Vitamin K antagonists in heart disease: Current status and perspectives (Section III)

Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease


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Summary

Oral anticoagulants are a mainstay of cardiovascular therapy, and for over 60 years vitamin K antagonists (VKAs) were the only available agents for long-term use. VKAs interfere with the cyclic interconversion of vitamin K and its 2,3 epoxide, thus inhibiting γ-carboxylation of glutamate residues at the amino-termini of vitamin K-dependent proteins, including the coagulation factors (F) II (prothrombin), VII, IX and X, as well as of the anticoagulant proteins C, S and Z. The overall effect of such interference is a dose-dependent anticoagulant effect, which has been therapeutically exploited in heart disease since the early 1950s. In this position paper, we review the mechanisms of action, pharmacological properties and side effects of VKAs, which are used in the management of cardiovascular diseases, including coronary heart disease (where their use is limited), stroke prevention in atrial fibrillation, heart valves and/or chronic heart failure. Using an evidence-based approach, we describe the results of completed clinical trials, highlight areas of uncertainty, and recommend therapeutic options for specific disorders. Although VKAs are being increasingly replaced in most patients with non-valvular atrial fibrillation by the new oral anticoagulants, which target either thrombin or FXa, the VKAs remain the agents of choice for patients with atrial fibrillation in the setting of rheumatic valvular disease and for those with mechanical heart valves.

Keywords

Coagulation, oral anticoagulants, vitamin K antagonists, coronary heart disease, atrial fibrillation, artificial heart valves, heart failure

Introduction

Drugs that interfere with blood coagulation (anticoagulants) are a mainstay of cardiovascular therapy and, until recently, vitamin K antagonists (VKAs) were the only available oral anticoagulants. Their unique mechanism of action and long half-life make them particularly suitable for extended use. Although first introduced in the 1950s (1), our knowledge about monitoring and dosing VKAs in order to maximise their efficacy and minimise haemorrhagic complications has increased dramatically. In addition, health systems have evolved to optimise the management of VKAs with the establishment of anticoagulation clinics, as well as self-monitoring and self-management programmes.

Although these changes have improved patient outcomes, VKAs have shortcomings. These include a slow onset of action, variable dose requirement that reflect, at least in part, common polymorphisms influencing the pharmacokinetics or pharmacodynamics of VKAs and differences in dietary vitamin K intake, and multiple drug-drug interactions. These limitations make coagulation monitoring and frequent dose adjustments necessary to ensure that the level of anticoagulation remains within the therapeutic range. The new oral anticoagulants overcome these prob-
blems because they can be given in fixed doses without the need for routine coagulation monitoring. Although these new agents are replacing VKAs in many patients with non-valvular atrial fibrillation, the VKAs remain the treatment of choice for patients with valvular atrial fibrillation and mechanical heart valves.

In this position paper, coagulation experts and clinical cardiologists appointed by the European Society of Cardiology (ESC) Working Group on Thrombosis review data on the use of VKAs in heart disease. This paper complements previous work by the group on mechanisms of coagulation and targets of anticoagulants (Section I) (2), parenteral anticoagulants (Section II) (3), and use of antiplatelet agents in cardiovascular disease (4), and represents an update of a previous comprehensive document on anticoagulants in heart disease that was published in 2007 (5). Another previous review by the same group has already addressed the use of new anticoagulants in atrial fibrillation and acute coronary syndromes (6). Planned future review papers in this series will be dedicated to an update on the use of the new anticoagulants in acute coronary syndromes (Section IV) and to special situations with the use of anticoagulants, including their use in pregnancy, renal and liver failure, and the management of bleeding (Section V).

**General pharmacology of VKAs**

**Structure**

The commonly used VKAs are 4-hydroxycoumarins, and include warfarin, phenprocoumon and acenocoumarol. The less commonly used VKAs phenindione and fluindione are 1,3-indandione derivatives. Structure and chemical names are shown in Figure 1 and Table 1.

**Mechanism of action**

VKAs exert their anticoagulant effect by interfering with the synthesis of the vitamin K-dependent coagulation factors by inhibiting the vitamin K epoxide reductase complex subunit 1 (VKORC1), an enzyme involved in vitamin K recycling in the liver (Figure 2). VKORC1 is an enzyme that catalyses the reduction of oxidised vitamin K into a form that serves as a cofactor for γ-glutamyl-carboxylase, which catalyses a post-translational modification of vitamin K-dependent proteins. This modification renders such proteins functionally competent by γ-carboxylation of glutamic acid residues, thereby forming the γ-carboxyl glutamic acid (Gla) domain (Figure 2). This is the calcium-binding domain that endows vitamin K-dependent coagulation factors with the capacity to bind to anionic cell surfaces. Vitamin K-dependent proteins include factor (F)II (prothrombin), FVII, FIX and FX, which are procoagulants; and proteins C, S and Z, which serve as anticoagulants (7).

**Pharmacokinetic properties**

The pharmacokinetic properties of the most commonly used VKAs are summarised in Table 1. Among those most widely used, phenprocoumon has the longest half-life, whereas acenocoumarol has the shortest. This difference does not appear to influence the quality of anticoagulation in different European countries (8).

**Dosing**

The dose of VKAs required to exert a therapeutic anticoagulant effect is highly variable from person to person. This variability reflects, at least in part, polymorphisms in genes that affect the pharmacokinetics and pharmacodynamics of VKAs and clinical variables.

**Role of polymorphisms in the pharmacokinetics and pharmacodynamics of VKAs**

The cytochrome P450 (CYP) 2C9 gene, which codes for the enzyme mainly responsible for the hepatic metabolism of VKAs, has two variants with reduced function, CYP2C9*2 and CYP2C9*3. These polymorphisms are relatively common in Cau-
casians, with frequencies of 11% and 8%, respectively, in a Swedish cohort (9). Persons with these reduced-function genotypes require lower doses of VKAs than those with the wild-type CYP2C9*1 genotype and are at increased risk of over-anticoagulation (10).

Patients possessing one or two variant alleles in one of several strongly correlated single nucleotide polymorphisms (SNP) sites in VKORC1 also require lower therapeutic doses of VKAs (11). The presence of variant alleles is highest in Asian populations, in agreement with the low dose requirements of VKAs for Asians, but is also common in Caucasians (11). African Americans require higher doses of VKAs than Caucasians, but this is only partially explained by the low frequency of these polymorphisms.

CYP2C9 and VKORC1 genotypes have been incorporated into dosing algorithms for VKAs. These algorithms contain varying clinical and demographic information and differ in the way that genetic variants are categorised (11, 12). The United States Food and Drug Administration (FDA) has added information about CYP2C9 and VKORC1 polymorphisms to the warfarin drug label, but has not provided directions for dosing based on pharmacogenetic information. Patients with high or low dose requirements are likely to benefit the most from genetic testing (12). Although other algorithms for acenocoumarol including clinical data as well as data on polymorphisms in VKORC1, CYP2C9, CYP4F2 and APOE genes have been developed (22, 23), and these have been found to perform better in providing a steady dose than algorithms only based on clinical variables. Although it has been estimated that the number of patients needed to genotype to avoid one over- or under-dosing is as low as 5 (23), no such algorithms have yet been tested in randomised trials.

There are apparently no interactions between the CYP2C9 and VKORC1 genotypes affecting the maintenance dose, time to severe over-anticoagulation and time to achieve stability for phenprocoumon and acenocoumarol (24).

For fluindione, VKORC1 genotype had a significant impact on the time to full anticoagulation, on the time required to reach optimal anticoagulation, and on predicting the dose requirements. CYP2C9, CYP4F2 and EPHX1 genotypes did not significantly influence the response to fluindione (25).

Although the pharmacogenetics of VKAs has been the subject of intense investigation and the information has been included in several dosing algorithms, it remains controversial whether incorporation of these algorithms into routine clinical care will reduce haemorrhagic complications in patients treated with VKAs or will

Table 1: Pharmacological characteristics of most used vitamin K antagonists.

