patients performing PSM seem to have at least the same time within therapeutic INR target range (range: 69.3 - 76.5 %) as that reported in the literature for the wide span of patients managed by general practitioner/hospital outpatient clinics and highly specialised anticoagulation clinics. Furthermore, it was demonstrated that PSM is feasible for various indications and in a wide range of age in selected patients.
Six studies used a cohort design, three being prospective (104, 130, 199) and three retrospective (90, 102, 122) Again, the basic-, target-, and sample population and the sampling of patients has not been accounted for. Furthermore, the selection of control groups was problematic in terms of matching criteria's. All six studies were small in size (mean: 36 patients, range: 17 - 84 patients (in each group)), and with a relatively short follow-up time (mean: 23 months, range: 8 - 42.5 months) using only surrogate endpoints. All studies found that PSM patients had a higher time within therapeutic INR target range than hospital outpatient clinics treatment, although only three provided a statistically significant result. In a nested case-control study no difference was found when PSM was compared with a highly specialised anticoagulation clinic (236). However, many studies have used a different frequency of testing (e.g. weekly versus monthly) between the different types of management tested. Moreover, different meth-

[18] M Connock, C Stevens, A Fry-Smith, S Jowett, D Fitzmaurice, D Moore and F Song. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modeling. Health Technology Assessment HTA. NHS R&D HTA Programme. Health Technology Assessment 2007; Vol. 11: No. 38.

[19] LH Rasmussen, J Jespersen, AMB Münster, J Godtfredsen, S Husted, JF Lassen, TD Christensen, HK Pilegaard, J Sørensen, Olsen J. Self-monitoring of oral anticoagulation therapy – a commented foreign Health Technology Assessment. The Danish Board of Health 2009.

ods (coagulometer and laboratory) for estimating INR are used with inherent bias as a consequence (see above).
Minor complications have only been estimated in a few studies, and the difficulty of estimating these complications makes further discussion redundant.
The variability of INR has only been tested in two studies (103, 236), and it will therefore not be further discussed.
The estimation of patient satisfaction/quality of life has been done by the use of stray/random questions using non-validated and not well-described methods (90, 102, 154) and/or using a case-series design, e.g. (105, 145, 289). These studies provide therefore no solid scientific information regarding patient satisfaction.
In conclusion, due to these specific problems and the general methodological problems regarding observational studies, conclusion should be drawn with caution. However, the feasibility of PSM was demonstrated in a wide span of patient categories, and the quality of treatment is acceptable.

Randomised controlled trials
Randomised controlled trials have many advantages and is considered as "state of the art", only exceeded by meta-analysis regarding the level of evidence.
Sixteen randomised controlled trials (4, 60, 103, 165, 196, 198, 234, 240, 245, 259, 290-294) (III, IV) has been published. There are some double publications (other aspects/focus of the paper, but based on the same patients), and these studies (2, 237, 295, 296) (IV) have been excluded. However, two studies by Körtke et al (4, 292) are both displayed, due to the divergence in endpoints and follow-up time. Horstkotte et al (259) merely published an abstract with inadequate presentation of data.
It is obviously not possible to conduct a double-blind study, since the patient is bound to know what treatment she/he is receiving. However, it is possible to blind the doctors taking care of the group randomised to conventional management. Only one study (234) has used partial blinding, and the risk of performance bias is therefore potential in the vast majority of studies.
Henaghan et al (193) estimated the drop-out rate in randomised controlled trials, finding a higher drop-out rate in the PSM group compared with controls, which inevitable leads to attrition bias. Further studies are needed to find characteristics of patients not able to conduct PSM.
In the included trials, the target- and sample population is often not well-described and there is a variation between the trials regarding in- and exclusion criteria. Furthermore, the information/knowledge of OAT given to the patients shows variation, both between trials and between randomised groups. A major problem in many studies is that only the PSM group is being trained (61).
A total of 3329 patients have been included in a randomised controlled trial . The studies are small in size (mean: 222 patients, median: 124 patients, range: 49 - 757 patients (in both groups)) and with a relatively short follow-up time (mean: 12 months, median: 12 months, range: 6 – 24 months). They are statistically powered predominantly to surrogate endpoints, except partly for (4, 198, 245, 292). All the studies reported a good follow-up and adherence to randomisation. In the calculation above regarding the number of patients and follow-up time, the study by Körtke et al (292) has not been included, since it is merely an extension of a former study (4).
The CONSORT[20] statement is used for assessing and improving the reporting of randomised controlled trials based on the conduction and design of the study (297), and only a small number of the trials have complied with these requirements.
Six trials have used the variability of the INR as an effect parameter; two not using external blood samples (245, 294) and four using it (60, 103) (III, IV). Sawicki et al only took three blood samples, and no difference was found between the groups (103). The studies by Christensen et al (III, IV) found a smaller variability with PSM compared to conventional management, which was in accordance with the findings from Cromheecke et al (60). Christensen et al (III, IV) used one reference laboratory for analysis of INR. All results were blinded for the investigators during the observation period, and the effect parameter used was validated in a subsequent study (VII). The internal and external validity of the study is therefore high, and the results seem well-founded. When applied and used optimally (blood-samples taken on a regular basis and INR estimated at an external laboratory), the variability of INR can be used as an indicator of treatment quality (III, IV). However, the method is predominantly applicable in trials, and not in the daily clinical setting.
Quality of life has been investigated in six studies (60, 103, 196, 240, 285, 298). Patients performing PSM seem to have a higher satisfaction/quality of life than those undergoing conventional management (60, 103), highly specialised management (196) and PST (298). Two studies could not demonstrate any difference (240, 285). The studies have predominantly used non-comparable parameters, so comparison between studies is difficult (V). Based on the available data, it can merely be concluded that the patient satisfaction regarding PSM is equally as good as or perhaps better than conventional management.
In general, the randomised controlled trials entail various methodological problems, which have to be considered when conclusions are drawn. In general, the internal validity is not optimal, and the external validity is compromised due to the different inclusion criteria's, concept of training, therapeutic INR target range and management of the control group. It is important to emphasize that just by participating in a trial the quality of treatment is increased (178) making the application of results to the standard population of patients difficult (250).
Christensen et al (III) included 100 patients in a randomised controlled trial, which was not powered for detection of difference in clinical complications. However, by using a composite score, the incidence of complications had a significant impact on the surrogate endpoints used. The results seem therefore more well-founded than if solely surrogate endpoints were used. It was concluded that the quality of PSM was at least as good as that provided by conventional management.
Based on the results of the low quality studies, no firm conclusion can be done. However, based on the high quality studies, it can be concluded that PSM is at least as good as that provided by conventional management.

Reviews, guidelines, systematic reviews and meta-analysis

Reviews and guidelines
Numerous reviews have been published (61, 85, 163, 299-306) focusing on PSM and/or the use and quality of the coagulometer. Most of these reviews have been in favour of PSM, but seldom very objective or sceptical, since no objective and uniform criteria

[20] Consolidated Standards of Reporting Trials.

for inclusion and assessment of trials have been given. This limits their use as a "scientific tool" compared with systematic reviews. This also include guidelines (86, 241), which can only serve as a practical "cookbook" when implementing PSM in a local setting.

Systematic reviews and meta-analysis

The findings from randomised controlled trials that have evaluated the efficacy of PSM compared with conventional management have been inconsistent and the scientific basis for implementing PSM can therefore be questioned (61). However, systematic reviews and meta-analysis are ideal references when evidence based treatments are to be implemented (307).

Five systematic reviews have been published (200, 308-310) (V). Siebenhofer et al concluded that PSM is safe, improves treatment related quality of life and the quality of OAT (309). However, this review included only four studies of which one was not a randomised controlled trial. A similar conclusion was found in a meta-analysis performed by Odegaard (310). These two meta-analyses do not bring any new knowledge due to the mixing of observational studies and randomised controlled trials as well as the lack of assessment of the methodological quality of included studies (V).

The remaining three systematic reviews (200, 308) (V) adhered to the requirement by QUAROM[21] (311).

Heneghan et al (308) concluded that: *'Self-management improves the quality of oral anticoagulation. Patients capable of self-monitoring[22] and self-adjusting[23] therapy have fewer thromboembolic events and lower mortality than those who self-monitor alone. However, self-monitoring is not feasible for all patients, and requires identification and education of suitable candidates'*. This first part of their conclusion can be questioned, since the quality assessment of the included trials does not seem optimal (V) and the distinction between PST and PSM was partly incorrect.

The Cochrane review by Garcia-Alamino et al (200) was done by the same research group that published the study by Heneghan et al (308), and it was an updated continuation with the addition of more trials. They concluded, that: *'Compared to standard monitoring, patients who self-monitor or self-manage can improve the quality of their oral anticoagulation therapy. The number of thromboembolic events and mortality were decreased without increases in harms. However, self-monitoring or self-management were not feasible for up to half of the patients requiring anticoagulant therapy. Reasons included patient refusal, exclusion by their general practitioner, and inability to complete training'.*

Christensen et al (V) concluded that: *'A majority of the existing trials have various methodological problems. However, self-management of oral anticoagulant therapy appeared at least as good and possible better than conventional management in highly selected patients'.* This is a more reluctant conclusion compared to that of Heneghan et al (308). It elucidates the diversity and the difficulty in interpreting the results from the randomised controlled trials, when performing a meta-analysis. Christensen et al (V) made no division regarding thromboembolism and bleeding complication, which could have been desirable. However, by pooling these two types of major events a more precise estimate of risk is found.

The events of death and major complications are relatively high in the study by M-Jándula et al (245) compared to that of Fitzmaurice et al (198). This could be due to differences in detecting events or differences of patients and care in the two studies. The methodological flaws in the included low-quality trials have to be taken into consideration when interpretations of these are done (V). The low quality studies found a more pronounced effect of PSM compared to those of high quality. This is in agreement with the fact, that high quality trials provide the most realistic estimate regarding the effect of a new treatment (297).

Including all 14 published studies till now and performing an updated meta-analysis using the methodology as done by Christensen et al (V), the overall conclusion does not change. The results are the same, except that the total number of minor complications becomes significantly lower in the PSM group and the risk of death becomes non-significant. Overall, the estimate becomes more valid as more studies are included. Bradburn et al (312) have advocated for using the Peto method in a meta-analysis when pooling rare events (< 1 %). However, using this method does not change the results. Major complications can be divided in to thromboembolism and bleeding events. PSM significantly reduces the incidence of thromboembolism, but no difference exists regarding bleeding events. This is in accordance with the findings in the Cochrane review (200). This is also supported by the results found by Christensen et al (IV), where PSM was associated with a higher median INR, and a higher dose of warfarin compared to conventional management, thereby potentially reducing the risk of thromboembolism. The incidence of minor complications exhibited significant heterogeneity in different trials (198, 245) and asymmetry when analysed in a funnel plot (V). It may be due to the difficulties in finding and reporting these complications and variation between the included studies in a precise definition of these complications (V).

No division is performed regarding minor complications, since these constitute of merely bleeding events, except for one trial (165).

The high heterogeneity and the asymmetry in the funnel plot found in a meta-analysis (V), when analysing time within therapeutic INR target range is most likely due to time within therapeutic INR target range being an inappropriate effect measure. Generally, assessing the quality of treatment using time within therapeutic INR target range has various limitations (see above).

