Management of antithrombotic therapy in venous and arterial thromboembolism

Vink, R.

Citation for published version (APA):
Chapter 2

MANAGEMENT OF ANTICOAGULANT THERAPY FOR PATIENTS
WITH PROSTHETIC HEART VALVES OR ATRIAL FIBRILLATION

Roel Vink, MD*; Renée B.A. van den Brink, MD†; Marcel Levi, MD‡
From the Departments of Vascular Medicine*, Cardiology† and Internal Medicine‡,
Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

Hematology 2004; 9(1): 1-9
ABSTRACT

There is a wide array of recommendations for the management of anticoagulant therapy in patients with mechanical heart valves. Especially the optimal intensity of vitamin K antagonists (VKA) is an ongoing matter of debate. On the basis of several studies, recommendations for daily clinical practice can be made. In this review, we discussed the studies and the different guidelines. Guidelines for the prevention of thromboembolic complications in patients with atrial fibrillation are more stringent. VKA with a target INR between 2.0 and 3.0 is more effective in the prevention of stroke than aspirin, especially in the presence of risk factors for thromboembolism (age above 65, previous thromboembolism, history of hypertension and diabetes, enlarged left atrial diameter and left ventricular dysfunction). In the absence of clinical or echocardiographical risk factors for thromboembolism, patients may be safely treated with aspirin.
INTRODUCTION

Thromboembolic complications frequently cause morbidity and mortality in patients with mechanical heart valves or atrial fibrillation. The incidence of these thromboembolic complications can be reduced by anticoagulant treatment but this treatment carries the risk of severe and sometimes fatal bleeding. Although there are several studies on the efficacy and safety of anticoagulant treatment in patients with mechanical heart valves or atrial fibrillation, the optimal anticoagulant strategy for these conditions is still a matter of debate and several issues remain to be resolved. These issues comprise the intensity of oral anticoagulant therapy in patients with mechanical heart valves. Also, the evidence for withholding anticoagulation in patients with bioprosthetic valves is unclear. Another area of interest concerns the use of alternative antithrombotic agents than vitamin K antagonists (VKA) for the prevention of thromboembolism in patients with atrial fibrillation.

PROSTHETIC HEART VALVES

Mechanical heart valves
Several mechanisms are responsible for the thrombogenicity in patients with mechanical heart valves. It can be attributed to the foreign material of the valves and the changes in bloodflow around the valve with local turbulence and stasis. Both mechanisms lead to activation of the coagulation system and this can result in valve thrombosis and systemic embolism. Therefore these patients require life-long anticoagulation with vitamin K antagonists (VKA). Since there is a strong correlation between the intensity of VKA and the incidence of bleeding complications, a level of anticoagulation must be found at which this risk for bleeding is low, while optimal prevention of thromboembolic events is achieved.

Risk factors
The position and the type of the prosthetic valve influence the thromboembolic risk. The incidence of valve thrombosis and thromboembolism is higher in patients with mitral valve prostheses as compared to patients with an aortic valve prosthesis. This is presumably due to lower blood flow velocity over the mitral valve. Differences in bloodflow characteristics may also be responsible for the variation in thromboembolic properties of prosthetic valves.

In general, three different types of valves can be defined. The caged-ball valves (Starr-Edwards) showed the highest incidence of thromboembolic complications (2.5 per 100 patient-years). The difference in thromboembolic potential between tilting-disc
Chapter 2

valves (Bjork-Shiley, Medtronic Hall) and bileaflet valves (St Jude) is smaller. An overall incidence of 0.5 per 100 patient-years for tilting disc versus 0.7 per 100 patient-years for bileaflet valves. Whether these differences in thrombogenicity have consequences for the recommendation of the intensity of anticoagulation will be discussed below. The combination of mechanical heart valve and the presence of atrial fibrillation will further increase the risk for thromboembolism.

Trials of anticoagulation and antiplatelet agents

Current guidelines for anticoagulant treatment vary greatly among Europe and the United States. The variation between the guidelines is remarkable, since these recommendations are based on the same studies, which presumably have been interpreted differently. A number of trials have been conducted in which different levels of anticoagulant therapy were compared.