<table>
<thead>
<tr>
<th>Common pharmacological name</th>
<th>IUPAC name</th>
<th>Trade names</th>
<th>Bioavailability</th>
<th>Protein binding</th>
<th>Metabolism</th>
<th>Terminal elimination half-life</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>warfarin</td>
<td>(RS)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one</td>
<td>Coumadin, Jantoven, Marevan, Lawarin, Waran, Wartant</td>
<td>100%</td>
<td>&gt;99%</td>
<td>Hepatic (mainly through CYP2C9)</td>
<td>approx. 160 h</td>
<td>Mostly renal</td>
</tr>
<tr>
<td>acenocoumarol</td>
<td>(RS)-4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2H-chromen-2-one</td>
<td>Asecumar, Neositron, Sincoumar, Sinkumar, Sinthrom, Sinthrome, Sintron, Syncoumar, Syncomar, Syntron, Zotil</td>
<td>96%</td>
<td>&gt;98%</td>
<td>Hepatic (mainly through CYP2C9)</td>
<td>8–11 h</td>
<td>Mostly renal</td>
</tr>
<tr>
<td>phenprocoumon</td>
<td>(RS)-4-hydroxy-3-(1-phenylpropyl)-2H-chromen-2-one</td>
<td>Marcoumar, Marcumar, Falithrom, Falithiom, Fencumar, Liquamar, Marcuphen</td>
<td>100%</td>
<td>&gt;99%</td>
<td>Hepatic (mainly through CYP2C9)</td>
<td>110–130 h</td>
<td>Mostly renal</td>
</tr>
<tr>
<td>phenindione</td>
<td>2-phenyl-1H-indene-1,3(2H)-dione</td>
<td>Dindevan, Fenindion, Phenindione</td>
<td>&gt;90%</td>
<td>88%</td>
<td>Hepatic</td>
<td>5–10 h</td>
<td>Mostly renal</td>
</tr>
<tr>
<td>fluindione</td>
<td>2-(4-fluorophenyl)indene-1,3-dione</td>
<td>Previscan</td>
<td>80%</td>
<td>70–97%</td>
<td>Hepatic</td>
<td>31 h</td>
<td>Mostly renal</td>
</tr>
</tbody>
</table>

Sources: (185–187). IUPAC, International Union for Pure and Applied Chemistry.
increase the TTR (26, 27). Although appropriate starting doses of VKAs may be more rapidly identified using pharmacogenetic information, it remains controversial whether dosing algorithms that include such information should be implemented in routine clinical care (26-28).

Clinical factors that influence the pharmacological effect of VKAs

Several patient-related factors can alter the pharmacokinetics and pharmacodynamics of VKAs. These include the dietary intake of vitamin K, and concomitant medications (7). Such environmental factors may influence the absorption, hepatic metabolism or plasma protein binding of VKAs, or may affect the synthesis of vitamin K-dependent coagulation factors.

The main source of dietary vitamin K, in the form of vitamin K$_1$ or phylloquinone, is green leafy vegetables, the daily intake of which is highly variable between subjects. Additionally, vitamin K (in the form of menaquinone, or vitamin K$_2$) is produced by bacteria in the colon. Although the correlation between dietary vitamin K intake and the dose of VKAs is not strong, patients with reduced vitamin K intake may be at risk for instability in their INR; a phenomenon that may explain why the daily administration of low-dose vitamin K can stabilise the INR in such patients (29). Dietary recommendations for patients treated with VKAs should therefore focus on maintaining a stable dietary intake of vitamin K rather than avoiding vitamin K-containing foods.

Drug interactions with VKAs can be classified as pharmacokinetic and pharmacodynamic. In case of pharmacokinetic interactions (the vast majority of cases) the dose of VKAs must be adapted. Pharmacodynamic interactions (e.g. the concomitant administration of antiplatelet agents) may increase the bleeding risk without influencing the INR. The major classes of drugs that interact with VKAs can be summarised as the 8 "As": antibiotics, antifungals, antidepressants, antiplatelet agents, amiodarone, anti-inflammatory drugs, acetaminophen, and alternative remedies (30). Commonly used statins (simvastatin and rosvastatin) have been found to enhance the anticoagulant effect of warfarin (31), particularly among carriers of the CYP2C9*3 allele (32).

Patients treated with VKAs often take a large number of concomitant prescription drugs, over-the-counter medicines and dietary supplements. Polypharmacy may influence the required dose of VKAs and increases the risk of adverse events (33). Therefore, it is recommended that the INR be monitored closely when any medication or dietary supplement is added or withdrawn (7). A negative influence of self-perceived stress on the stability of VKAs treatment has recently been indicated in a prospective study, but the mechanism linking stress to reduced TTR remains to be elucidated (34).

Laboratory monitoring of VKAs

The prothrombin time (PT) assay is sensitive to the reduction in the vitamin K-dependent coagulation factors induced by VKAs, and has been used for decades to monitor the intensity of such therapy. The PT is performed by adding calcium and thromboplastin to patient’s plasma to that of plasma from healthy control subjects. When simply expressed in seconds or as a ratio of the value of the patient’s plasma to that of plasma from healthy control subjects. Indeed, the dose of warfarin, the most widely used of the VKAs, was shown to differ in various countries (35, 36) depending on the type of thromboplastin that was used to determine the PT. In countries where higher doses of warfarin were used, the risk of bleeding was higher. The problem was mainly due to differences in the sensitivity of the various thromboplastin reagents to reductions in the plasma levels of the vitamin K-dependent coagulation factors. An unresponsive (“insensitive”) thromboplastin produces less prolongation of the PT for a given reduction in vitamin K-dependent coagulation factors than a responsive (“sensitive”) one. Thus, in North America, where less sensitive thromboplastin reagents of rabbit brain origin were used, higher doses of warfarin were administered. In contrast, lower doses of warfarin were prescribed in Europe, where more sensitive thromboplastin reagents, many of
To promote standardisation, the World Health Organization (WHO) introduced a PT standardisation scheme based on the INR in 1983 (35, 39). This scheme depends on first determining the responsiveness of thromboplastin reagents to reductions in the levels of the vitamin K-dependent coagulation proteins relative to a sensitive standard, a value designated as the international sensitivity index (ISI). Highly sensitive thromboplastins (with ISI values near 1.0) are now available. These can either be extracted from tissues, such as the placenta, or can be synthesised by relipidating recombinant human tissue factor in well-defined phospholipid preparations. Reporting of PT values is now done by converting the PT ratio measured with the local thromboplastin reagent into an INR, which is calculated as follows: 

\[
\text{INR} = \left( \frac{\text{patient PT/geomaric mean normal PT}}{} \right)^{\text{ISI}}
\]

or 

\[
\log \text{INR} = \text{ISI} (\log \text{observed PT ratio})
\]

where ISI denotes the ISI of the thromboplastin used at the local laboratory to perform the PT measurement (40) (see Table 2 for definitions of terms).

The history of standardisation of the PT has been extensively reviewed by Poller (37, 38). The INR system of PT standardisation was originally based on manual determination of the PT and envisaged the assignment of a single ISI value for each batch of thromboplastin reagent (35, 36). However, the PT is now determined using coagulometers, and many studies have shown that the ISI value of a given thromboplastin reagents may differ depending on the instrument that is used for its determination (41-44). Although some manufacturers have introduced an “instrument-specific” ISI, this does not fully overcome the problem because of the large number of potential instrument/reagent combinations and because the ISI value of a particular thromboplastin may differ even with instruments of the same type. ISI calibration using the local PT system appears to be essential to ensure the appropriate thromboplastin/coagulometer combination. ISI calibration using the WHO-recommended procedure is not often feasible in routine hospital laboratories because it requires manual PT testing, which is no longer done in many laboratories, with a WHO reference standard thromboplastin, which is not readily available. Furthermore, the WHO procedure requires newly acquired plasma samples from at least 60 patients on stable doses of VKAs and 20 healthy subjects. Such samples are difficult to obtain on an ongoing basis. Finally, the local ISI needs to be calculated using orthogonal regression analysis, which is a resource-intensive procedure. As a result of these complexities, calibration of the INR has become increasingly difficult to implement at the local level, and has been falling into disfavour.

The problems of manual PT testing have led to the use of lyophilised plasmas with certified INR values to determine the local ISI, so that dependable INR values can be reported (45). Although one such scheme was approved by the FDA for the local ISI calibration, even this procedure is rarely used because it is too complex for most laboratories and/or because the necessary 20 abnormal and seven normal lyophilised certified plasmas have not been available.

To avoid these constraints, many laboratories calibrate their own local system (i.e. instrument/reagent combination) using certified plasmas supplied by manufacturers or reference laboratories. A working group of the International Society of Thrombosis and Haemostasis (ISTH)-Subcommittee on Control of Anticoagulation (SSC) has published guidelines on the preparation, certification and use of certified plasmas; these are directed to manufacturers and users of certified plasmas (46).

More recently, a new and simplified method entitled the PT/INR Line was reported (47, 48), which is an extension of the so-called ‘direct INR’ method of Houbouyan and Goguel (49). The PT/INR Line was modified in the SSC Guidelines and in the Clinical and Laboratory Standards Institute document (50). Using a small set of certified plasmas, the system was evaluated as part of a multicentre international randomised study of computer-assisted dosage. The measurement of INR at 28 participating centres was the subject of an external quality control during the five years of the study (51). The first description of the new development was followed by a further report showing that this simplified PT stan-

Table 2: Definitions and nomenclature of test reagents and indices for VKA monitoring (46).