The conclusion by Christensen et al (V) seems scientifically well-based, also in an updated edition; the quality assessment of studies and the analysis is performed conservatively, so that the effect of the intervention (PSM) is not overestimated.

Therefore, in conclusion; a majority of the existing trials have various methodological problems. However, PSM appeared at least as good as and possibly better than conventional management in highly selected patients.

CONCLUSION

The clotting activity of coagulation factors II, VII, IX, and X and CAT exhibited no variability over a 6-week period. The activity of the coagulation factors and CAT was significantly associated with the INR, so these two tests can be used concomitantly and/or interchangeably with the INR. Approximately 50 % of the total variability of the coagulation factor activities and CAT was reflected by the INR, whereas the remaining variability was within the subject (patient). Coagulation factor activities and CAT can therefore potentially be used to provide further information to the risk of bleeding and thromboembolism, since almost 50 % of the variability within the subject is not displayed in the INR value. Yet it remains uncertain if these methods can predict complications in

[21] Quality of Reporting of Meta-analyses.
[22] Patient Self-Testing (PST).
[23] Patient Self-Management (PSM).

individual patients on OAT. Larger clinical trials with a long follow-up period, preferably using clinical endpoints, are needed in order to draw any firm conclusions regarding the clinical consequences. However, measurement of coagulation factor activities and CAT may improve measurement of coagulation activity in patients prescribed OAT beyond the parameters currently clinical available.

The CoaguChek® S and XS coagulometers used for PSM were found to have an adequate precision. Regarding the accuracy, the INR measurements tended to be lower on the coagulometers, compared with the laboratory. A large proportion of the measurements on the coagulometers deviated more than 15 % from the laboratory measurements. However, only one laboratory was used for comparison and the original WHO method (gold standard) for estimating INR was not used. Furthermore, the inherent limitations of the INR have to be taken into consideration, and the results have to be viewed in this context. The accuracy of the coagulometers seems in this respect acceptable and they can be used in a clinical setting. However, external quality control is essential.

In the observational studies, it was found that PSM was feasible and provides satisfactory treatment quality for various indications and in a wide range of patient age. In a randomised controlled trial, using a documented blinded composite endpoint, PSM was found to provide a treatment quality that was at least as good as that provided by conventional management. Additionally it was found, that training and implementation of PSM lead to a smaller variance in INR measurements, a higher median INR and a higher dose of coumarins compared to that obtained for conventionally managed patients.

Further evidence was provided in a systematic review and meta-analysis, where it was documented, that PSM appears at least as good as and possibly better than conventional management in highly selected patients.

FUTURE PERSPECTIVES

The future of OAT will probably change in the coming years with more specialised OAT centres managing/controlling many patients on OAT, providing a variety of methods of managing OAT within the centre (e.g. computer-based dosing program, PST and PSM), which can be offered on an individualised basis (8). The use of information technology will also increase in the coming years (313-315), such as interactive anticoagulant home pages, e-learning, interactive voice response systems, home patient testing performed by district nurses and dosage provided on-line (188, 289, 315-317).

PSM in these settings seems natural, but the degree of success depends on many factors, e.g. economy, tradition, trends and patient demands. However, PSM is rapidly developing and is likely to grow over the coming years (303). The introduction and distribution of PSM should be based on solid scientific evaluations, and the studies included in this thesis have enhanced the potential for making implementation of PSM evidence based.

New anticoagulant drugs will be developed, and an example of these is direct thrombin inhibitors, that can be administrated orally and subcutaneously (318-321). Laboratory monitoring of this treatment is probably not required. However, the initially most promising oral drug Ximelegatran (Exanta®) was withdrawn from the marked due to many side effects (322), and a subcutaneously administrated drug have in clinical trials been found inferior compared to coumarins (323). In 2009 the RE-LY study was published (324), where the oral direct thrombin inhibitor Dabigatran in different dosages was compared to coumarins in patients with atrial fibrillation. A reduced incidence of complications was found, but the results have been debated, e.g. (325).

At present, no universal substitute for coumarins is available. Yet, it is likely that new drugs will be approved for sale in the coming years (303, 326). Initially they will predominantly be indicated for patients with a relative low risk of thromboembolism, e.g. atrial fibrillation (324), but not for patients with a high risk, e.g. mechanical heart valves. Furthermore, many patients already performing PSM will probably continue with this, if they experience no complications and are satisfied with PSM. Therefore, coumarins and PSM as a management option will still be relevant for many years.

In order to replace the coumarins, the new drugs will have to be at least as effective and safe in terms of complications, such as the incidence of thromboembolism and bleedings events (327). The consideration for the patient is the most important factor: what is the best-known available treatment. The recommendations should be based on evidence.

SUMMARY

This doctoral thesis has been materialised under my employment at the Department of Cardiothoracic and Vascular Surgery & Institute of Clinical Medicine, Aarhus University Hospital, Skejby, Aarhus, Denmark.

The thesis is based on eight original articles, all published in international peer-reviewed journals.

Oral anticoagulation therapy (OAT) with coumarins (e.g. warfarin (Marevan®) and phenprocoumon (Marcoumar®)) is prescribed for both prophylactic and therapeutic use to patients at increased risk of thromboembolism. OAT has a narrow therapeutic index, and monitoring is based on the International Normalized Ratio (INR) conventionally determined on citrated plasma obtained by venepuncture. Based on the INR measurements, health care providers determine the appropriate dose of coumarins. Hence, the INR is used as guidance for the coumarin dose.

Optimised management of OAT improves the quality of treatment. A new method is patient self-management (PSM), which implies that the patient analyses a drop of blood using a portable coagulometer (INR-monitor). The coagulometer displays the INR, which the patient uses for dosage of coumarins. A precondition for this treatment is a thorough investigation of the coagulometer used.

INR has proven adequate for adjusting dosages. However, it is doubtful that the level of INR reflects the overall haemostatic capacity or thrombotic potential of individual patients. Furthermore, the predictive value of the INR in estimating individual patients' risk of complications is questionable. Nearly 50 % of all major complications occur even when the INR is within therapeutic INR target range. Accordingly, it is important to obtain knowledge of parameters that can bring additional information in order to predict complications. Measurement of continuous calibrated automated thrombin generation (CAT) may serve as a more sensitive and global haemostatic parameter and potentially with better performance in predicting risk of complications in patients on OAT. In addition, coumarins main effect is by depression of the coagulation factors II, VII, IX, and X. It may be speculated, that determination of the clotting activity of these coagulation factors could provide supplementary predictive information regarding risk of complications. However, in order to be able to predict complications in the individual patient, it is important to further characterise these tests; to estimate the variability of these tests

over time, to see if the results are associated with the INR, their practical and clinical application and whether or not these new methods will bring additional information regarding the overall coagulation activity.
The aims of this thesis were to:

- Estimate the variability of coagulation factors II, VII, IX and X and continuous calibrated automated thrombin generation in patients on stable oral anticoagulation therapy.
- Compare and evaluate coagulation factor activities (II, VII, IX and X) and continuous calibrated automated thrombin generation with the International Normalized Ratio (INR) in patients on stable oral anticoagulation therapy.
- To assess the variability of INR, coagulation factor activities, (II, VII, IX and X) and continuous calibrated automated thrombin generation during 24 hours of storage of blood samples at ambient temperature.
- Estimate the precision and accuracy of the coagulometers used for patient self-management of oral anticoagulation therapy.
- Determine the feasibility and quality of patient self-management of oral anticoagulation therapy prescribed to different patient categories such as mechanical heart valve patients and children.
- Compare patient self-management of oral anticoagulation therapy with conventional management in a randomised controlled trial.
- Evaluate the efficacy and safety of patient self-management of oral anticoagulation therapy in a systematic review and meta-analysis.

Study I was a case-series study where mechanical heart valve patients (N = 94) were trained in home blood analysis of INR using a coagulometer and coumarin dosage adjustment. After training, the patients were followed by weekly INR measurements. The mean observation time was 2.1 years (range: 0.04 - 6.2 years), and the total number of patient-years was 197. The patients were within therapeutic INR target range for a median of 76.0 % (range: 32.1 - 100.0 %) of the time. There were two major thromboembolic events and five major bleedings events. All the events required short hospitalisation, and after treatment all the patients were discharged from the hospital without any sequelae or other complications. It was concluded, that PSM provided a good treatment quality for mechanical heart valve patients. PSM was considered an equally as good or potentially better treatment option than conventional management for selected patients.
Study II was a case-series study including children (N = 22) with congenital heart disease. The mean observation time was 3.6 years (range: 0.9 - 5.8 years). The patients were within therapeutic INR target range for a median of 73.1 % (range: 30.3 - 91.0 %) of the time. None of the patients experienced thromboembolic or bleeding complications requiring doctoral intervention. It was concluded that PSM is safe and provides a good quality of treatment in selected children with congenital heart disease.
Study III was a randomised controlled trial where 100 patients were randomised to either PSM (including a teaching program of self-management followed by 6 months of self-management) or 6 months of conventional management. The primary endpoint was an intention-to-treat analysis of a composite score combining the variance of the INR measurements (using a blinded control sample analysed monthly by a reference laboratory), death, major complications, or discontinuation from the study. Secondary endpoints – assessed in a per-protocol analysis – were the variance of the INR measurements (using the blinded control sample), and time within therapeutic INR target range using the INR measurements from the coagulometer and laboratory measurement. There was no significant difference in the primary endpoint between PSM and conventional management (composite score 0.16 vs. 0.24, respectively, p = 0.09). PSM was significantly better (0.16 vs. 0.24, p = 0.003) regarding the variance in a per-protocol analysis. The difference in time within therapeutic INR target range was not significantly better (78.7 vs. 68.9 %, p = 0.14) using PSM. In conclusion, the quality of PSM was at least as good as that provided by conventional management.
Study IV used data collected from study III. The endpoints were the variance (median square of the standard deviation) of the INR measurements, the median INR measurements (using a blinded control sample analysed monthly by a reference laboratory), and the dose of coumarins. PSM was associated with a statistically significant smaller variance of INR measurements, a higher median INR and a higher dose of warfarin compared to conventional management. Training and implementation of PSM lead to a smaller variance in INR measurements, a higher median INR and a higher dose of coumarins compared to results obtained for conventionally managed patients.
Study V was a systematic review and meta-analysis including randomised controlled trials with highly selected patients comparing PSM with conventional treatment. Data were extracted in terms of study characteristics, quality of trials, and outcome (death, minor and major complications (thromboembolic and bleeding events) and time within therapeutic INR target range). Ten trials with a total of 2724 patients were included. Two of the trials could be classified as high quality trials. Considering all trials, PSM was associated with a reduced risk of death (Relative Risk (RR) = 0.48 (95 % Confidence Interval (CI), 0.29 – 0.79; p = 0.004)), major complications (RR = 0.58 (95 % CI, 0.42 – 0.81; p = 0.001)), and with increasing time within therapeutic INR target range (weighted mean difference = 6.53 (95 % CI, 2.24 – 10.82; p = 0.003)). No clear effect was found regarding minor complications (RR = 0.98 (95 % CI, 0.49 – 1.99; p = 0.96)). It was concluded, that a majority of the existing trials had various methodological problems. However, PSM appeared at least as good and possible better than conventional management in highly selected patients.
Study VI evaluated the precision and accuracy of the used coagulometers (CoaguChek® S and XS). It was found that the precision of the coagulometers was adequate, but only the CoaguChek® XS had a precision within the predefined limit of 3 %. Regarding analytical accuracy, the INR measurements tended to be lower on the coagulometers, compared to the laboratory. A large proportion of measurement of the coagulometers deviated more than 15 % from the laboratory measurements. However, only one laboratory was used as comparison and the original WHO method (gold standard) for estimating the INR was not used. Furthermore, the inherent limitations of the INR have to be taken into consideration, and the results have to be viewed in this context. The coagulometers accuracy seems in this respect acceptable and they can be used in a clinical setting. However, external quality control is essential.
In study VII the aims were to assess the variability of INR, coagulation factor activities, and CAT, during 24 hours of storage of blood samples at ambient temperature. It was found that patients individual INR, coagulation factor activities, and CAT are not signifi-

cantly influenced by 24 hours storage of blood samples. However, the CAT analyses displayed a trend toward time dependency.