In 1990 Saour and colleagues published their randomised trial of 258 patients comparing a moderate intensity of VKA (target INR 2.65) with high intensity VKA (target INR 9.0). Thromboembolism occurred with similar frequency in the two groups (4.0 and 3.7 events per 100 patient-years). The total number of minor and major bleeding complications was more common in the high intensity group (12.1 episodes per 100 patient-years versus 6.2 episodes per 100 patient-years in the low intensity group, p<0.002). The difference in major bleeding episodes was not statistically significant between the groups.

In 1995 Canregieter et al. described, based on a discrepancy between targeted and achieved INR, the relation between the effectiveness of anticoagulation and the actually achieved intensities. The intensity-specific incidence was calculated as the number of events that occurred at a certain intensity of anticoagulation. The study included 1608 patients who were followed during 6475 patient-years. The INR was monitored by specialised regional anticoagulation clinics. The study showed that the optimal intensity of anticoagulation, resulting in the fewest events thromboembolic and bleeding events is achieved between INR levels of 2.5 to 4.9. The incidence of events rises sharply above or below this range. As a target range, they recommended an INR of 3.0 to 4.0 for both aortic and mitral valves, since in their study the lowest event rates occurred with an INR between 3.0 and 3.9 for aortic valves and between 3.0 and 4.0 for mitral valves. The risk of thromboembolic complications appeared to vary with the position of the valve. Valves in the aortic position had the lowest event rate (0.5 per 100 patient-years) as compared with valves in the mitral position (0.9 per 100 patient-years).

The AREVA-trial compared a target INR between 2.0 and 3.0 with an INR between 3.0 and 4.5 after single mechanical valve replacement with a bileaflet valve. Of the 380 patients, 364 patients had an aortic valve. The incidence of thromboembolic events was similar between the INR 2.0 to 3.0 and INR 3.0 to 4.5 groups: 1.9 and 1.7 events
per 100 patient-years, respectively. The rate of major bleeding complications did not differ between the two groups. Although the results of this study can be used as evidence for a low intensity regimen in bileaflet aortic prostheses, the results of the AREVA-trial must be interpreted with caution, since only low risk patients (e.g. without atrial fibrillation, no history of thromboembolism) were included in the study.

On the basis of several observational studies and the AREVA-trial, the American College of Chest Physicians (ACCP), the European Society of Cardiology (ESC) and the American Heart Association (AHA) decided to a regimen of moderate anticoagulation for patients with newer generation valves. This recommendation is in contrast with a recently published meta-analysis on the optimal intensity VKA in patients with mechanical heart valves. The analysis included 35 studies with 23,145 patients followed for more than 100,000 patient-years. The studies were classified into low intensity VKA (mean target INR of 3.0 or lower) or high intensity VKA (mean target INR above 3.0). The analysis showed that for patients with a newer generation aortic valve, high intensity results in a lower incidence of thromboembolic events (RR=0.73) with an increased bleeding risk (RR=1.23). In the mitral valve group, the incidence rate for thromboembolism was lower in the high intensity group (RR=0.74) without a significantly increased bleeding incidence (RR=1.08). The total number of thromboembolic and bleeding events, the most important parameter, was decreased in the high intensity group as compared to low intensity VKA therapy for both aortic and mitral valve prostheses (RR=0.94 and 0.84) respectively.

The studies previously discussed provide the best evidence for the recommendations, which are summarized in Table I. For patients with a low risk mechanical heart valve (defined as a bileaflet and Medtronic Hall, or second generation valve) the ACCP, ACC/AHA and the ESC-guidelines recommend low intensity VKA with a target INR between 2.0 and 3.5. For patients with an additional riskfactor or a valve with a high thromboembolic potential, a higher INR is advocated. The British guidelines recommend VKA with a target INR between 3.0 and 4.0, without risk stratification. The differences between the guidelines are less obvious for patients with a mechanical valve in the mitral position. An intermediate intensity (INR 2.5-3.5) is recommended by the ACCP and the ACC/AHA, whereas the BCSH and the ESC advocate a higher INR (3.0-4.5).
Table I. Overview of guidelines for the management of antithrombotic therapy in patients with prosthetic heart valves.