<table>
<thead>
<tr>
<th>Certified plasma</th>
<th>Plasma with assigned prothrombin time (PT) (in seconds) or International Normalized Ratio (INR) value.</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Sensitivity Index (ISI) calibration</td>
<td>Determination of International Sensitivity Index according to 1999 WHO Guidelines</td>
</tr>
<tr>
<td>Mean normal prothrombin time (MNPT) according to 1999 WHO Guidelines</td>
<td>The geometric (antilogarithmic) mean of the prothrombin times of the healthy adult population. For practical purposes, the geometric mean of the prothrombin time calculated from at least 20 fresh samples from healthy individuals, including those of both sexes, is a reliable approximation of MNPT.</td>
</tr>
<tr>
<td>Test system</td>
<td>Combination of thromboplastin and instrument for prothrombin time determination.</td>
</tr>
<tr>
<td>Local test system ISI calibration</td>
<td>Determination of local test system ISI using certified plasmas.</td>
</tr>
<tr>
<td>“Direct” INR determination</td>
<td>Alternative approach to INR determination using certified plasmas without employing an ISI and MNPT.</td>
</tr>
</tbody>
</table>
dardisation gives reliable INR values and is very robust, not needing a species-specific thromboplastin (Figure 3). The sets of five ECAA certified calibrant plasmas (FDA-approved calibrants) are now being made available by the ECAA via Hart Biologicals Ltd (Hartlepool, UK).

Despite advances in laboratory control, important clinical trials of warfarin continue to be published without evidence of validation of the stated INR. For example, the local INR values reported in the three pivotal trials that compared the new oral anticoagulants with warfarin (52-54) might realistically be classified only as “claimed INR values” (55). This consideration complicates cross-trial comparisons of warfarin management.

External quality control for INR performance is available with a number of national and international schemes, including the WHO.

Practical issues with VKA dosing

A worldwide increase in the use of VKAs has followed the publication of studies demonstrating the value of anticoagulation with these drugs in a widening spectrum of clinical disorders. The benefit/risk ratio of VKAs has improved as a result of the use of lower doses with the introduction of the INR system of laboratory control (35, 36). With increasing use of VKAs, medical, technical, nursing and administrative staff in hospitals and clinics in many countries are becoming overwhelmed by the numbers of patients requiring regulation of VKA dosage. In addition, the quality of anticoagulation has decreased with devolvement of management to community-based centres. One potential way to preserve the standard of care achieved in specialised centres is to use computerised programs to determine anticoagulant dosages. The ECAA computerised dosage study is the first multicentre randomised evaluation of the safety and effectiveness of computerised treatment with VKAs (56). The results of this study favour computer dosing; patients randomised to computerised dosing had a highly significant overall benefit in achieving the target INR in the five participating centres (56).

The usual practice of VKA treatment in most cases is to start with the expected maintenance dose (stabilisation period) and to adjust the daily dose according to the INR results from blood samples taken over the following 5-7 days. High loading doses of VKAs are not to be given to avoid rapid reductions in the levels of the vitamin K-dependent anticoagulant proteins (particularly proteins C and S) prior to reduction in the levels of procoagulant proteins (57, 58). With maintenance doses of VKAs, levels of protein C and FVII decrease at similar rates, which may be a safer approach (59). However, a loading dose can be – and is frequently – applied, especially with VKAs with a long half-life, such as warfarin and phenprocoumon, when there is a need to reach an adequate anticoagulant effect in an acceptable time (5-7 days). In such cases, the dosage is adjusted according to INR results after 2-3 days.

Because the anticoagulant effect of VKAs is delayed, a rapidly-acting parenteral anticoagulant, such as heparin, a low-molecular-weight heparin (LMWH), or fondaparinux, should be overlapped with VKAs in the initial stages of treatment if the patient has established thrombosis or is at high risk of thrombotic events. The parenteral anticoagulant can be stopped once the target INR is achieved, and treatment with the VKA can then be continued at the maintenance dose (stable period).

Traditionally, TTR (Figure 4) (60) has been used as a measure of the quality of VKA treatment. TTR varies in the stabilisation and in the stable periods. It is generally accepted that a TTR above 68-70% reflects high-quality VKA management. In clinical practice, the TTR is often lower, as shown in a number of clinical and observational studies (56), indicating that there is considerable room for improvement. Patients must undergo periodic blood tests to ensure that their target INR is maintained. After a stabilisation period of 3-4 weeks, the interval between laboratory tests may be increased to 4-6 weeks or even longer, provided that regular contacts of the patients with the anticoagulation centre can be assured (61). However, when the INR is out of range, it is important to bring the patients back after 3-7 days to assess the effect of the dose adjustment and to determine whether additional changes in dose are required.

Recently, a simple and practical score – SAMe-TT2R2 – for assessing the likelihood of poor INR control in atrial fibrillation (AF) patients initiated on VKAs has been validated using easily obtainable patient-related clinical parameters (62). This score (Table 3) could help with decision making by identifying those AF patients that would do well on VKAs (SAMe-TT2R2 score=0-1), thereby potentially circumventing the need to use the new oral anticoagulants (62). Conversely, those with SAMe-TT2R2 scores of 2 or more may require additional interventions to achieve acceptable anticoagulation control with VKAs, or may be best treated with a new oral anticoagulant. The needed additional validation of this score in independent cohorts is ongoing.

Figure 3: Use of the prothrombin time (PT)/International Normalised Ratio (INR) Line for reagent calibration in INR measurements. Certified INRs are plotted against the local prothrombin time (PT) results of the five European Concerted Action on Anticoagulation (ECAA) calibrant plasmas on natural logarithm (ln) scale. The PT/INR Line fitted using linear regression (solid line) is used to determine local INR after correction (48, 184). INR of the validation plasma gave a PT of 25 s (broken line: ln(25 s) = 3.22) is directly derived using the PT/Line (INR: e(0.93)= 2.53).
The dose of VKAs required to achieve the desired INR can be estimated using algorithms and treatment tables. Computerised decision support systems (CDSS) have been developed in order to simplify the process of anticoagulation monitoring and to improve dosing decisions. CDSS systems can also help identifying patients with inadequate INR control, and to suggest intervals for re-testing (56). The reliability of two commercial CDSS systems – PARMA 5 and DAWN AC – was compared with manual dosing in 32 centres in 13 countries. Included in this randomised comparison that involved more than 18,000 patient-years of anticoagulant treatment, were the clinical end points of bleeding and thrombosis, as well as the surrogate end point of TTR (51). The study showed that even in specialised anticoagulation clinics, VKA treatment can be improved and the number of clinical events reduced with computer-assisted dosing (63). Based on these results, a simplified minimum procedure has been described within the ISTH framework for screening the safety and effectiveness of marketed programs for VKA dosing (64).

Point-of-care testing

The high demand for VKAs has increased the interest in new testing procedures, such as the point-of-care INR determination using whole-blood samples. Although there is general consensus that point-of-care testing is simpler than traditional methods, optimal calibration and quality control systems are mandatory to ensure that the results are transferable to a higher order of calibration [65, 66], and below]. Point-of-care test monitors must give dependable INR values because the safety and effectiveness of VKA treatment depends on maintaining the INR within the therapeutic range. Thrombotic events increase disproportionately when the INR falls below 2.0 and the risk of bleeding complications increases with INR values over 4.5 (67, 68).

Home INR monitors can conform with WHO standards (69), reliable quality assessment procedures have been developed (70), and the results of a feasibility evaluation have been published (71, 72). Testing at home or at a local community clinic is convenient for patients. In general, such systems save time and reduce transportation costs. However, INR monitors need appropriate calibration (66), and quality control schemes need to comply with the WHO PT standardisation. A recent comprehensive review concluded that point-of-care testing, either at home or in the clinic, is an acceptable option in terms of precision and accuracy for INR determinations (73).