In study VIII the CAT and clotting activity of coagulation factors II, VII, IX, and X displayed no variability over a 6-week period. The activity of the coagulation factors and CAT was significantly associated with the INR, so the results of these two tests can be used concomitantly and/or interchangeably with the INR. Approximately 50 % of the total variability of the coagulation factor activities and CAT was reflected by the INR, whereas the remaining variability was within the subject (patient). Coagulation factor activities and CAT can therefore potentially be used to provide further information to the risk of bleeding and thromboembolism, since almost 50 % of the variability within the subject is not displayed in the INR value. This residual variability could therefore encompass additional information regarding the clotting activity within the individual patient. Yet it remains uncertain if these methods can predict complications in individual patients on OAT. Larger clinical trials with a longer follow-up period, preferably using clinical endpoints, are needed in order to draw any firm conclusions regarding the clinical consequences. However, measurement of coagulation factor activities and CAT may improve measurement of coagulation activity in patients prescribed OAT beyond the parameters currently clinical available.

ABSTRACT

Oral anticoagulation therapy (OAT) with coumarins (vitamin K-antagonists) is prescribed for both prophylactic and therapeutic use to patients at increased risk of thromboembolism. OAT has a narrow therapeutic index, and monitoring is based on the International Normalized Ratio (INR) conventionally determined on citrated plasma obtained by venepuncture. Based on the INR measurements, health care providers determine the appropriate dose of coumarins (e.g. warfarin (Marevan®). Optimised management of OAT improves the quality of treatment. Patient self-management (PSM) is a new concept where the patient takes an active part in his or her own treatment. PSM in OAT implies that the patient analyses a drop of blood using a portable coagulometer (INR-monitor). The coagulometer displays the INR, which the patient uses for coumarins dosage. It is still not clarified which subset of patients (in terms of indication for OAT, age, co-morbidity etc.) that potentially will benefit from PSM, and how large this potential effect is.

A precondition for a correct dosage of coumarins is a correct estimation of the INR, and the method and apparatus used for providing the INR measurements is in this context essential. The coagulometers used for PSM have not been investigated adequately in terms of precision and agreement, so this is warranted. INR has proven adequate for adjusting dosages. It is doubtful that the level of INR reflects the overall haemostatic capacity or thrombotic potential of individual patients.

Measurement of continuous calibrated automated thrombin generation (CAT) and coagulation factors activities may serve as a more sensitive and global haemostatic parameter and potentially with better performance in predicting risk of complications in patients on OAT.

We found that the clotting activity of coagulation factors II, VII, IX, and X and CAT exhibited no variability over a 6-week period. The activity of the coagulation factors and CAT was significantly associated with the INR, so these two tests can be used concomitantly and/or interchangeably with the INR. Approximately 50 % of the total variability of the coagulation factor activities and CAT was reflected by the INR, whereas the remaining variability was within the subject (patient). Coagulation factor activities and CAT can therefore potentially be used to provide further information to the risk of bleeding and thromboembolism, since almost 50 % of the variability within the subject is not displayed in the INR value. Yet it remains uncertain if this method can predict complications in individual patients on OAT. Larger clinical trials with a longer follow-up period, preferably using clinical endpoints, are needed in order to draw any firm conclusions regarding the clinical consequences. However, measurement of coagulation factor activities and CAT may improve measurement of coagulation activity in patients prescribed OAT beyond the parameters currently clinical available.

The CoaguChek® S and XS coagulometers used for PSM were found to have an adequate precision. Regarding the accuracy, the INR measurements tended to be lower on the coagulometers, compared with the laboratory. A large proportion of the measurements on the coagulometers deviated more than 15 % from the laboratory measurements. However, only one laboratory was used for comparison and the original WHO method (gold standard) for estimating INR was not used. Furthermore, the inherent limitations of the INR have to be taken into consideration, and the results have to be viewed in this context. The accuracy of the coagulometers seems in this respect acceptable and they can be used in a clinical setting. However, external quality control is essential.

In the observational studies, it was found that PSM was feasible and provides satisfactory treatment quality for various indications and in a wide range of patient age. In a randomised controlled trial, using a documented blinded composite endpoint, PSM was found to provide a treatment quality that was at least as good as that provided by conventional management. Additionally it was found, that training and implementation of PSM lead to a smaller variance in INR measurements, a higher median INR and a higher dose of coumarins compared to that obtained for conventionally managed patients.

Further evidence was provided in a systematic review and meta-analysis, where it was documented, that PSM appears at least as good as and possibly better than conventional management in highly selected patients.

REFERENCES

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:160S-98S.
2. Eitz T, Schenk S, Fritzsche D, et al. International normalized ratio self-management lowers the risk of thromboembolic events after prosthetic heart valve replacement. Ann Thorac Surg 2008; 85:949-54.
3. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003; 349:631-9.
4. Körtke H, Körfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? Ann Thorac Surg 2001; 72:44-8.

5. Lindh JD, Holm L, Dahl ML, Alfredsson L, Rane A. Incidence and predictors of severe bleeding during warfarin treatment. J Thromb Thrombolysis 2008; 25:151-9.
6. Steffensen FH, Kristensen K, Ejlersen E, Dahlerup JF, Sørensen HT. Major haemorrhagic complications during oral anticoagulant therapy in a Danish population-based cohort. J Intern Med 1997; 242:497-503.
7. Butchart EG, Payne N, Li HH, Buchan K, Mandana K, Grunkemeier GL. Better anticoagulation control improves survival after valve replacement. J Thorac Cardiovasc Surg 2002; 123:715-23.
8. Ansell JE, Hughes R. Evolving models of warfarin management: anticoagulation clinics, patient self-monitoring, and patient self-management. Am Heart J 1996; 132:1095-100.
9. Errichetti AM, Holden A, Ansell J. Management of oral anticoagulant therapy. Experience with an anticoagulation clinic. Arch Intern Med 1984; 144:1966-8.
10. Roudaut R. Self-control of long-term oral anticoagulation using a point-of-care device. Arch Cardiovasc Dis 2008; 101:683-4.
11. Poller L, Shiach CR, MacCallum PK, et al. Multicentre randomised study of computerised anticoagulant dosage. European Concerted Action on Anticoagulation. Lancet 1998; 352:1505-9.
12. Holm T. The quality of oral anticoagulant therapy in primary care, in secondary care, and in a shared care programme. Evaluation based on the Laboratory Information System. Ph.D. thesis. Faculty of Health Sciences, Aarhus University, Denmark 2002.
13. Thompson JL, Sundt TM, Sarano ME, Santrach PJ, Schaff HV. In-patient international normalized ratio self-testing instruction after mechanical heart valve implantation. Ann Thorac Surg 2008; 85:2046-50.
14. Sönksen PH, Judd SL, Lowy C. Home monitoring of blood-glucose. Method for improving diabetic control. Lancet 1978; 1:729-32.
15. Tattersall R, Gale E. Patient self-monitoring of blood glucose and refinements of conventional insulin treatment. Am J Med 1981; 70:177-82.
16. Walford S, Gale EA, Allison SP, Tattersall RB. Self-monitoring of blood-glucose. Improvement of diabetic control. Lancet 1978; 1:732-5.
17. Sawicki PT, Mühlhauser I, Didjurgeit U, Baumgartner A, Bender R, Berger M. Intensified antihypertensive therapy is associated with improved survival in type 1 diabetic patients with nephropathy. J Hypertens 1995; 13:933-8.
18. Guevara JP, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. BMJ 2003; 326:1308-9.
19. White RH, McCurdy SA, von Marensdorff H, Woodruff DE, Jr., Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. A randomized, prospective study. Ann Intern Med 1989; 111:730-7.
20. Erdman S, Vidne B, Levy MJ. A self control method for long term anticoagulation therapy. J Cardiovasc Surg (Torino) 1974; 15:454-7.
21. Jacobson AK. Patient Self-Management of Oral Anticoagulant Therapy: An International Update. J Thromb Thrombolysis 1998; 5 Suppl 1:25-8.
22. Brummel KE, Paradis SG, Branda RF, Mann KG. Oral anticoagulation thresholds. Circulation 2001; 104:2311-7.
23. D'Angelo A, Della VP, Crippa L, Fattorini A, Pattarini E, Vigano DS. Relationship between international normalized ratio values, vitamin K-dependent clotting factor levels and in vivo prothrombin activation during the early and steady phases of oral anticoagulant treatment. Haematologica 2002; 87:1074-80.
24. Mann KG. The challenge of regulating anticoagulant drugs: focus on warfarin. Am Heart J 2005; 149:S36-S42.
25. Oake N, Fergusson DA, Forster AJ, van WC. Frequency of adverse events in patients with poor anticoagulation: a meta-analysis. CMAJ 2007; 176:1589-94.
26. Gatt A, van Veen JJ, Bowyer A, et al. Wide variation in thrombin generation in patients with atrial fibrillation and therapeutic International Normalized Ratio is not due to inflammation. Br J Haematol 2008; 142:946-52.
27. Poller L. International Normalized Ratios (INR): the first 20 years. J Thromb Haemost 2004; 2:849-60.
28. Van den Besselaar AM, Barrowcliffe TW, Houbouyan-Réveillard LL, et al. Guidelines on preparation, certification, and use of certified plasmas for ISI calibration and INR determination. J Thromb Haemost 2004; 2:1946-53.
29. Olson JD, Brandt JT, Chandler WL, et al. Laboratory reporting of the international normalized ratio: progress and problems. Arch Pathol Lab Med 2007; 131:1641-7.
30. Van den Besselaar AM. Accuracy, precision, and quality control for point-of-care testing of oral anticoagulation. J Thromb Thrombolysis 2001; 12:35-40.
31. Tripodi A, Chantarangkul V, Mannucci P. Near-patient testing devices to monitor oral anticoagulant therapy. Br J Haematol 2001; 113:847-52.
32. Sarode R, Rawal A, Lee R, Shen YM, Frenkel EP. Poor correlation of supratherapeutic international normalised ratio and vitamin K-dependent procoagulant factor levels during warfarin therapy. Br J Haematol 2006; 132:604-7.
33. Costa IM, Soares PJ, Afonso M, Ratado P, Lanaot JM, Falcao AC. Therapeutic monitoring of warfarin: the appropriate response marker. J Pharm Pharmacol 2000; 52:1405-10.
34. Van Geest-Daalderop JH, Hutten BA, Péquériaux NC, Haas FJ, Levi M, Sturk A. The influence on INRs and coagulation factors of the time span between blood sample collection and intake of phenprocoumon or acenocoumarol: consequences for the assessment of the dose. Thromb Haemost 2007; 98:738-46.
35. Watala C, Golanski J, Kardas P. Multivariate relationships between international normalized ratio and vitamin K-dependent coagulation-derived parameters in normal healthy donors and oral anticoagulant therapy patients. Thromb J 2003; 1:7.
36. Paul B, Oxley A, Brigham K, Cox T, Hamilton PJ. Factor II, VII, IX and X concentrations in patients receiving long term warfarin. J Clin Pathol 1987; 40:94-8.
37. Lind SE, Callas PW, Golden EA, Joyner KA, Jr., Ortel TL. Plasma levels of factors II, VII and X and their relationship to the international normalized ratio during