<table>
<thead>
<tr>
<th></th>
<th>ACCP	extsuperscript{49}</th>
<th>ACC/AHA	extsuperscript{50}</th>
<th>BCSH	extsuperscript{51}</th>
<th>ESC	extsuperscript{52}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mechanical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aorta</td>
<td>VKA 2.0-3.0 (bileaflet, MH)</td>
<td>VKA 2.0-3.0 (bileaflet, MH)</td>
<td>VKA 3.0-4.0</td>
<td>VKA 3.0-4.5 (first generation)</td>
</tr>
<tr>
<td></td>
<td>VKA 2.5-3.5 (AF)</td>
<td>VKA 2.5-3.5 (risk factor, St-Edw.)</td>
<td>VKA 2.5-3.0 (second generation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VKA 2.5-3.5 + aspirin 80mg/d (caged ball)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mitral</td>
<td>VKA 2.5-3.5</td>
<td>VKA 2.5-3.5</td>
<td>VKA 3.0-4.0</td>
<td>VKA 3.0-4.5 (first generation).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VKA 3.0-3.5 (second generation)</td>
</tr>
<tr>
<td><strong>bioprosthesi</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aorta</td>
<td>VKA 2.0-3.0 for 3 months, after 3 months aspirin 80-100 mg/d</td>
<td>VKA 2.5-3.5 for 3 months, after 3 months aspirin 80-100 mg/d</td>
<td>VKA 2.0-3.0 first 3 months, consider aspirin after 3 months</td>
<td>VKA 2.0-3.0 for 3 months, consider aspirin after 3 months</td>
</tr>
<tr>
<td>mitral</td>
<td>VKA 2.0-3.0 for 3 months, after 3 months aspirin 80-100 mg/d</td>
<td>VKA 2.5-3.5 for 3 months, after 3 months aspirin 80-100 mg/d</td>
<td>VKA 2.0-3.0 first 3 months, consider aspirin after 3 months</td>
<td>VKA 2.0-3.0 for 3 months, consider aspirin after 3 months</td>
</tr>
<tr>
<td>aorta with risk factor</td>
<td>VKA 2.0-3.0 long-term.</td>
<td>VKA 2.0-3.0 long-term.</td>
<td>VKA 2.0-3.0 long-term.</td>
<td>n.s.</td>
</tr>
<tr>
<td>mitral with risk factor</td>
<td>VKA 2.0-3.0 long-term.</td>
<td>VKA 2.0-3.5 long-term</td>
<td>VKA 2.0-3.0 long-term</td>
<td>VKA 2.0-3.0 long-term.</td>
</tr>
</tbody>
</table>

ACCP = American College of Chest Physicians  
ACC/AHA = American College of Cardiology/American Heart Association  
BCSH = British Committee for Standards in Haematology  
ESC = European Society of Cardiology  
VKA = vitamin K antagonists

Sec gen = St Jude, Medtronic Hall, Monostrut  
First gen = Starr-Edwards, Bjork Shiley  
MH = Medtronic Hall  
AF = atrial fibrillation  
n.s. = not specified
The role of antiplatelet therapy in patients with mechanical heart valves remains controversial. Two randomised trials evaluated the effects of adding aspirin to VKA treatment. Turpie et al showed that aspirin (100mg/d) in combination with VKA (INR 3.0-4.5) was associated with fewer thromboembolic events than VKA alone\(^6\). The study population included 370 patients with mechanical valves or tissue valves with an associated risk factor (atrial fibrillation or previous thromboembolism) and the patients were followed for a mean of 2.5 years. The rate of major bleeding was increased in the combination therapy group. Messchengieser and colleagues demonstrated in their trial that aspirin (100mg/d) in combination with VKA (INR 2.5-3.5) was as effective as VKA (INR 3.5-4.5) alone\(^7\). The results from these studies cannot be considered as sufficient evidence for recommending combination therapy. In exceptional cases of patients with thromboembolic complications despite adequate VKA therapy, the addition of antiplatelet therapy can be considered for the prevention of thromboembolic events.