Self-management of VKAs

In the self-management of oral anticoagulation, the patient – using a fingerstick sample of capillary blood inserted into a point-of-care monitoring device – performs one or repeated PT tests himself/herself (self-testing/self-monitoring). He/she then decides whether a dosing adjustment of the anticoagulant is necessary. Prior to participating in a self-management programme of oral anticoagulation patients have to follow an intensive training course on how to use the point-of-care device, on the management of their diet

Table 3: Acronym and definition of the SAMe-TTR score for predicting patients that would do well on VKA, with high Time in Therapeutic Range.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definitions</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Sex (female)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age (less than 60 years)</td>
<td>1</td>
</tr>
<tr>
<td>M</td>
<td>Medical history</td>
<td>1</td>
</tr>
<tr>
<td>T</td>
<td>Treatment (interacting Rx, e.g. amiodarone for rhythm control)</td>
<td>1</td>
</tr>
<tr>
<td>R</td>
<td>Tobacco use (within 2 years)</td>
<td>2</td>
</tr>
<tr>
<td>R</td>
<td>Race (non Caucasian)</td>
<td>2</td>
</tr>
<tr>
<td>Maximum points</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

*2 or more of the following: hypertension, diabetes, myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease. From (62)

Figure 4: Method for the calculation of the percentage of time in the therapeutic range (TTR, TIR) for the INR control using the method by Rosendaal et al. (60). When INR is recorded at one visit and another INR is recorded at a subsequent visit, a line can be drawn between the two points. The time between the two points in terms of number of days a patient is in range can be estimated according to the extent that the line is within a patient’s therapeutic range by linear interpolation. In the Figure: D1: INR recorded after at one visit; Dnext: INR recorded at the next visit. Days in Range = D2 – D1, where D1 is an interpolated value estimating the last day after D1 when the patient was still in the therapeutic range. This can be done for all INR visits of a patient’s time in therapy. % Time in Therapeutic Range (TTR) can then be expressed as

\[
\frac{\sum \text{Days in Range}}{\sum \text{Interval(s)}} \times 100\%
\]

where \( \sum \) is the Sum of days.

Example: Patients INR = 2.5 (D1); next INR = 3.5 (Dnext); Therapeutic range 2.0–3.0; Interval between visits = 30 days. By linear interpolation, D2 = 15 days, D1 = 0 days; Days in Range = 15 – 0 = 15; % Time in Therapeutic Range = 15/30 x 100% = 50%.
Limitations of VKAs

Although VKAs clearly have efficacy in preventing thrombosis, and actually have the greatest efficacy in preventing stroke in AF among the treatments available until a few years ago, they carry a substantial risk of major bleeding, even when the patient is within the therapeutic range. In addition, the therapeutic window is narrow, necessitating frequent coagulation monitoring to ensure appropriate dosing (81). The marked variability in the dose-response relationship often makes it difficult to remain within the target INR. Although absorption from the gastrointestinal tract of the various VKAs is generally quite good, their dose response is influenced by several factors, including: 1) numeric drug interactions; 2) the dietary intake of vitamin K; 3) hepatic dysfunction; 4) changes in gut flora; 5) patient compliance; and 6) alcohol intake. These factors are common, so that even within the controlled setting of a clinical trial it has not been unusual to stay within the therapeutic window for only around 50% of the time (82). This increases the necessity of unpleasant, frequent and assiduous monitoring of the PT in every patient treated with VKAs in order to reduce the risk of serious bleeding on the one hand, and of undertreatment on the other. Even with careful monitoring, patient selection is required to screen out patients who might be at increased risk of haemorrhage (83-86). Several trials used specific criteria to exclude patients from enrolment: dementia, elevated creatinine, anaemia with haemoglobin below 100 g/l, blood pressure >180/100 mmHg despite treatment, severe chronic alcoholism, previous intracranial haemorrhage, severe bleeding with a therapeutic INR while receiving a VKA, predisposition to head trauma, and requirement for non-steroidal anti-inflammatory drugs (87-90).

Other reasons why VKAs are so poorly tolerated and even impractical for many patients include the clear disadvantage of having to be tied to the medical system for a life-long anticoagulation monitoring, with restriction of travelling, anxiety, cost, loss of freedom, the need of avoiding most non-steroidal anti-inflammatory drugs, the need to carefully control alcohol consumption, caution in the use of other drugs, and the need to adjust dietary patterns because of potential drug and food interactions.

In summary, therapy with VKAs is complex, associated with considerable risks, and not easily accepted by the patients, and this has resulted in considerable difficulty in convincing physicians and patients to adhere to current practice guidelines, with resulting under-treatment in a considerable proportion of patients at risk (91). This is ample justification for the need for safer, more convenient, alternatives to VKAs.

The use of VKAs in different countries

The use of VKAs across countries has been investigated especially in the area of AF. Although the profile of AF patients in Western Europe is well known, few comparative data concerning management decisions in different European countries are available. The PREFER in AF registry enrolled 7,243 patients in France (FR), Germany (GE), Italy (IT), Spain (SP) and the United Kingdom (UK) from January 2012 to January 2013 (8). The mean age was 71.5 years, with very similar prevalence of thromboembolic risk factors across countries. Despite this overall homogeneity, the anticoagulation management showed important discrepancies: the proportion of patients receiving VKAs was 86.0% in FR, 80.0% in SP, 79.1% in GE, 75.1% in UK and 71.4% in IT. The type of VKAs was very different: warfarin was used predominantly in UK and IT (74.9% and 62.0%, respectively), phenprocoumon in GE (74.1%), acenocoumarol in SP (67.2%), and fluindione in FR (61.8%), but these variations did not apparently result in different anticoagulation quality or AF outcomes (8). Warfarin is practically the only VKA used in the USA.

A novel vitamin K antagonist: tecarfarin

Tecarfarin is a novel vitamin K antagonist currently in clinical trials (92). The advantage of tecarfarin over warfarin or other traditional VKAs is that it is metabolised by carboxylesterases and not the cytochrome P450 (CYP450) pathway. This difference should decrease many of the drug-drug, drug-food, and genetic
interactions resulting from the CYP450 system that afflict the other VKAs (93). Tecarfarin can be monitored with the PT in terms of INR.

Clinical indications

Coronary heart disease

Major complications of coronary heart disease are usually caused by coronary plaque rupture followed by coronary thrombosis. In addition to activation of platelets, the process involves activation of coagulation with the formation of fibrin. Besides antiplatelet therapy, oral anticoagulation with VKAs has shown to be effective in the prevention of coronary thrombosis.

Primary prevention

Primary prevention of coronary heart disease with warfarin, with a mean INR intensity of 1.5, reduced the risk of fatal myocardial infarction (MI) by 39%, with an acceptable bleeding risk in over 2,500 healthy high-risk males (94). However, this principle has not been incorporated into general practice for primary prevention – and we do not advise it – given the uncompelling benefit-risk ratio and the widespread introduction of other preventive therapeutic approaches.

Acute coronary syndromes/secondary prevention

Several major, but now fairly outdated studies have demonstrated the benefit of VKAs in patients with a previous MI (95-98). VKAs on top of antiplatelet therapy with aspirin vs aspirin alone have been studied in at least eight randomised controlled trials in patients who survived an ACS, both as ST-elevation acute myocardial infarction (STEMI) and as non-ST elevation (NSTEMI)-ACS: ATACS (99, 100), CARS (101), OASIS-2 (102), CHAMP (103), APRICOT-2 (104), ASPECT-2 (98), WARIS-2 (97), LoWASA (105) (Table 4). For these indications, VKA therapy, alone or added to antiplatelet therapy, does not seem to show benefit when the INR is below 2.0. When the INR is between 2.0 and 3.0, larger

Table 4: Randomised aspirin-controlled studies of warfarin plus aspirin in acute coronary syndromes and percutaneous coronary interventions.

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Year</th>
<th>n</th>
<th>INR target / dose</th>
<th>INR reached</th>
<th>Aspirin dose (mg/d)</th>
<th>Death/reinfarction</th>
<th>RR</th>
<th>P-value</th>
<th>FU (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATACS (99, 100)</td>
<td>1994</td>
<td>214</td>
<td>2.0–3.0</td>
<td>2.3</td>
<td>163</td>
<td>4/105 (3.8%)</td>
<td>9/109 (8.3%)</td>
<td>0.46 (0.14–1.49)</td>
<td>0.004†</td>
</tr>
<tr>
<td>OASIS-2 (102)</td>
<td>2001</td>
<td>3712</td>
<td>1 mg q.d.</td>
<td>1.1</td>
<td>80</td>
<td>237/2028 (8.8%)*</td>
<td>160</td>
<td>380/ 3393 (8.6%)*</td>
<td>0.95 (0.81–1.12)</td>
</tr>
<tr>
<td>CHAMP (103)</td>
<td>2002</td>
<td>5059</td>
<td>1.5–2.5</td>
<td>1.8</td>
<td>160/80**</td>
<td>780/2522 (30.9%)*</td>
<td>771/2537 (30.4%)*</td>
<td>1.04 (0.95–1.14)</td>
<td>0.77</td>
</tr>
<tr>
<td>ASPECT-2 (98)</td>
<td>2002</td>
<td>668</td>
<td>2.0–3.0</td>
<td>2.4</td>
<td>80</td>
<td>15/332 (4.5%)*</td>
<td>28/336 (8.3%)*</td>
<td>0.52 (0.27–0.92)</td>
<td>0.03</td>
</tr>
<tr>
<td>WARIS-2 (97)</td>
<td>2002</td>
<td>2414</td>
<td>2.0–2.5</td>
<td>2.2</td>
<td>160/75**</td>
<td>181/1208 (15.0%)*</td>
<td>241/1206 (20.0%)*</td>
<td>0.71 (0.60–0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>LoWASA (105)</td>
<td>2004</td>
<td>3300</td>
<td>1.25 mg q.d.</td>
<td>n.a.</td>
<td>75</td>
<td>466/1659 (28.1%)*</td>
<td>473/1641 (28.8%)*</td>
<td>0.98 (0.88–1.09)</td>
<td>0.67</td>
</tr>
<tr>
<td>TOTAL</td>
<td>24470</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*compare with combination 1 and 3 mg warfarin, ** aspirin alone / combination groups, *** including stroke; n.a., not analysed; FU, follow-up; PCI, percutaneous coronary intervention. † P after 14 days, P = 0.06 after 3 months FU, ‡ at 30 days including stroke and target-lesion revascularisation.
studies tend to demonstrate a significant reduction in the risk of (re-)infarction, stroke, and the combination of death, MI and stroke, with possible acceptable safety (1.9 ischaemic events prevented vs 1.5 major bleeds caused per 100 treated patients) (106). Two of these studies (ATACS and OASIS-2) were performed only in NSTE-ACS patients (Table 4). The current clinical applicability of such information is limited, because more modern antiplatelet therapy, with apparent similar efficacy and better safety (107), has become standard for the first 12 months.