chronic warfarin therapy. Blood Coagul Fibrinolysis 1997; 8:48-53.
38. Musial J, Brzezinska-Kolarz B, Zolcinski M, Lelakowski J, Szczeklik A. Ex Vivo Thrombin Generation in Patients With Venous Thromboembolic Disease or Atrial Fibrillation on Long-Term Oral Anticoagulation. Clin Appl Thromb Hemost 2010.
39. Shikata E, Ieiri I, Ishiguro S, et al. Association of pharmacokinetic (CYP2C9) and pharmacodynamic (factors II, VII, IX, and X; proteins S and C; and gamma-glutamyl carboxylase) gene variants with warfarin sensitivity. Blood 2004; 103:2630-5.
40. Hemker HC, Béguin S. Phenotyping the clotting system. Thromb Haemost 2000; 84:747-51.
41. Gatt A, van Veen JJ, Woolley AM, Kitchen S, Cooper P, Makris M. Thrombin generation assays are superior to traditional tests in assessing anticoagulation reversal in vitro. Thromb Haemost 2008; 100:350-5.
42. Hemker HC, Al DR, De SE, Béguin S. Thrombin generation, a function test of the haemostatic-thrombotic system. Thromb Haemost 2006; 96:553-61.
43. Gatt A, Riddell A, van Veen JJ, Kitchen S, Tuddenham EG, Makris M. Optimizing warfarin reversal-an ex vivo study. J Thromb Haemost 2009; 7:1123-7.
44. Brocal I, Marco P, Lucas J, Verdu J, Tarin F. Thrombin generation test in patients under anticoagulant therapy with vitamin k antagonists. Thromb Haemost 2009; 101:594-5.
45. Van Veen JJ, Gatt A, Bowyer AE, Cooper PC, Kitchen S, Makris M. Calibrated automated thrombin generation and modified thromboelastometry in haemophilia A. Thromb Res 2009; 123:895-901.
46. Spronk HM, Dielis AW, Panova-Noeva M, et al. Monitoring thrombin generation: is addition of corn trypsin inhibitor needed? Thromb Haemost 2009; 101:1156-62.
47. Dargaud Y, Francillon S, Negrier C. Intraindividual thrombin generation measurement variability in healthy adults over a one year period. Thromb Res 2009; 124:237-8.
48. Stender MT, Larsen TB, Lundbye-Christensen S, Yilmaz MK, Thorlacius-Ussing O. Haemostatis activity in rectal cancer patients exposed to preoperative radiotherapy: a clinical prospective cohort study. Blood Coagul Fibrinolysis 2009; 20:276-82.
49. Sørensen B, Johansen P, Christiansen K, Woelke M, Ingerslev J. Whole blood coagulation thrombelastographic profiles employing minimal tissue factor activation. J Thromb Haemost 2003; 1:551-8.
50. Sørensen B, Johansen P, Nielsen GL, Sørensen JC, Ingerslev J. Reversal of the International Normalized Ratio with recombinant activated factor VII in central nervous system bleeding during warfarin thromboprophylaxis: clinical and biochemical aspects. Blood Coagul Fibrinolysis 2003; 14:469-77.
51. Bruns DE, Huth EJ, Magid E, Young DS. Toward a checklist for reporting of studies of diagnostic accuracy of medical tests. Clin Chem 2000; 46:893-5.
52. Van den Besselar AM. A comparison of INRs determined with a whole blood prothrombin time device and two international reference preparations for thromboplastin. Thromb Haemost 2000; 84:410-2.
53. Kjeldsen J, Lassen JF, Petersen PH, Brandslund I. Biological variation of International Normalized Ratio for prothrombin times, and consequences in monitoring oral anticoagulant therapy: computer simulation of serial measurements with goal-setting for analytical quality. Clin Chem 1997; 43:2175-82.
54. Anderson DR, Harrison L, Hirsh J. Evaluation of a portable prothrombin time monitor for home use by patients who require long-term oral anticoagulant therapy. Arch Intern Med 1993; 153:1441-7.
55. Douketis JD, Lane A, Milne J, Ginsberg JS. 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. Thromb Res 1998; 92:11-7.
56. Poller L, Keown M, Ibrahim SA, et al. Quality assessment of CoaguChek point-of-care prothrombin time monitors: comparison of the European community-approved procedure and conventional external quality assessment. Clin Chem 2006; 52:1843-7.
57. Van den Besselaar AM, Poller L, Tripodi A. Definition of the International Normalized Ratio (INR) and its consequences for the calibration procedure of thromboplastin preparations: a rebuttal. J Thromb Haemost 2004; 2:1490-1.
58. Van Geest-Daalderop JH, Mulder AB, Boonman-de Winter LJ, Hoekstra MM, van den Besselaar AM. Preanalytical variables and off-site blood collection: influences on the results of the prothrombin time/international normalized ratio test and implications for monitoring of oral anticoagulant therapy. Clin Chem 2005; 51:561-8.
59. Leeming DR, Craig S, Stevenson KJ, Taberner DA. The determination of INR in stored whole blood. J Clin Pathol 1998; 51:360-3.
60. Cromheecke ME, Levi M, Colly LP, et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. Lancet 2000; 356:97-102.
61. Christensen TD. Self-management of oral anticoagulant therapy: a review. J Thromb Thrombolysis 2004; 18:127-43.
62. Adcock D, Kressin D, Marlar RA. The effect of time and temperature variables on routine coagulation tests. Blood Coagul Fibrinolysis 1998; 9:463-70.
63. McGlasson DL. A review of variables affecting PTs/INRs. Clin Lab Sci 1999; 12:353-8.
64. Davis KD, Danielson CF, May LS, Han ZQ. Use of different thromboplastin reagents causes greater variability in international normalized ratio results than prolonged room temperature storage of specimens. Arch Pathol Lab Med 1998; 122:972-7.
65. Awad MA, Selim TE, Al-Sabbagh FA. Influence of storage time and temperature on international normalized ratio (INR) levels and plasma activities of vitamin K dependent clotting factors. Hematology 2004; 9:333-7.
66. Rao LV, Okorodudu AO, Petersen JR, Elghetany MT. Stability of prothrombin time and activated partial thromboplastin time tests under different storage conditions. Clin Chim Acta 2000; 300:13-21.
67. Froom P, Abramova D, Bar-El M, Barak M. Reliability of delayed prothrombin time INR determinations in a

central laboratory using off-site blood sampling. Clin Lab Haematol 2001; 23:189-92.
68. Brigden ML, Graydon C, McLeod B, Lesperance M. Prothrombin time determination. The lack of need for a discard tube and 24-hour stability. Am J Clin Pathol 1997; 108:422-6.
69. Kitchen D, Murray E, Kitchen S, et al. External quality assessment for prothrombin time/international normalised ratio using point-of-care devices: split-sample or conventional external quality assessment using control samples? Scand J Clin Lab Invest 2007; 67:673-5.
70. Baglin T, Luddington R. Reliability of delayed INR determination: implications for decentralized anticoagulant care with off-site blood sampling. Br J Haematol 1997; 96:431-4.
71. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. J Biopharm Stat 2007; 17:571-82.
72. Lassen JF, Brandslund I, Antonsen S. International normalized ratio for prothrombin times in patients taking oral anticoagulants: critical difference and probability of significant change in consecutive measurements. Clin Chem 1995; 41:444-7.
73. Lassen JF, Kjeldsen J, Antonsen S, Hyltoft PP, Brandslund I. Interpretation of serial measurements of international normalized ratio for prothrombin times in monitoring oral anticoagulant therapy. Clin Chem 1995; 41:1171-6.
74. WHO. WHO Expert Committee on Biological Standardization Guidelines for Thrombo-plastins and Plasma Used to Control Oral Anticoagulant Therapy. WHO Technical Report Series no. 889. Geneva: WHO, 1999:64-93.
75. Favaloro EJ, Adcock DM. Standardization of the INR: how good is your laboratory's INR and can it be improved? Semin Thromb Hemost 2008; 34:593-603.
76. Kitchen S, Kitchen DP, Jennings I, Woods TA, Walker ID, Preston FE. Point-of-care International Normalised Ratios: UK NEQAS experience demonstrates necessity for proficiency testing of three different monitors. Thromb Haemost 2006; 96:590-6.
77. Hirsh J, Poller L. The international normalized ratio. A guide to understanding and correcting its problems. Arch Intern Med 1994; 154:282-8.
78. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001; 119:8S-21S.
79. Van den Besselaar AM, Witteveen E, van der Meer FJ. Influence of haematocrit on international normalised ratio (INR) differences between a whole blood point-of-care coagulation monitor and reference prothrombin time in plasma. Thromb Haemost 2008; 100:1181-4.
80. Adcock DM, Johnston M. Evaluation of frozen plasma calibrants for enhanced standardization of the international normalized ratio (INR): a multi-center study. Thromb Haemost 2002; 87:74-9.
81. 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.
82. Fairweather RB, Ansell J, van den Besselaar AM, et al. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of oral anticoagulant therapy. Arch Pathol Lab Med 1998; 122:768-81.
83. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999; 8:135-60.
84. Lucas FV, Duncan A, Jay R, et al. A novel whole blood capillary technic for measuring the prothrombin time. Am J Clin Pathol 1987; 88:442-6.
85. Braun S, Spannagl M, Völler H. Patient self-testing and self-management of oral anticoagulation. Anal Bioanal Chem 2009; 393:1463-71.
86. Ansell J, Jacobson A, Levy J, Völler H, Hasenkam JM. Guidelines for implementation of patient self-testing and patient self-management of oral anticoagulation. International consensus guidelines prepared by International Self-Monitoring Association for Oral Anticoagulation. Int J Cardiol 2005; 99:37-45.
87. Spinler SA, Nutescu EA, Smythe MA, Wittkowsky AK. Anticoagulation monitoring part 1: warfarin and parenteral direct thrombin inhibitors. Ann Pharmacother 2005; 39:1049-55.
88. Gosselin R, Owings JT, White RH, et al. A comparison of point-of-care instruments designed for monitoring oral anticoagulation with standard laboratory methods. Thromb Haemost 2000; 83:698-703.
89. Loebstein R, Kurnik D, Lubetsky A, Ezra D, Halkin H. Potential dosing errors using portable prothrombin time monitoring devices. Blood Coagul Fibrinolysis 2003; 14:479-83.
90. Ansell JE, Patel N, Ostrovsky D, Nozzolillo E, Peterson AM, Fish L. Long-term patient self-management of oral anticoagulation. Arch Intern Med 1995; 155:2185-9.
91. Le DT, Weibert RT, Sevilla BK, Donnelly KJ, Rapaport SI. The international normalized ratio (INR) for monitoring warfarin therapy: reliability and relation to other monitoring methods. Ann Intern Med 1994; 120:552-8.
92. Ansell J, Holden A, Knapic N. Patient self-management of oral anticoagulation guided by capillary (fingerstick) whole blood prothrombin times. Arch Intern Med 1989; 149:2509-11.
93. Kaatz SS, White RH, Hill J, Mascha E, Humphries JE, Becker DM. Accuracy of laboratory and portable monitor international normalized ratio determinations. Comparison with a criterion standard. Arch Intern Med 1995; 155:1861-7.
94. White RH, Becker DM, Gunther-Maher MG. Outpatient use of a portable international normalized ratio/prothrombin time monitor. South Med J 1994; 87:206-10.
95. Jennings I, Luddington RJ, Baglin T. Evaluation of the Ciba Corning Biotrack 512 coagulation monitor for the control of oral anticoagulation. J Clin Pathol 1991; 44:950-3.
96. Rigelsky JM, Choe HM, Curtis DM, Brosnan MJ, Mitrovich S, Streetman DS. Accuracy of the avosure PT pro system compared with a hospital laboratory standard. Ann Pharmacother 2002; 36:380-5.
97. Prothrombin measurement using a patient self-testing system. Oral Anticoagulation Monitoring Study Group. Am J Clin Pathol 2001; 115:280-7.

98. Point-of-care prothrombin time measurement for professional and patient self-testing use. A multicenter clinical experience. Oral Anticoagulation Monitoring Study Group. Am J Clin Pathol 2001; 115:288-96.
99. Kitchen S, Preston FE. Monitoring oral anticoagulant treatment with the TAS near-patient test system: comparison with conventional thromboplastins. J Clin Pathol 1997; 50:951-6.
100. Cachia PG, McGregor E, Adlakha S, Davey P, Goudie BM. Accuracy and precision of the TAS analyser for near-patient INR testing by non-pathology staff in the community. J Clin Pathol 1998; 51:68-72.
101. Karon BS, McBane RD, Chaudhry R, Beyer LK, Santrach PJ. Accuracy of capillary whole blood international normalized ratio on the CoaguChek S, CoaguChek XS, and i-STAT 1 point-of-care analyzers. Am J Clin Pathol 2008; 130:88-92.
102. Hasenkam JM, Kimose HH, Knudsen L, et al. Self management of oral anticoagulant therapy after heart valve replacement. Eur J Cardiothorac Surg 1997; 11:935-42.
103. Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. Working Group for the Study of Patient Self-Management of Oral Anticoagulation. JAMA 1999; 281:145-50.
104. Watzke HH, Forberg E, Svolba G, Jimenez-Boj E, Krinninger B. A prospective controlled trial comparing weekly self-testing and self-dosing with the standard management of patients on stable oral anticoagulation. Thromb Haemost 2000; 83:661-5.
105. Braun S, Watzke H, Hasenkam JM, et al. Performance evaluation of the new CoaguChek XS system compared with the established CoaguChek system by patients experienced in INR-self management. Thromb Haemost 2007; 97:310-4.
106. Phillips EM, Buchan DA, Newman N, Rajan A, Zia S. Low-molecular-weight heparin may alter point-of-care assay for international normalized ratio. Pharmacotherapy 2005; 25:1341-7.
107. Van Cott EM. Point-of-care testing in coagulation. Clin Lab Med 2009; 29:543-53.
108. Perry SL, Samsa GP, Ortel TL. Point-of-care testing of the international normalized ratio in patients with antiphospholipid antibodies. Thromb Haemost 2005; 94:1196-202.
109. Biasiolo A, Rampazzo P, Furnari O, Filippi B, Pengo V. Comparison between routine laboratory prothrombin time measurements and fingerstick determinations using a near-patient testing device (Pro-Time) Thromb Res 2000; 97:495-8.
110. Chapman DC, Stephens MA, Hamann GL, Bailey LE, Dorko CS. Accuracy, clinical correlation, and patient acceptance of two handheld prothrombin time monitoring devices in the ambulatory setting. Ann Pharmacother 1999; 33:775-80.
111. Gardiner C, Longair I, Hills J, Cohen H, Mackie IJ, Machin SJ. Performance evaluation of a new small-volume coagulation monitor: the SmartCheck INR system. Am J Clin Pathol 2008; 129:500-4.
112. McBane RD, Felty CL, Hartgers ML, Chaudhry R, Beyer LK, Santrach PJ. Importance of device evaluation for point-of-care prothrombin time international normalized ratio testing programs. Mayo Clin Proc 2005; 80:181-6.
113. Murray ET, Fitzmaurice DA, Allan TF, Hobbs FD. A primary care evaluation of three near patient coagulometers. J Clin Pathol 1999; 52:842-5.
114. Taborski U, Braun SL, Völler H. Analytical performance of the new coagulation monitoring system INRatio for the determination of INR compared with the coagulation monitor Coaguchek S and an established laboratory method. J Thromb Thrombolysis 2004; 18:103-7.
115. Morsdorf S, Erdlenbruch W, Taborski U, et al. Training of patients for self-management of oral anticoagulant therapy: standards, patient suitability, and clinical aspects. Semin Thromb Hemost 1999; 25:109-15.
116. Attermann J, Kynde K, Hasenkam JM. Precision of patients' measurements of the international normalized ratio (INR) using a patient operated whole blood home coagulometer. Thromb Res 1998; 92:287-91.
117. Kapiotis S, Quehenberger P, Speiser W. Evaluation of the new method Coaguchek for the determination of prothrombin time from capillary blood: comparison with Thrombotest on KC-1. Thromb Res 1995; 77:563-7.
118. Van den Besselaar AM, Breddin K, Lutze G, et al. Multicenter evaluation of a new capillary blood prothrombin time monitoring system. Blood Coagul Fibrinolysis 1995; 6:726-32.
119. Cosmi B, Palareti G, Moia M, et al. Accuracy of a portable prothrombin time monitor (Coagucheck) in patients on chronic oral anticoagulant therapy: a prospective multicenter study. Thromb Res 2000; 100:279-86.
120. Marzinotto V, Monagle P, Chan A, et al. Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and the home setting. Pediatr Cardiol 2000; 21:347-52.
121. Christensen TD, Attermann J, Hjortdal VE, Maegaard M, Hasenkam JM. Self-management of oral anticoagulation in children with congenital heart disease. Cardiol Young 2001; 11:269-76.
122. Christensen TD, Attermann J, Pilegaard HK, Andersen NT, Maegaard M, Hasenkam JM. Self-management of oral anticoagulant therapy for mechanical heart valve patients. Scand Cardiovasc J 2001; 35:107-13.
123. Hasenkam JM, Knudsen L, Kimose HH, et al. Practicability of patient self-testing of oral anticoagulant therapy by the international normalized ratio (INR) using a portable whole blood monitor. A pilot investigation. Thromb Res 1997; 85:77-82.
124. Bussey HI, Chiquette E, Bianco TM, et al. A statistical and clinical evaluation of fingerstick and routine laboratory prothrombin time measurements. Pharmacotherapy 1997; 17:861-6.
125. Finck KM, Doetkott C, Miller DR. Clinical impact of interlaboratory variation in international normalized ratio determinations. Am J Health Syst Pharm 2001; 58:684-8.
126. Van den Besselaar AM, Meeuwisse-Braun J, Schaefer-van Mansfeld H, van Rijn C, Witteveen E. A comparison between capillary and venous blood international normalized ratio determinations in a portable