Coronary bypass graft surgery

Low-intensity warfarin (INR <2.0) has been compared with placebo after coronary artery bypass graft (CABG) surgery in only one large long-term trial. Warfarin vs placebo did not lead to better vein graft patency, but in the long term – unexpectedly – led to a highly significant 35% relative reduction in all-cause mortality and a 24% relative reduction in non-fatal MI (108) (Table 4).

Percutaneous coronary interventions

Early and late complications of percutaneous coronary interventions (PCI) are probably related to the occurrence of procedure-related coronary thrombosis. Therefore, VKAs (essentially warfarin) have been evaluated in the prevention of these sequelae. One trial, in over 1,000 patients, compared aspirin 80 mg daily plus warfarin (INR 2.1–4.8), started at least 1 week before PCI, with aspirin alone on peri-procedural outcomes, the angiographic outcome at six months, and clinical events at one year, when trial medication was discontinued (109). The combined end point of death, MI, stroke, or urgent revascularisation was significantly diminished by warfarin by 47% at 30 days and 29% at one year (Table 4). Bleeding was increased: there was a 1% absolute excess of major peri-procedural bleeding events and a 1% absolute excess of major bleeding during the follow-up, but life-threatening bleeding was similar. Interestingly, the clinical benefit of VKAs was shown not only in non-stented, but also in stented patients, in whom – by protocol – warfarin was switched to ticlopidine after the procedure, suggesting that pretreatment with VKAs could be useful in preventing thrombotic complications during the first

Table 5: Stroke risk stratification with the CHADS2 and CHA2DS2-VASc scores (A) and bleeding risk scoring with HAS-BLED score (B).

<table>
<thead>
<tr>
<th>A</th>
<th>Letter</th>
<th>CHADS2 acronym</th>
<th>Score</th>
<th>Letter</th>
<th>CHA2DS2-VASc acronym</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive heart failure</td>
<td>1</td>
<td>C</td>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Aged ≥ 75 years</td>
<td>1</td>
<td>A</td>
<td>Aged ≥ 75 years</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Diabetes mellitus</td>
<td>1</td>
<td>D</td>
<td>Diabetes mellitus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>S</td>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Maximum score 6

| A | Aged 65–74 years | 1 |
| S | Sex category (i.e. female gender) | 1 |

Maximum score 9

Abbreviations: TIA, transient ischaemic attack; TE, thromboembolism; LV, left ventricular; MI, myocardial infarction; PAD, peripheral arterial disease.

<table>
<thead>
<tr>
<th>B</th>
<th>Letter</th>
<th>Clinical characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Bleeding tendency or predisposition</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Elderly (e.g. age &gt;65 years, frail condition)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Drugs (e.g. concomitant aspirin or NSAID) or alcohol excess (1 point each)</td>
<td>1 or 2</td>
<td></td>
</tr>
</tbody>
</table>

Maximum score 9

Abbreviations: INR, international normalised ratio; NSAID, non-steroidal anti-inflammatory drugs.
days after stenting, awaiting the delayed onset of action of ticlopidine.

Because of the introduction of dual antiplatelet therapy in PCI with stenting (this latter now routinely used after several trials (110-114) demonstrating the superiority of aspirin plus ticlopidine/clopidogrel therapy in preventing stent thrombosis), VKAs are not, currently, standard-of-care in this setting.

### Atrial fibrillation

The risk of stroke in patients with AF is increased approximately five-fold, but is quite variable and dependent upon the presence of associated stroke risk factors. "Valvular" AF – intended to be rheumatic AF (i.e. AF accompanying mitral stenosis), and AF in the presence of a mechanical heart valve – has a very high risk of thromboembolism, and here VKA therapy remains the only approved therapeutic strategy. Indeed, a phase II trial with dabigatran has been recently aborted because of an excess of thromboembolic and bleeding events (115, 116). Some stroke risk factors in non-valvular AF are well established from the (now historical) placebo-controlled trials, such as prior stroke/TIA, age ≥75, hypertension, and diabetes, whilst a "history of heart failure" is a non-significant risk factor (117, 118). However, moderate-severe systolic impairment on 2D transthoracic echocardiography is clearly a risk factor for stroke (117). Other factors, such as peripheral artery disease (119-122), MI (123, 124), and age 65-74 (118), are also independent risk factors in AF for stroke and vascular events.

These risk factors have been used to formulate stroke risk stratification schemes (Table 5), the simplest being the CHADS$_2$ score [Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or TIA] (125). However, there are several limitations with the CHADS$_2$ score (126). Also, the artificial division of stroke risk into low-, moderate- and high-risk strata was initially proposed, so that the "high-risk" patients, given their limitations and disadvantages, could be particularly targeted for anticoagulation with VKAs. More recently, the initial focus has been to identify the "truly low-risk" patients with AF, who do not need any antithrombotic therapy as the first decision-making step. Subsequent to this evaluation, all other patients with ≥1 stroke risk factors can be offered effective stroke prevention, which is oral anticoagulation.

The CHA$_2$DS$_2$-VASc score (Table 5) was initially recommended to complement the CHADS$_2$ score in the 2010 ESC guidelines on AF management (127), and the most recent 2012 focused update of the ESC guidelines only recommends use of the CHA$_2$DS$_2$-VASc score for stroke risk assessment (Figure 5). The ESC guidelines de-emphasise the artificial low/moderate/high risk categorisation, and place greater emphasis on a risk factor-based approach to assess stroke risk, defining "major risk factors" as age ≥75 years and previous stroke/TIA/thromboembolism, by allocating two points to each, with one point for the presence of each of the other "clinically relevant non-major" risk factors, with total scores ranging from 0 to 9. Since its original validation study (128), the CHA$_2$DS$_2$-VASc has been validated independently in a number of cohorts (129). Of note, patients with a CHADS$_2$ score of 0-1 were not "low-risk", but those categorised as "low-risk" using CHA$_2$DS$_2$-VASc (score=0) were "truly low-risk" for thromboembolism, with an annual event rate of 0.78 (130).

The CHA$_2$DS$_2$-VASc score is also featured in the Afib Toolkit proposed by the American College of Cardiology (http://www.cardiosource.org/Science-And-Quality/Clinical-Tools/Atrial-Fibrillation-Toolkit.aspx).

![Figure 5: Algorithm for thromboprophylaxis in atrial fibrillation, based on the 2010–2012 ESC guidelines, and highlighting (red box) the current role of VKAs in the thromboprophylaxis for patients with atrial fibrillation. *Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc. ** Antiplatelet therapy with aspirin plus clopidogrel, or -less effectively - aspirin only, may be considered in patients who refuse any OAC. Colour: CHA$_2$DS$_2$-VASc score: green = 0, blue = 1, red = ≥2. Line: Solid: best option; Dashed: alternative option. If absolute contraindications to any oral anticoagulant or antiplatelet therapy, left atrial appendage closure device can be considered. Abbreviations: AF, atrial fibrillation; NOACS, novel oral anticoagulants; VKAs, vitamin K antagonist. Reproduced, with permission, from (127, 131).](http://www.thrombosis-online.com)
Based on the ESC guidelines, patients with a CHA\textsubscript{2}-DS\textsubscript{2}-VASc score of $\geq 2$ are recommended oral anticoagulation, either with well-controlled VKAs or with one of the new oral anticoagulants (Class I recommendation). In patients with a CHA\textsubscript{2}-DS\textsubscript{2}-VASc score=1 oral anticoagulants should be considered, based on patient's values and preferences, balancing stroke risk against the potential for bleeding and/or the inconvenience of monitoring if VKAs are used (Class IIa recommendation). In truly low-risk patients [age $<65$ and lone AF (including females) or CHA\textsubscript{2}-DS\textsubscript{2}-VASc score=0], no antithrombotic therapy is preferred over aspirin (131).