prothrombin time device. Blood Coagul Fibrinolysis 2000; 11:559-62.
127. Vacas M, Fernandez MA, Martinez-Brotons F, et al. Comparative study of a portable prothrombin time monitor employing three different systems in oral anticoagulant units. Haemostasis 2001; 31:18-25.
128. Poller L, Keown M, Chauhan N, et al. European Concerted Action on Anticoagulation (ECAA): multicentre international sensitivity index calibration of two types of point-of-care prothrombin time monitor systems. Br J Haematol 2002; 116:844-50.
129. Vacas M, Lafuente PJ, Cuesta S, Iriarte JA. Comparative study of a portable monitor for prothrombin time determination, Coaguchek, with three systems for control of oral anticoagulant treatment. Haemostasis 1998; 28:321-8.
130. Eldor A, Schwartz J. Self-management of oral anticoagulants with a whole blood prothrombin-time monitor in elderly patients with atrial fibrillation. Pathophysiol Haemost Thromb 2002; 32:99-106.
131. Taborski U, Plesch W. Equivalence of capillary versus venous INR results and patient- versus professional-determined INR values using the CoaguChek S system. Clin Appl Thromb Hemost 2002; 8:187-9.
132. Plesch W, Klimpel P. Performance evaluation of the CoaguChek S system. Haematologica 2002; 87:557-9.
133. Havrda DE, Hawk TL, Marvin CM. Accuracy and precision of the CoaguChek S versus laboratory INRs in a clinic. Ann Pharmacother 2002; 36:769-75.
134. Poller L, Keown M, Chauhan N, et al. Reliability of international normalised ratios from two point of care test systems: comparison with conventional methods. BMJ 2003; 327:30-2.
135. Tripodi A, Bressi C, Carpenedo M, Chantarangkul V, Clerici M, Mannucci PM. Quality assurance program for whole blood prothrombin time-international normalized ratio point-of-care monitors used for patient self-testing to control oral anticoagulation. Thromb Res 2004; 113:35-40.
136. Shiach CR, Campbell B, Poller L, Keown M, Chauhan N. Reliability of point-of-care prothrombin time testing in a community clinic: a randomized crossover comparison with hospital laboratory testing. Br J Haematol 2002; 119:370-5.
137. Jackson SL, Bereznicki LR, Peterson GM, et al. Accuracy, reproducibility and clinical utility of the CoaguChek S portable international normalized ratio monitor in an outpatient anticoagulation clinic. Clin Lab Haematol 2004; 26:49-55.
138. Khoschnewis S, Hannes FM, Tschopp M, Wuillemin WA. INR comparison between the CoaguChek® Pro PT^N and a standard laboratory method. Thromb Res 2004; 113:327-32.
139. Vacas M, Lafuente PJ, Unanue I, Iriarte JA. Comparative study of two portable systems for oral anticoagulant monitoring. Hematol J 2004; 5:35-8.
140. Lizotte A, Quessy I, Vanier MC, et al. Reliability, validity and ease of use of a portable point-of-care coagulation device in a pharmacist-managed anticoagulation clinic. J Thromb Thrombolysis 2002; 14:247-54.
141. Vacas M, Lafuente PJ, Unanue I, Santos M, Iriarte JA. Therapeutic concordance of two portable monitors and two routine automatic oral anticoagulant monitoring systems using as reference the manual prothrombin time technique. Hematol J 2003; 4:214-7.
142. Sirithunyanont C, Bhuripanyo K, Kangkagate C, Winyarat W, Srichaya P, Wangtip K. Accuracy of international normalized ratio determined by portable venous-blood coagulation monitor versus a central laboratory. J Med Assoc Thai 2003; 86 Suppl 1:S67-S75.
143. Jackson SL, Bereznicki LR, Peterson GM, et al. Accuracy and clinical usefulness of the near-patient testing CoaguChek S international normalised ratio monitor in rural medical practice. Aust J Rural Health 2004; 12:137-42.
144. Gardiner C, Williams K, Mackie IJ, Machin SJ, Cohen H. Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring. Br J Haematol 2005; 128:242-7.
145. Jackson SL, Peterson GM, Bereznicki LR, Misan GM, Jupe DM, Vial JH. Improving the outcomes of anticoagulation in rural Australia: an evaluation of pharmacist-assisted monitoring of warfarin therapy. J Clin Pharm Ther 2005; 30:345-53.
146. Hentrich DP, Fritschi J, Müller PR, Wuillemin WA. INR comparison between the CoaguChek® S and a standard laboratory method among patients with self-management of oral anticoagulation. Thromb Res 2007; 119:489-95.
147. Berkovsky A, Sergeeva EV, Suvorov AV, et al. A modified method of prothrombin time/International Normalised Ratio determination in capillary blood and monitoring oral anticoagulant therapy. Clin Chem Lab Med 2006; 44:1214-7.
148. Bereznicki LR, Jackson SL, Peterson GM, Jeffrey EC, Marsden KA, Jupe DM. Accuracy and clinical utility of the CoaguChek XS portable international normalised ratio monitor in a pilot study of warfarin home-monitoring. J Clin Pathol 2007; 60:311-4.
149. Nam MH, Roh KH, Pak HN, et al. Evaluation of the Roche CoaguChek XS handheld coagulation analyzer in a cardiac outpatient clinic. Ann Clin Lab Sci 2008; 38:37-40.
150. Bauman ME, Black KL, Massicotte MP, et al. Accuracy of the CoaguChek XS for point-of-care international normalized ratio (INR) measurement in children requiring warfarin. Thromb Haemost 2008; 99:1097-103.
151. Hemkens LG, Hilden KM, Hartschen S, et al. A randomized trial comparing INR monitoring devices in patients with anticoagulation self-management: evaluation of a novel error-grid approach. J Thromb Thrombolysis 2008; 26:22-30.
152. Sobieraj-Teague M, Daniel D, Farrelly B, Coghlan D, Gallus A. Accuracy and clinical usefulness of the CoaguChek S and XS Point of Care devices when starting warfarin in a hospital outreach setting. Thromb Res 2009; 123:909-13.
153. Plesch W, Wolf T, Breitenbeck N, et al. Results of the performance verification of the CoaguChek XS system. Thromb Res 2008.
154. Kong MC, Lim TG, Ng HJ, Chan YH, Lee LH. Feasibility, cost-effectiveness and patients' acceptance of point-of-care INR testing in a hospital-based anticoagulation clinic. Ann Hematol 2008; 87:905-10.

155. Plesch W, Van den Besselaar AM. Validation of the international normalized ratio (INR) in a new point-of-care system designed for home monitoring of oral anticoagulation therapy. Int J Lab Hematol 2009; 31:20-5.
156. Williams VK, Griffiths AB. Acceptability of CoaguChek S and CoaguChek XS generated international normalised ratios against a laboratory standard in a paediatric setting. Pathology 2007; 39:575-9.
157. Torreiro EG, Fernandez EG, Rodriguez RM, Lopez CV, Nunez JB. Comparative study of accuracy and clinical agreement of the CoaguChek XS portable device versus standard laboratory practice in unexperienced patients. Thromb Haemost 2009; 101:969-74.
158. Attermann J. Monitoring oral anticoagulant therapy; measuring coagulant activity. Ph.D. thesis. Faculty of Health Sciences, Aarhus University, Denmark 2000.
159. Guide-lines for near patient testing: haematology. Near Patient Testing Working Party. General Haematology Task Force of BCSH. Thrombosis and Haemostasis Task Force of BCSH. Clin Lab Haematol 1995; 17:301-10.
160. Ng VL. Anticoagulation monitoring. Clin Lab Med 2009; 29:283-304.
161. Poller L. Precision and accuracy of CoaguChek S and XS monitors: The need for external quality assessment. Thromb Haemost 2009; 101:419-21.
162. Fitzmaurice DA, Machin SJ. Recommendations for patients undertaking self management of oral anticoagulation. BMJ 2001; 323:985-9.
163. Murray ET, Fitzmaurice DA, McCahon D. Point of care testing for INR monitoring: where are we now? Br J Haematol 2004; 127:373-8.
164. Murray ET, Jennings I, Kitchen D, Kitchen S, Fitzmaurice DA. Quality assurance for oral anticoagulation self management: a cluster randomized trial. J Thromb Haemost 2008; 6:464-9.
165. Sidhu P, O'Kane HO. Self-managed anticoagulation: results from a two-year prospective randomized trial with heart valve patients. Ann Thorac Surg 2001; 72:1523-7.
166. Bhavnani M, Shiach CR. Patient self-management of oral anticoagulation. Clin Lab Haematol 2002; 24:253-7.
167. Murray ET, Kitchen DP, Kitchen S, et al. Patient self-management of oral anticoagulation and external quality assessment procedures. Br J Haematol 2003; 122:825-8.
168. Sølvik UO, Stavelin A, Christensen NG, Sandberg S. External quality assessment of prothrombin time: the split-sample model compared with external quality assessment with commercial control material. Scand J Clin Lab Invest 2006; 66:337-49.
169. Meijer P, Kluft C, Poller L, et al. A national field study of quality assessment of CoaguChek point-of-care testing prothrombin time monitors. Am J Clin Pathol 2006; 126:756-61.
170. Jespersen J, Poller L, van den Besselaar AM, et al. External quality assessment (EQA) for CoaguChek monitors. Thromb Haemost 2010; 103:936-41.
171. Barcellona D, Fenu L, Cornacchini S, Marongiu F. Point-of-care (POCT) prothrombin time monitors: is a periodical control of their performance useful? Thromb Res 2009; 123:775-9.
172. Poller L, Keown M, Chauhan N, et al. European concerted action on anticoagulation. Use of plasma samples to derive international sensitivity index for whole-blood prothrombin time monitors. Clin Chem 2002; 48:255-60.
173. Poller L, Keown M, Chauhan N, et al. European concerted action on anticoagulation--comparison of fresh plasma and whole blood multicentre ISI calibrations of CoaguChek Mini and TAS PT-NC whole blood prothrombin time point-of-care monitors. Thromb Haemost 2002; 87:859-66.
174. Poller L, Keown M, Chauhan N, et al. Minimum numbers of fresh whole blood and plasma samples from patients and healthy subjects for ISI calibration of CoaguChek and RapidPointCoag monitors. Am J Clin Pathol 2002; 117:892-9.
175. Poller L, Keown M, Chauhan N, et al. European concerted action on anticoagulation. Minimum numbers of lyophilized plasma samples for ISI calibration of CoaguChek and TAS point-of-care whole blood prothrombin time monitors. Am J Clin Pathol 2003; 119:232-40.
176. Leichsenring I, Plesch W, Unkrig V, et al. Multicentre ISI assignment and calibration of the INR measuring range of a new point-of-care system designed for home monitoring of oral anticoagulation therapy. Thromb Haemost 2007; 97:856-61.
177. Ansell JE. Anticoagulation Management as a Risk Factor for Adverse Events: Grounds for Improvement. J Thromb Thrombolysis 1998; 5 Suppl 1:13-8.
178. Van WC, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: a systematic review and metaregression. Chest 2006; 129:1155-66.
179. Cortelazzo S, Finazzi G, Viero P, et al. Thrombotic and hemorrhagic complications in patients with mechanical heart valve prosthesis attending an anticoagulation clinic. Thromb Haemost 1993; 69:316-20.
180. Nichol MB, Knight TK, Dow T, et al. Quality of anticoagulation monitoring in nonvalvular atrial fibrillation patients: comparison of anticoagulation clinic versus usual care. Ann Pharmacother 2008; 42:62-70.
181. Fitzmaurice DA, Murray ET, Hobbs FD. Self-management of oral anticoagulation. Lancet 2000; 356:1437.
182. Prisco D, Antonucci E, Grifoni E, et al. Different models for oral anticoagulation management may be applied provided that minimal assistance criteria are fulfilled: an Italian experience. Semin Thromb Hemost 2009; 35:568-73.
183. Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. Ann Intern Med 2000; 133:687-95.
184. Fitzmaurice DA, Hobbs FD, Murray ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. Arch Intern Med 2000; 160:2343-8.
185. Dauphin C, Legault B, Jaffeux P, et al. Comparison of INR stability between self-monitoring and standard laboratory method: preliminary results of a prospective study in 67 mechanical heart valve patients. Arch Cardiovasc Dis 2008; 101:753-61.