Oral anticoagulation with VKAs has been shown to be highly effective for stroke prevention in AF, reducing the risk of stroke by 64% compared with placebo/control, as well as significantly reducing the risk of all-cause death by 26% (132). In contrast, antiplatelet therapy reduces the risk of stroke by 22% compared with placebo/control, and – when analysis was confined to the aspirin-only trials – there was a non-significant 19% (95% CI -1 to 35%) reduction in the incidence of stroke, essentially driven by one single positive trial, the SPAF-1 trial (133). The latter had major internal heterogeneity for the aspirin effect against anticoagulation-eligible and anticoagulation-ineligible patients, and only tested aspirin at a dose of 325 mg daily (133).

In the meta-analysis by Hart et al. (132), VKAs were associated with a 39% (95% CI 0.22 to 0.50) risk reduction compared with antiplatelet therapy. In low-risk patients, aspirin appears to be no better than control in reducing thromboembolism, with a trend towards more major bleeding events (134). In elderly patients with AF, VKAs were superior to aspirin for stroke prevention, with no significant difference in major bleeding (and intracranial haemorrhage) between VKAs and aspirin (135).

Thus, for effective stroke prevention in AF with $\geq 1$ stroke risk factors, oral anticoagulants remain the best option, and aspirin has no convincing role for stroke thromboprophylaxis in AF. In one trial in “VKAs-unsuitable” patients with AF, combination therapy with aspirin plus clopidogrel yielded a relative reduction in stroke rate of 28% compared with aspirin alone, but combination therapy was associated with increased rates of major bleeding (approximately 2%/year absolute increase) and intracranial haemorrhage (136). In a similar population, one of the new oral anticoagulants, the direct FXa inhibitor apixaban, performed much better than aspirin in efficacy for stroke prevention, with comparable safety (137).

In patients with AF and the need for dual antiplatelet therapy due to ACS and/or stent implantation “triple” therapy is recommended for the shortest necessary duration. This usually consist of aspirin (100 mg/day), clopidogrel (75 mg/day) and a VKA (INR goal 2.0-2.5) (138-140). While the European approach to this specific situation prefers a shorter duration of “triple” therapy in order to better guarantee patient’s safety to the patients, the North American approach with longer recommendation for “triple”-therapy in certain situations stands for more efficacy (141).

New treatment guidelines by the ESC (127, 131) and the Canadian Cardiovascular Society (CCS) (142) also recommend for each patient a bleeding risk assessment. Bleeding risk, which is clearly multifactorial, should be assessed proactively when evaluating a patient with AF for antithrombotic therapy. Until recently, bleeding risk scores have been complicated, with only one score being derived and validated in an AF population on VKA treatment (143). In all such schemes there is an overlap between stroke and bleeding risk factors. Apart from patients with stable risk factors for bleeding, doctors should also be aware that there are high-risk periods when VKA therapy is initiated (144).

Given the importance of bleeding risk assessment and management in AF patients, the European Heart Rhythm Association (EHRA) recently published a position document, endorsed by the ESC Working Group on Thrombosis, summarising such “best practice” principles when approaching antithrombotic therapy in AF patients (145). Both the ESC and CCS now recommend the use of the HAS-BLED score (Table 5) to assess bleeding risk in AF populations, where a score of $\geq 3$ is indicative of a bleeding risk high enough to necessitate caution and/or regular review of the patient, as well as to address the correctable risk factors for bleeding (e.g. uncontrolled hypertension, concomitant aspirin use). This simple score for bleeding risk on VKAs has been well-validated in several independent cohorts (128, 146, 147). Moreover, the HAS-BLED score has been shown to be as good as more complex older scores (e.g. HEMORRHAGES) – or even superior to the new ATRIA score (148-150). HAS-BLED is also validated in Far East populations (151) in non-VKA anticoagulated patients (152), and is the only score predictive of intracranial haemorrhage (148), the most severe complication of anticoagulation therapy. Other studies have shown how the HAS-BLED score is predictive of major bleeding during bridging therapy (153) and during PCI (154), as well as in non-AF populations (155).

When the net clinical benefit balancing the risk of ischemic stroke and intracranial haemorrhage is assessed, there is a negative net clinical benefit with VKAs only at a CHA\textsubscript{2}-DS\textsubscript{2}-VASc score=0 (reflecting the ‘truly low-risk’ status of these patients) and a non-negative (i.e. neutral or positive) net clinical benefit (ischaemic stroke vs intracranial haemorrhage) in patients with a CHADS\textsubscript{2} score of $>0$, and CHA\textsubscript{2}-DS\textsubscript{2}-VASc score of $\geq 1$, indicating possible or definite advantage (156). More importantly, the net clinical benefit is even greater at HAS-BLED scores of $\geq 3$, again suggesting that a high risk of bleeding should not immediately constitute an absolute contraindication to oral anticoagulation. Patients with no stroke risk factors (e.g. CHA\textsubscript{2}-DS\textsubscript{2}-VASc score=0) are, conversely, clearly at so low risk that either aspirin 75–325 mg daily or – preferably – no antithrombotic therapy is recommended. Similar conclusions have been drawn from the Swedish AF cohort (157), whereby modelling new oral anticoagulants into such nationwide cohort data clearly show a net clinical benefit for patients with a CHA\textsubscript{2}-DS\textsubscript{2}-VASc score $\geq 1$ (158).

In summary, the landscape of thromboprophylaxis in AF has evolved, so that a more comprehensive stroke risk assessment is now advised; AF patients with $\geq 1$ stroke risk factor should be considered for oral anticoagulants, given that this is the most effective way to prevent stroke and thromboembolism in such a condition. Thus, as the first decision step, the emphasis has shifted from grading risk scores to a more comprehensive stroke risk assessment, with the aim of identifying patients at high risk for stroke or bleeding, and tailoring antithrombotic therapy accordingly.
ify the truly low-risk patients with AF, who do not need antithrombotic therapy. Clinicians also need to have an informed way to assess bleeding risk, and bleeding risk assessment (for VKA treatment) has been incorporated into recent guidelines.

Valvular heart disease

Rheumatic mitral valve disease

This situation, of which mitral stenosis is the landmark, is thought to carry the greatest risk of systemic thromboembolism of any common form of acquired native valvular disease, even in the absence of AF, although such estimates are based on old literature (159). Characteristics in mitral stenosis that may increase the risk of systemic embolism include the presence of a left atrial thrombus and significant aortic regurgitation (160). Current recommendations are based on a paucity of information, and are all based on a low level of evidence (C). In agreement with the American College of Chest Physicians (ACCP) (161), we recommend anticoagulation in rheumatic mitral valve disease in the presence of left atrial enlargement (>55 mm diameter) or in the presence of left atrial thrombus. In such cases, as in cases complicated with atrial fibrillation, we recommend the same anticoagulation intensity (INR 2-3) as in most other forms of AF.

Prosthetic mechanical valves

The introduction of mechanical heart valves with better flow profiles has diminished haemolysis and the risk of valve thrombosis and thromboembolic complications. The recommended intensity of oral anticoagulation with VKAs has been therefore adjusted in recent ESC guidelines (162, 163) to lower levels compared with previous statements. Intensity of anticoagulation in such cases is adjusted according to the thrombogenicity of the prosthesis, the position (aortic vs mitral/tricuspid/pulmonary), and associated thromboembolic risk factors, as summarised in Table 6 (164, 165). The post-operative anticoagulant therapy should be started during the first days. The initiation of anticoagulation treatment immediately after valve replacement requires attention, with careful INR measurement, because of increased risk of both thromboembolic complications and bleeding caused by increased sensitivity to VKAs postoperatively. Bridging therapy of VKA treatment with unfractionated heparin or LMWH is generally accepted to enable rapid anticoagulation until INR is stable on VKA treatment, although there is no proof that such a strategy is effective and safe in this regard.