186. Ryan F, Byrne S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. J Thromb Haemost 2009; 7:1284-90.
187. Holm T, Lassen JF, Husted SE, Christensen P, Heickendorff L. A randomized controlled trial of shared care versus routine care for patients receiving oral anticoagulant therapy. J Intern Med 2002; 252:322-31.
188. Poller L, Keown M, Ibrahim S, et al. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. J Thromb Haemost 2008; 6:935-43.
189. Poller L, Keown M, Ibrahim S, et al. A multicentre randomised clinical endpoint study of PARMA 5 computer-assisted oral anticoagulant dosage. Br J Haematol 2008; 143:274-83.
190. Wilson SJ, Wells PS, Kovacs MJ, et al. Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: a randomized controlled trial. CMAJ 2003; 169:293-8.
191. Claes N, Buntinx F, Vijgen J, et al. The Belgian Improvement Study on Oral Anticoagulation Therapy: a randomized clinical trial. Eur Heart J 2005; 26:2159-65.
192. Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. Br J Haematol 2004; 126:557-64.
193. Heneghan C, Perera R, Ward AA, Fitzmaurice D, Meats E, Glasziou P. Assessing differential attrition in clinical trials: self-monitoring of oral anticoagulation and type II diabetes. BMC Med Res Methodol 2007; 7:18.
194. Stigendal L, Andre U. Workshop: Patient Self-Management: Update of Ongoing Studies in Sweden. J Thromb Thrombolysis 1998; 5 Suppl 1:63-4.
195. Taborski U, Müller-Berghaus G. State-of-the-art patient self-management for control of oral anticoagulation. Semin Thromb Hemost 1999; 25:43-7.
196. Soliman Hamad MA, van EE, van AT, van Straten AH. Self-management program improves anticoagulation control and quality of life: a prospective randomized study. Eur J Cardiothorac Surg 2009; 35:265-9.
197. Murray E, Fitzmaurice D, McCahon D, Fuller C, Sandhur H. Training for patients in a randomised controlled trial of self management of warfarin treatment. BMJ 2004; 328:437-8.
198. Fitzmaurice DA, Murray ET, McCahon D, et al. Self management of oral anticoagulation: randomised trial. BMJ 2005; 331:1057.
199. Gardiner C, Longair I, Pescott MA, et al. Self-monitoring of oral anticoagulation: does it work outside trial conditions? J Clin Pathol 2009; 62:168-71.
200. Garcia-Alamino JM, Ward AM, Alonso-Coello P, et al. Self-monitoring and self-management of oral anticoagulation. Cochrane Database Syst Rev 2010, Issue 4. Art. No.: CD003839. DOI:10.1002/14651858.CD003839.pub2.
201. Perera R, Heneghan C, Fitzmaurice D, et al. Individual patient meta-analysis of self-monitoring of an oral anticoagulation protocol. J Heart Valve Dis 2008; 17:233-8.
202. Palareti G, Manotti C, DAngelo A, et al. Thrombotic events during oral anticoagulant treatment: results of the inception-cohort, prospective, collaborative ISCOAT study: ISCOAT study group (Italian Study on Complications of Oral Anticoagulant Therapy). Thromb Haemost 1997; 78:1438-43.
203. Fihn SD, McDonell M, Martin D, et al. Risk factors for complications of chronic anticoagulation. A multicenter study. Warfarin Optimized Outpatient Follow-up Study Group. Ann Intern Med 1993; 118:511-20.
204. Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. Arch Intern Med 2005; 165:1527-32.
205. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med 1993; 95:315-28.
206. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet 1996; 348:423-8.
207. Penning-van Beest FJ, van Meegen E, Rosendaal FR, Stricker BH. Characteristics of anticoagulant therapy and comorbidity related to overanticoagulation. Thromb Haemost 2001; 86:569-74.
208. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. Chest 2001; 119:108S-21S.
209. Van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briët E. Assessment of a bleeding risk index in two cohorts of patients treated with oral anticoagulants. Thromb Haemost 1996; 76:12-6.
210. Palareti G, Cosmi B. Bleeding with anticoagulation therapy - who is at risk, and how best to identify such patients. Thromb Haemost 2009; 102:268-78.
211. Ansell JE. Oral anticoagulant therapy-50 years later. Arch Intern Med 1993; 153:586-96.
212. Rombouts EK, Rosendaal FR, van der Meer FJ. Subtherapeutic oral anticoagulant therapy: Frequency and risk factors. Thromb Haemost 2009; 101:552-6.
213. Landefeld CS, Rosenblatt MW, Goldman L. Bleeding in outpatients treated with warfarin: relation to the prothrombin time and important remediable lesions. Am J Med 1989; 87:153-9.
214. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briët E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995; 333:11-7.
215. Taube J, Halsall D, Baglin T. Influence of cytochrome P-450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over-anticoagulation in patients on long-term treatment. Blood 2000; 96:1816-9.
216. Kamali F, Khan TI, King BP, et al. Contribution of age, body size, and CYP2C9 genotype to anticoagulant response to warfarin. Clin Pharmacol Ther 2004; 75:204-12.
217. Takahashi H, Wilkinson GR, Padrini R, Echizen H. CYP2C9 and oral anticoagulation therapy with acenocoumarol and warfarin: similarities yet differences. Clin Pharmacol Ther 2004; 75:376-80.
218. Schalekamp T, Geest-Daalderop JH, Vries-Goldschmeding H, Conemans J, Bernsen MM, de Boer A. Acenocoumarol stabilization is delayed in CYP2C93 carriers. Clin Pharmacol Ther 2004; 75:394-402.

219. Hummers-Pradier E, Hess S, Adham IM, Papke T, Pieske B, Kochen MM. Determination of bleeding risk using genetic markers in patients taking phenprocoumon. Eur J Clin Pharmacol 2003; 59:213-9.
220. Higashi MK, Veenstra DL, Kondo LM, et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. JAMA 2002; 287:1690-8.
221. Lindh JD, Holm L, Andersson ML, Rane A. Influence of CYP2C9 genotype on warfarin dose requirements-a systematic review and meta-analysis. Eur J Clin Pharmacol 2009; 65:365-75.
222. Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005; 7:97-104.
223. Tabrizi AR, Zehnbauer BA, Borecki IB, McGrath SD, Buchman TG, Freeman BD. The frequency and effects of cytochrome P450 (CYP) 2C9 polymorphisms in patients receiving warfarin. J Am Coll Surg 2002; 194:267-73.
224. Klein TE, Altman RB, Eriksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009; 360:753-64.
225. Kulkarni UP, Swar BD, Karnad DR, et al. A pilot study of the association of pharmacokinetic and pharmacodynamic parameters of warfarin with the dose in patients on long-term anticoagulation. Br J Clin Pharmacol 2008; 65:787-90.
226. Harrington DJ, Gorska R, Wheeler R, et al. Pharmacodynamic resistance to warfarin is associated with nucleotide substitutions in VKORC1. J Thromb Haemost 2008; 6:1663-70.
227. Yang L, Ge W, Yu F, Zhu H. Impact of VKORC1 gene polymorphism on interindividual and interethnic warfarin dosage requirement - A systematic review and meta analysis. Thromb Res 2009; 125:e159-e166.
228. Kurnik D, Loebstein R, Halkin H, Gak E, Almog S. 10 years of oral anticoagulant pharmacogenomics: what difference will it make? A critical appraisal. Pharmacogenomics 2009; 10:1955-65.
229. Gadisseur AP, van der Meer FJ, Adriaansen HJ, Fihn SD, Rosendaal FR. Therapeutic quality control of oral anticoagulant therapy comparing the short-acting acenocoumarol and the long-acting phenprocoumon. Br J Haematol 2002; 117:940-6.
230. Fihn SD, Gadisseur AA, Pasterkamp E, et al. Comparison of control and stability of oral anticoagulant therapy using acenocoumarol versus phenprocoumon. Thromb Haemost 2003; 90:260-6.
231. Jensen CF, Christensen TD, Maegaard M, Hasenkam JM. Quality of oral anticoagulant therapy in patients who perform self management: warfarin versus phenprocoumon. J Thromb Thrombolysis 2009; 28:276-81.
232. Pattacini C, Manotti C, Pini M, Quintavalla R, Dettori AG. A comparative study on the quality of oral anticoagulant therapy (warfarin versus acenocoumarol). Thromb Haemost 1994; 71:188-91.
233. Barcellona D, Vannini ML, Fenu L, Balestrieri C, Marongiu F. Warfarin or acenocoumarol: which is better in the management of oral anticoagulants? Thromb Haemost 1998; 80:899-902.
234. Gadisseur AP, Breukink-Engbers WG, van der Meer FJ, van den Besselaar AM, Sturk A, Rosendaal FR. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands: a randomized clinical trial. Arch Intern Med 2003; 163:2639-46.
235. Claes N, Moeremans K, Frank B, et al. Estimating the Cost-Effectiveness of Quality-Improving Interventions in Oral Anticoagulation Management within General Practice. Value Health 2006; 9:369-76.
236. Cosmi B, Palareti G, Carpanedo M, et al. Assessment of patient capability to self-adjust oral anticoagulant dose: a multicenter study on home use of portable prothrombin time monitor (COAGUCHECK). Haematologica 2000; 85:826-31.
237. Körtke H, Minami K, Bairaktaris A, Wagner O, Körfer R. INR self-management following mechanical heart valve replacement. J Thromb Thrombolysis 2000; 9 Suppl 1:S41-S45.
238. Piso B, Jimenz-Boj E, Krinninger B, Watzke H. The quality of oral anticoagulation before, during and after a period of patient self-management. Thromb Res 2002; 106:101-4.
239. Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. Arch Intern Med 1997; 157:545-52.
240. Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FD. A randomised controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. J Clin Pathol 2002; 55:845-9.
241. Fitzmaurice DA, Gardiner C, Kitchen S, Mackie I, Murray ET, Machin SJ. An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation. Br J Haematol 2005; 131:156-65.
242. Wofford JL, Wells MD, Singh S. Best strategies for patient education regarding anticoagulation with warfarin: a systematic review. BMC Health Serv Res 2008; 8:40.
243. Acar J, Iung B, Boissel JP, et al. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation 1996; 94:2107-12.
244. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Lancet 1994; 343:499-503.
245. Menéndez-Jándula B, Souto JC, Oliver A, et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. Ann Intern Med 2005; 142:1-10.
246. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994; 89:635-41.
247. Ansell J, Hirsh J, Dalen J, et al. Managing oral anticoagulant therapy. Chest 2001; 119:22S-38S.
248. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3:692-4.