The systematic prescription of antiplatelet drugs in addition to oral anticoagulation in patients with mechanical valves is an area of major controversy, which is scientifically unresolved due to lack of appropriate trials with modern prosthetic valves. The ACC/AHA 2006 guidelines update (166) recommend the addition of aspirin to warfarin for all patients with mechanical valves, but the evidence on which they base this advice is not compelling. After reviewing all available data, the 2007 and 2012 ESC guidelines (162, 163) have recommended that antiplatelet drugs should not be prescribed for all patients with mechanical valves. Instead, the addition of antiplatelet drugs to anticoagulation should be individualised, balancing risk and benefit, restricted to specific indications, and only combined with relatively low-intensity anticoagulation (INR ≤3.0). Relative indications include recurrent embolism, but only after full investigation, treatment of amenable risk factors, and optimisation of anticoagulation control. The coexistence of a prosthetic valve with coronary heart disease or other arterial disease is currently not considered a reason to add an antiplatelet agent to an anticoagulant (131, 167). Triple therapy with warfarin, aspirin and clopidogrel may be necessary after intracor-

<table>
<thead>
<tr>
<th>Table 6: Recommendations for target intensity of anticoagulation (INR values) with VKA in patients with mechanical heart valves, by adjusting target INR to intra-cardiac conditions and prosthesis thrombogenicity.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROSTHESIS THROMBOGENICITY (as determined by valve thrombosis rates)</strong></td>
</tr>
<tr>
<td>Without risk factors</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>SR</strong></td>
</tr>
<tr>
<td>LA &lt;50 mm</td>
</tr>
<tr>
<td>MV gr 0</td>
</tr>
<tr>
<td>LV normal</td>
</tr>
<tr>
<td>SEC 0</td>
</tr>
<tr>
<td>AVR</td>
</tr>
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<td>low</td>
</tr>
<tr>
<td>medium</td>
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<td>high</td>
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</tbody>
</table>

*Prosthesis thrombogenicity: Low = Medtronic Hall, St. Jude Medical (without Silzone), Carbomedics AVR, bioprostheses; Medium = Bileaflet valves with insufficient data, Bjork-Shiley valves; High = Lillehei Kaster, Omnisience, Starr Edwards. SR, sinus rhythm; AF, atrial fibrillation; LA, left atrium; MVgr, mitral valve gradient; LV, left ventricle; EF, ejection fraction; SEC, spontaneous echo contrast; AVR, MVR, TVR, PVR, aortic, mitral tricuspid and pulmonary valve replacement, respectively. ** There is considerable uncertainty in recommending such high-intensity anticoagulation in this group. Modified from: Butchart et al., 2005 (164).
The risk of thromboembolic complications is increased in patients with advanced chronic heart failure and severe left ventricular dysfunction (169). Venous thromboembolism, cardio-embolic stroke and sudden death occur in about 30% of heart failure patients (169). The combination of left ventricular dysfunction and AF is very common, increasing dramatically the risk of thromboembolism. According to all current guidelines the indication for anticoagulation in this group of patients is not questionable.

However, in patients with left ventricular dysfunction or heart failure, but in sinus rhythm there are currently few recommendations from guidelines, given the limited evidence. In patients with heart failure caused by either dilated cardiomyopathy or ischaemic heart disease, a cardio-embolic risk of 1.5–4.5%/year has been observed, with the highest risk related to very low ejection fraction and severe clinical heart failure (170). A hypercoagulable state caused by several mechanisms is responsible for an enhanced risk of embolism and stroke (171). In post-infarction patients, the cardio-embolic risk is especially high with ejection fraction <30% (172, 173) or with persisting or protruding thrombus (174, 175).

A few randomised trials have addressed this issue. The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial (176, 177) randomised 1,587 heart failure patients to anticoagulation (target INR 2.5) or antiplatelet therapy (blinded aspirin 162 mg or clopidogrel 75 mg), and found no significant difference in the composite end point of death/MI/stroke between the three groups (20.5% vs 21% vs 19.8% for aspirin, clopidogrel and warfarin, respectively). Planned to randomise more than 5,000 patients, this trial was prematurely stopped because of problems with patient recruitment. This decision was vigorously criticised (178). Another important concern regarded the lack of a placebo arm, making it difficult to assess if any treatment was more effective than no antithrombotic treatment.

The Warfarin/Aspirin Study in Heart Failure (WASH) study (179) randomised 279 patients to no antithrombotic treatment, aspirin (300 mg/day) and warfarin (target INR 2.5) with 627 patient-years exposure accumulated over a mean follow-up time of 27 ± 1 months, and found no difference in the primary end points of death, non-fatal MI or non-fatal stroke between the three arms (26%, 32% and 26% in patients on placebo, aspirin and warfarin, respectively). In both trials, patients on warfarin were hospitalised less frequently than those allocated to aspirin. A third clinical trial addressing this issue has been the Heart failure Long-term Anti-thrombotic Study (HELAS) (180). In this trial a small group of 312 patients with dilated cardiomyopathy were randomly allocated to receive either warfarin or placebo. The incidence of thromboembolism was very low, and the active treatment was not associated with improved outcome.

Another recent randomised trial, the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial (181), compared warfarin (INR 2-3) with aspirin (325 mg/day) in patients in sinus rhythm who had a reduced left ventricular ejection fraction (LVEF). Following 2,305 patients for up to six years, the primary outcome of ischaemic stroke, intracerebral haemorrhage, or death from any cause was not significantly different among the three groups. Warfarin, as compared with aspirin, was associated with a significant reduction in the rate of ischaemic stroke throughout the follow-up period (HR, 0.52; 95% CI, 0.33 to 0.82; p=0.005; 0.72 events vs 1.36 events per 100 patient years), but at the cost of an increased rate of major haemorrhage [1.78 events per 100 patient-years in the warfarin group as compared with 0.87 in the aspirin group (p<0.001)]. A reduced risk of ischaemic stroke with warfarin was offset by an increased risk of major haemorrhage (181).

A joint consensus document of the Heart Failure Association (EHFA) of the ESC and the ESC Working Group on Thrombosis (169) concluded that in heart failure patients with reduced LVEF who are in sinus rhythm there is no evidence of an overall benefit of VKAs on mortality and stroke. There is, however, the potential for...
for a reduction in ischaemic stroke, balanced by an increased risk in haemorrhagic stroke. Thus, there is currently no compelling reason to use VKAs routinely for these patients. Risk factors associated with increased risk of thromboembolic events should be identified, and decisions regarding use of anticoagulation individualised. Patient values and preferences are important determinants when balancing the risk of thromboembolism against the risk of bleeding. VKA treatment should probably be considered in patients with heart failure in sinus rhythm in cases of a very low ejection fraction, severe clinical heart failure, ventricular thrombi, and prior cardio-embolic episodes (169).

Conclusions and future directions

VKAs remain the treatment of choice for prevention of stroke and systemic thromboembolism in patients with AF in association with rheumatic valve disease and in patients with mechanical heart valves. VKAs are also indicated in patients with non-valvular AF who are unwilling to take or unable to afford a new oral anticoagulant, and in those who are not candidates for the new oral agents because of impaired renal function with a creatinine clearance below 30 ml/minute (127, 131). Patients who frequently miss doses of medications may also do better with long acting VKAs, such as warfarin or phenprocoumon, than with the short-acting new oral anticoagulants.

VKAs should be considered in patients with a ventricular thrombus and/or severe heart failure associated with a low ejection fraction, particularly if there is a history of a prior cardioembolic event. Although rarely used for this indication, VKAs, alone or in conjunction with aspirin, are of proven benefit for prevention of recurrent ischaemic events after MI; the benefit-to-risk profile of such therapy relative to single or dual antiplatelet therapy remains uncertain.

With the recent licensing of dabigatran etexilate, rivaroxaban and apixaban for stroke prevention in non-valvular atrial fibrillation in Europe, the United States and several other countries, the use of VKAs for this indication is likely to decrease. Nonetheless, VKAs will remain the treatment of choice for AF patients with rheumatic valve disease or severe renal impairment and those with mechanical heart valves. In addition, because the new oral anticoagulants have not yet been evaluated in patients with heart failure with or without left ventricular thrombi, VKAs will continue to be used for these indications.

Although the use of the new oral anticoagulants is increasing, with the potential for accumulation in patients with severe renal impairment and the recent failure of dabigatran etexilate in patients with mechanical heart valves, it is becoming increasingly clear that the new agents will not replace VKAs for all indications (182, 183), as summarised in Table 7.

Table 7: Vitamin K antagonists in heart disease: areas where they will likely remain the front-line long-term oral anticoagulants in the near future.