249. Samsa GP, Matchar DB. Relationship between test frequency and outcomes of anticoagulation: a literature review and commentary with implications for the design of randomized trials of patient self-management. J Thromb Thrombolysis 2000; 9:283-92.
250. Levi M, Hovingh GK, Cannegieter SC, Vermeulen M, Büller HR, Rosendaal FR. Bleeding in patients receiving vitamin K antagonists who would have been excluded from trials on which the indication for anticoagulation was based. Blood 2008; 111:4471-6.
251. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. The European Atrial Fibrillation Trial Study Group. N Engl J Med 1995; 333:5-10.
252. Van LY, Rosendaal FR, Cannegieter SC. Prediction of hemorrhagic and thrombotic events in patients with mechanical heart valve prostheses treated with oral anticoagulants. J Thromb Haemost 2008; 6:451-6.
253. Poli D, Antonucci E, Gensini GF, Abbate R, Prisco D. Asymptomatic excessive coumarin anticoagulation is a risk factor for thrombotic and bleeding complications of oral anticoagulant therapy. J Thromb Haemost 2003; 1:1840-1.
254. White HD, Gruber M, Feyzi J, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007; 167:239-45.
255. Holm T, Deutch S, Lassen JF, Jastrup B, Husted SE, Heickendorff L. Prospective evaluation of the quality of oral anticoagulation management in an outpatient clinic and in general practices. Thromb Res 2002; 105:103-8.
256. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69:236-9.
257. Hutten BA, Prins MH, Redekop WK, Tijssen JG, Heisterkamp SH, Büller HR. Comparison of three methods to assess therapeutic quality control of treatment with vitamin K antagonists. Thromb Haemost 1999; 82:1260-3.
258. Azar AJ, Deckers JW, Rosendaal FR, et al. Assessment of therapeutic quality control in a long-term anticoagulant trial in post-myocardial infarction patients. Thromb Haemost 1994; 72:347-51.
259. Horstkotte D, Piper C, Schulte HD, Schultheiss HP. Improvement of Prognosis by Home Prothrombin Estimation in Patients With Life-Long Anticoagulant Therapy (abstr). Eur Heart J 1996;17 (suppl):230.
260. Horstkotte D, Piper C, Wiemer M. Optimal Frequency of Patient Monitoring and Intensity of Oral Anticoagulation Therapy in Valvular Heart Disease. J Thromb Thrombolysis 1998; 5 Suppl 1:19-24.
261. Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation. A systematic review. Circ Cardiovasc Qual Outcomes 2008; 1:84-91.
262. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992; 305:160-4.
263. Wenzel T, Morsdorf S, Sibitz I, et al. Dimensions of quality of life and self-monitoring therapy with oral anticoagulants--still research or everyday practice? Semin Thromb Hemost 1999; 25:117-21.
264. Massicotte P, Marzinotto V, Vegh P, Adams M, Andrew M. Home monitoring of warfarin therapy in children with a whole blood prothrombin time monitor. J Pediatr 1995; 127:389-94.
265. Günther T, Mazzitelli D, Schreiber C, et al. Mitral-valve replacement in children under 6 years of age. Eur J Cardiothorac Surg 2000; 17:426-30.
266. Nowatzke WL, Landt M, Smith C, Wilhite T, Canter C, Luchtman-Jones L. Whole blood international normalization ratio measurements in children using near-patient monitors. J Pediatr Hematol Oncol 2003; 25:33-7.
267. Mähönen S, Riikonen P, Vaatainen RL, Tikanoja T. Oral anticoagulant treatment in children based on monitoring at home. Acta Paediatr 2004; 93:687-91.
268. Newall F, Monagle P, Johnston L. Home INR monitoring of oral anticoagulant therapy in children using the CoaguChek S point-of-care monitor and a robust education program. Thromb Res 2006; 118:587-93.
269. Reiss N, Blanz U, Breymann T, Kind K, Bairaktaris A, Körfer R. Mechanical valve replacement of the systemic atrioventricular valve in children. ASAIO J 2006; 52:559-61.
270. Bauman ME, Black K, Bauman ML, et al. EMPoWarMENT: Edmonton Pediatric Warfarin Self-Management Pilot Study in Children with Primarily Cardiac Disease. Thromb Res 2010 [Epub ahead of print].
271. Stewart S, Cianciotta D, Alexson C, Manning J. The long-term risk of warfarin sodium therapy and the incidence of thromboembolism in children after prosthetic cardiac valve replacement. J Thorac Cardiovasc Surg 1987; 93:551-4.
272. Cabalka AK, Emery RW, Petersen RJ, et al. Long-term follow-up of the St. Jude Medical prosthesis in pediatric patients. Ann Thorac Surg 1995; 60:S618-S623.
273. Andrew M, Marzinotto V, Brooker LA, et al. Oral anticoagulation therapy in pediatric patients: a prospective study. Thromb Haemost 1994; 71:265-9.
274. Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest 1995; 108:506S-22S.
275. Andrew M. Indications and drugs for anticoagulation therapy in children. Thromb Res 1996; 81:S61-S73.
276. Vosa C, Renzulli A, Lombardi PF, Damiani G. Mechanical valve replacement under 12 years of age: 15 years of experience. J Heart Valve Dis 1995; 4:279-83.
277. Spevak PJ, Freed MD, Castaneda AR, Norwood WI, Pollack P. Valve replacement in children less than 5 years of age. J Am Coll Cardiol 1986; 8:901-8.
278. Streif W, Andrew M, Marzinotto V, et al. Analysis of warfarin therapy in pediatric patients: A prospective cohort study of 319 patients. Blood 1999; 94:3007-14.
279. Bauman ME, Black K, Kuhle S, et al. KIDCLOT: the importance of validated educational intervention for optimal long term warfarin management in children. Thromb Res 2009; 123:707-9.
280. Paioni P, Kroiss S, Kagi E, et al. Self-monitoring of oral anticoagulation therapy in children. Acta Haematol 2009; 122:58-63.
281. Greenway A, Ignjatovic V, Summerhayes R, et al. Point-of-care monitoring of oral anticoagulation therapy in children. Comparison of the CoaguChek XS system with venous INR and venous INR using an International

Reference Thromboplastin preparation (rTF/95). Thromb Haemost 2009; 102:159-65.
282. Geitona M, Hollandezos M, Souliotis K, Athanasakis K, Kyriopoulos J. Cost-minimisation analysis of oral anticoagulant therapy monitoring methods: the case for prothrombin time self-monitoring. Hellenic J Cardiol 2008; 49:388-96.
283. Taborski U, Wittstamm FJ, Bernardo A. Cost-effectiveness of self-managed anticoagulant therapy in Germany. Semin Thromb Hemost 1999; 25:103-7.
284. Lafata JE, Martin SA, Kaatz S, Ward RE. Anticoagulation clinics and patient self-testing for patients on chronic warfarin therapy: A cost-effectiveness analysis. J Thromb Thrombolysis 2000; 9 Suppl 1:S13-9.:S13-S19.
285. Jowett S, Bryan S, Murray E, et al. Patient self-management of anticoagulation therapy: a trial-based cost-effectiveness analysis. Br J Haematol 2006; 134:632-9.
286. Heidinger KS, Bernardo A, Taborski U, Müller-Berghaus G. Clinical outcome of self-management of oral anticoagulation in patients with atrial fibrillation or deep vein thrombosis. Thromb Res 2000; 98:287-93.
287. Sunderji R, Campbell L, Shalansky K, Fung A, Carter C, Gin K. Outpatient self-management of warfarin therapy: a pilot study. Pharmacotherapy 1999; 19:787-93.
288. Fritschi J, Raddatz-Müller P, Schmid P, Wuillemin WA. Patient self-management of long-term oral anticoagulation in Switzerland. Swiss Med Wkly 2007; 137:252-8.
289. Finkelstein J, Khare R, Ansell J. Feasibility and patients' acceptance of home automated telemanagement of oral anticoagulation therapy. Proc AMIA Symp 2003;230-4.
290. Gardiner C, Williams K, Longair I, Mackie IJ, Machin SJ, Cohen H. A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing. Br J Haematol 2006; 132:598-603.
291. Sunderji R, Gin K, Shalansky K, et al. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. Can J Cardiol 2004; 20:1117-23.
292. Körtke H, Zittermann A, Wagner O, Körfer R. Self-management of oral anticoagulation therapy improves long-term survival in patients with mechanical heart valve replacement. Ann Thorac Surg 2007; 83:24-9.
293. Siebenhofer A, Rakovac I, Kleespies C, Piso B, Didjurgeit U. Self-management of oral anticoagulation reduces major outcomes in the elderly. A randomized controlled trial. Thromb Haemost 2008; 100:1089-98.
294. Völler H, Glatz J, Taborski U, Bernardo A, Dovifat C, Heidinger K. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). Z Kardiol 2005; 94:182-6.
295. Körtke H, Zittermann A, Mommertz S, El-Arousy M, Litmathe J, Körfer R. The Bad Oeynhausen concept of INR self-management. J Thromb Thrombolysis 2005; 19:25-31.
296. Körtke H, Zittermann A, Tenderich G, et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J 2007; 28:2479-84.
297. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Ann Intern Med 2001; 134:657-62.
298. Gadisseur AP, Kaptein AA, Breukink-Engbers WG, van der Meer FJ, Rosendaal R. Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life. J Thromb Haemost 2004; 2:584-91.
299. Sunderji R, Fung A, Gin K, Shalansky K, Carter C. Patient self-management of oral anticoagulation: a review. Can J Cardiol 2003; 19:931-5.
300. Hambleton J. Home monitoring of anticoagulation. J Thromb Thrombolysis 2003; 16:39-42.
301. Yang DT, Robetorye RS, Rodgers GM. Home prothrombin time monitoring: a literature analysis. Am J Hematol 2004; 77:177-86.
302. Fitzmaurice DA. Oral anticoagulation control: the European perspective. J Thromb Thrombolysis 2006; 21:95-100.
303. Levi M. Self-management of anticoagulation. Expert Rev Cardiovasc Ther 2008; 6:979-85.
304. Douketis JD. Patient self-monitoring of oral anticoagulant therapy: potential benefits and implications for clinical practice. Am J Cardiovasc Drugs 2001; 1:245-51.
305. Levi M, de Peuter OR, Kamphuisen PW. Management strategies for optimal control of anticoagulation in patients with atrial fibrillation. Semin Thromb Hemost 2009; 35:560-7.
306. Oertel LB, Libby EN. Is patient self-testing a good thing? J Thromb Thrombolysis 2010; 29:214-8.
307. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]. In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. Issue 3, 2005
308. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. Lancet 2006; 367:404-11.
309. Siebenhofer A, Berghold A, Sawicki PT. Systematic review of studies of self-management of oral anticoagulation. Thromb Haemost 2004; 91:225-32.
310. Odegaard KJ. Self-management in anticoagulation - a meta-analysis [Norwegian language]. Tidsskr Nor Laegeforen 2004; 124:2900-3.
311. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. QUOROM Group. Br J Surg 2000; 87:1448-54.
312. Bradburn MJ, Deeks JJ, Berlin JA, Russell LA. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007; 26:53-77.
313. Barcellona D, Fenu L, Minozzi M. Oral anticoagulant therapy and telemedicine. Intern Emerg Med 2006; 1:166-7.
314. Gardiner C, Williams K, Mackie IJ, Machin SJ, Cohen H. Can oral anticoagulation be managed using telemedicine and patient self-testing? A pilot study. Clin Lab Haematol 2006; 28:122-5.
315. Salvador CH, Ruiz-Sanchez A, Gonzalez de Mingo MA, et al. Evaluation of a telemedicine-based service for the follow-up and monitoring of patients treated with oral

anticoagulant therapy. IEEE Trans Inf Technol Biomed 2008; 12:696-706.
316. O'shea SI, Arcasoy MO, Samsa G, et al. Direct-to-patient expert system and home INR monitoring improves control of oral anticoagulation. J Thromb Thrombolysis 2008; 26:14-21.
317. Oake N, van WC, Rodger MA, Forster AJ. Effect of an interactive voice response system on oral anticoagulant management. CMAJ 2009; 180:927-33.
318. Ansell JE. Patient self-testing and patient self-management of oral anticoagulation: is it too late? Isr Med Assoc J 2002; 4:1035-6.
319. Macik BG. The future of anticoagulation clinics. J Thromb Thrombolysis 2003; 16:55-9.
320. Harenberg J, Ingrid J, Tivadar F. Treatment of venous thromboembolism with the oral thrombin inhibitor, ximelagatran. Isr Med Assoc J 2002; 4:1003-5.
321. Cleland JG, Coletta AP, Nikitin N, Louis A, Clark A. Update of clinical trials from the American College of Cardiology 2003. EPHESUS, SPORTIF-III, ASCOT, COMPANION, UK-PACE and T-wave alternans. Eur J Heart Fail 2003; 5:391-8.
322. Weitz JI. Factor Xa or thrombin: is thrombin a better target? J Thromb Haemost 2007; 5 Suppl 1:65-7.:65-7.
323. Bousser MG, Bouthier J, Buller HR, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet 2008; 371:315-21.
324. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139-51.
325. Poller L, Jespersen J, Ibrahim S. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:2673-4.
326. Cohen AT, Maillardet L, Yavin Y. Will a once-weekly anticoagulant for the treatment and secondary prevention of thromboembolism improve adherence? Thromb Haemost 2009; 101:422-7.
327. Hirsh J. New anticoagulants. Am Heart J 2001; 142:S3-S8.