<table>
<thead>
<tr>
<th>Subsets of patients with non-valvular atrial fibrillation</th>
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<tr>
<td>good renal function</td>
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<tr>
<td>patients with expected poor compliance, in whom monitoring can serve to improve adherence*</td>
</tr>
<tr>
<td>patients with sufficiently stable INR*</td>
</tr>
<tr>
<td>patients who will not be able to afford the increased direct costs of the new oral anticoagulants</td>
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*: relative contra-indications to the use of novel agents

Conflicts of interest

Dr. De Caterina receives consultant and speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Lilly; and research grants from AstraZeneca and BoehringerIngelheim. Dr. Husted receives advisory board or speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim and Bristol-Myers Squibb; and research grants from AstraZeneca, Bayer, Pfizer, Boehringer Ingelheim, and Bristol-Myers Squibb. Dr. Wallentin receives consultant fees from Athera, Behring, Evolva, Portola, and Roche Diagnostics; and institutional research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer, and Schering-Plough. Dr. Andreotti receives consultant or speaker fees from Amgen, Bayer, Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, and Eli Lilly. Dr. Huber receives lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, and The Medicines Company. Dr. Kristensen receives lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Pfizer, and The Medicines Company. Dr. Lip receives lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Sanofi-Aventis; and Consultant fees from Astellas, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Merck, Sanofi-Aventis, Portola, and Pfizer. Dr. Lip receives consultant fees from AstraZeneca, Bayer, Japa Records, MSD, Lilly Portugal, and Merck. Dr. L. Lip receives consultant fees from Bayer, Daiichi Sankyo, Pfizer, Eli Lilly, Merck, and The Medicines Company; and educational and research grants from Bayer, Boehringer Ingelheim, Eli Lilly, and Roche. Dr. Weitz receives consultant fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen Pharmaceuticals, Merck, Pfizer, Portola and Sanofi. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
Boxed Recommendations

Classes of Recommendations and Levels of Evidence are given according to the European Society of Cardiology (ESC) Practice Guidelines. For laboratory tests, Levels of Evidence are graded from A – full consensus based on converging data – to C – expert opinion.

General recommendations

- At the present time we do not recommend dosing algorithms based on pharmacogenetics in routine clinical care of VKA-anticoagulated patients [III – B]
- Dietary recommendations for VKA-treated patients should not be aimed at avoiding vitamin K-rich food items, but at trying to maintain a stable and not-too-low daily intake [IIa – B]
- For patients with unexplained instability of the international normalised ratio [INR], low-dose vitamin K supplementation may be beneficial and recommended [IIa – B], although such patients would probably nowadays be better treated with one of the new oral anticoagulants [IIa – A]
- We recommend that the INR be monitored closely when any medication or dietary supplement is added or withdrawn in VKA-treated patients [I – B]

Laboratory testing

- We advise ISI calibration with the local PT system (i.e. thromboplastin/coagulometer combination) for an adequate assessment of VKAs therapy [IIa – B]
- We advise that laboratories calibrate their own local system (i.e. instrument/reagent combination) using certified plasmas supplied by manufacturers or reference laboratories [IIa – B]
- We advise in favour of the use of the PT/INR Line to perform PT standardisation without the need for ISI calibration, using only five abnormal FDA-approved ECAA calibrant plasmas [IIa – B]

Use of VKA therapy

- We recommend starting VKA therapy with the expected VKA maintenance dose [stabilisation period], and adjust the daily dose according to the INR results from blood samples taken over the following 5–7 days [I – A].
- Because there is a delay before the onset of the clinical effects of warfarin, in the initial stages of treatment unfractionated heparin or a low-molecular-weight heparin should be given concomitantly if patients are thrombosis-prone or currently have active thrombosis. Once the patient has achieved the target INR, treatment is continued with a maintenance dose of VKAs [stable period] [IIa – B]
- High-quality VKAs treatment is defined as a TTR above 70% [IIa – B].
- The SAMeTT2R2 score may help to identify AF patients who would do less well on VKAs (with a poor TTR) and who would require additional interventions to achieve acceptable anticoagulation control, or be best treated with a new oral anticoagulant instead of a VKA [IIb-B]
- Patients must undergo periodic blood tests to ensure that their target INR is maintained [I – A]
- With long-term treatment, after a stabilisation period of 3–4 weeks, the interval between laboratory tests may be increased to 4–6 weeks or even longer in optimal conditions [IIa – B]
- Appropriately calibrated point-of-care testing PT monitors are acceptable in a clinical setting with respect to precision and accuracy [IIa – B]
- Self-monitoring and self-management of VKAs treatment are a safe option for suitable patients of all ages [I – A]
- Self-monitoring and self-management of VKAs therapy usually result in a better quality of life [IIa – A]

Clinical indications

Coronary heart disease

Primary and secondary prevention

- We advise against primary prevention of coronary heart disease with INR-adjusted warfarin due to uncertainties in the benefit-risk balance [III – B]
- For secondary prevention of coronary heart disease we advise against the use of VKA therapy alone or added to antiplatelet therapy at INR < 2.0 [III – B]
- For secondary prevention of coronary heart disease alone, we do not recommend VKA therapy instead of modern antiplatelet therapy [III – B]

Coronary bypass graft surgery

- We do not recommend routine VKA therapy for the maintenance of coronary bypass graft patency [III – B]

Percutaneous coronary interventions

- We do not recommend routine VKA therapy after percutaneous coronary interventions [III – B]

Atrial fibrillation

- We recommend anticoagulation with a VKA in all patients with “valvular” AF, defined as AF in the context of rheumatic moderate/severe mitral stenosis or in the context of mechanical heart valves [I – A]
- We recommend use of the CHA2DS2-VASC score for a comprehensive assessment of the thromboembolic risk in AF instead of the CHADS2 score [I – A]
- We recommend oral anticoagulants (either with well-controlled VKAs or with one of the new oral anticoagulants) in AF patients with a CHA2DS2-VASC score of ≥2 [I – A]
We recommend oral anticoagulants (either with well-controlled VKAs or with one of the new oral anticoagulants) in AF patients with a CHA2DS2-VASC score=1, based on patient’s values and preferences, balancing stroke risk against the potential for bleeding and/or the inconvenience of monitoring if VKAs are used [Iia – B]

In truly low-risk AF patients (CHA2DS2-VASC score=0), we recommend no antithrombotic therapy rather than aspirin [Iia – B]

Only where patients with AF totally refuse any oral anticoagulants (either with well-controlled VKAs or with one of the new oral anticoagulants) for stroke prevention, the use of antiplatelet therapy with aspirin-clopidogrel combination therapy (or less effectively, aspirin alone) may be considered [IIb – B]

The risk of major bleeding (and intracranial haemorrhage) with antiplatelet therapy should be considered as being similar to oral anticoagulants, especially in the elderly [Iia-A]

In patients with AF and stable vascular disease, we recommend that antiplatelet therapy should not be added to oral anticoagulants, given the limited additive efficacy and a major increase in serious bleeding [I-A].

Bleeding risk assessment

We recommend a bleeding risk assessment in all patients with atrial fibrillation [I – B]

We recommend the use of the HAS-BLED score over other bleeding risk scores to assess bleeding risk in AF populations [Iia – B]

We recommend caution and regular clinical review during use of oral anticoagulants (either with well-controlled VKAs or with one of the new oral anticoagulants) in AF patients with a CHA2DS2-VASC score of ≥1 and a HAS-BLED score of ≥3, as a high risk of bleeding should not constitute an absolute contraindication to oral anticoagulants [Iia – B]

Correctable risk factors for bleeding should be addressed, e.g. uncontrolled blood pressure, labile INR (if on a VKA), concomitant aspirin/NSAID use, alcohol excess, etc.

Valvular heart disease

We recommend VKA therapy (target INR, 2.5; range, 2.0–3.0) for patients with rheumatic mitral valve disease complicated by the presence of left atrial thrombus [I – A].

We suggest VKA therapy (target INR 2.5; range, 2.0–3.0) in patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 55 mm [Iia – C].

We recommend VKA therapy (target INR, 2.5; range, 2.0–3.0) for patients with rheumatic mitral valve disease complicated by atrial fibrillation, previous systemic embolism, or both [I – C]

We recommend anticoagulation with a VKAs in all patients with a mechanical heart valve [I – A]

We recommend adjusting the intensity of anticoagulation in such cases according to three features, namely the thrombogenicity of the prosthesis, the position (aortic vs mitral/tricuspid/pulmonary), and associated thromboembolic risk factors [I – B]

We recommend that antiplatelet drugs are not routinely prescribed for all patients with mechanical valves [Iib – B]

We recommend that the addition of antiplatelet drugs to anticoagulation is individualised, balancing risk and benefit, restricted to specific indications, and only combined with relatively low-intensity anticoagulation (INR <3.0) [Iia – B]

We specifically recommend against the routine addition of aspirin to VKAs in patients with a mechanical prosthetic valve in cases of co-existent coronary heart disease [Iib – B]

We recommend avoiding drug-eluting stents in patients with mechanical valves to shorten the duration of dual or triple therapy with one or two antiplatelet agents plus a VKAs [III – A]

We recommend that patients with bioprosthetic valves in the mitral position are treated with VKAs during the first three months after valve insertion [Iia – B]

Heart failure

We recommend against the routine use of a VKA in patients with heart failure in sinus rhythm [III – A]

VKA treatment may be considered in patients with HF in sinus rhythm in cases of a very low ejection fraction, severe clinical heart failure, ventricular thrombi, and prior cardio-embolic episodes [Iib – C]

References


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