**Bioprosthetic valves**

Bioprosthetic heart valves have a lower thromboembolic potential than mechanical heart valves. The risk of thromboembolism is mainly limited to the first three months after valve replacement, probably due to the lack of endothelialization of the newly implanted valve. In a study of Heras et al, the incidence of thromboembolic episodes was high in the first weeks after valve implantation for patients with aortic and mitral bioprosthetic valve replacements, especially when anticoagulation was not administered\(^8\). The rate of thromboembolism was 41% and 55% per year for aortic and mitral valve replacement, respectively, during the first 10 days postoperatively. After three months, the rate of thromboembolic events was decreased to 1.9%/year for aortic valves and 2.4%/year for mitral valves. This study indicates that during the first three months after tissue valve replacement the use of oral anticoagulants is justified.

In 1988 Turpie and colleagues showed in their randomised trial that during the first 3 months after tissue valve replacement a less intense anticoagulation regimen (INR 2.0 to 2.25) resulted in fewer bleeding complications than an INR between 2.5 and 4.0\(^9\). The number of thromboembolic complications did not differ between the two groups.

In contrast to the common beliefs and although there are several follow-up data on long-term results of bioprostheses the incidence of thromboembolic events without prolonged anticoagulation has never been properly established. Only a few cohort studies reported on incidences of thromboembolism in patients without atrial fibrillation and a tissue valve in the aortic position. The reported yearly incidences are low and varies between 0.2% and 0.5\(^{10,11}\). Data on the incidence of thromboembolic events in patients with tissue mitral valves without anticoagulant therapy are equally scarce, since the majority of the patients with tissue mitral valves received anticoagulant
therapy, reinstituted by their physician after discharge from the hospital. Thus, the recommendation that patients with bioprosthetic valves can safely withheld anticoagulant therapy are infact not based on adequate literature. Similarly, prescribing aspirin in this group of patients is also questionable. There is only one small observational study regarding the use of aspirin. One hundred forty-four patients with a porcine aortic bioprosthesis without atrial fibrillation were treated with aspirin 75mg/day and followed for a mean period of 2 years. The thromboembolic event rate was 1.3% per patient-year. The overall bleeding rate was 0.39% per patient-year. This uncontrolled cohort study with only a small number of participants showed that the use of aspirin is relatively safe\textsuperscript{12}. Although the evidence is weak, the ACCP and the ACC/AHA recommends the long-term use of aspirin (80 mg/day) for patients who do not have an indication for VKA.

Thus as shown in Table I, VKA are given during the first three months after bioprosthetic valve replacement until the valve has been endothelialized. The European guidelines consider to continue aspirin for both aortic and mitral valves. However, the American guidelines strongly recommend the long-term use aspirin in these patients. Patients with a bioprosthetic valve and the presence of a thromboembolic risk factor are recommended to use long-term VKA in the United States as well in Europe. Evidence for this recommendation is mainly derived from studies on the optimal therapy of atrial fibrillation, which showed that VKA is more effective than aspirin in this patient group (this is discussed later)\textsuperscript{13}.

**Anticoagulation in older patients with prosthetic valves**

With the growth of the older age population, there is a trend towards increased valve replacements in this group. In patients with a mechanical valve life long anticoagulant treatment is indicated, with the potential risk of complications related to anticoagulation. The advantage of the use of bioprosthetic heart valves is that the indication for long-term anticoagulation is less strong. There are several studies reporting on an increased risk of bleeding complications in elderly patients treated with VKA. In a cohort study of outpatients followed by the Dutch Thrombosis Service, a relative risk for major bleeding of 1.5 every 10 years increase above the age of 40 years was found\textsuperscript{14}. In a study of Fihn et al, only an age of 80 years or older appeared to be a risk factor for bleeding\textsuperscript{15}. On the other hand, the risk for thromboembolism seems to be increased in the elderly as well\textsuperscript{2}. Somewhat in contrast to these findings, Masters et al found in their cohort-study of 1245 patients no difference in thromboembolic and bleeding complications in the group above 65 years of age as compared to the patients younger than 65 years\textsuperscript{16}. These patients were treated with VKA with a target INR between 2.5 and 3.5.
Chapter 2

Pregnancy in patients with mechanical prosthetic valves

Since pregnancy induces changes in hemostasis predisposing to thromboembolic complications, it is essential that pregnant women with mechanical heart valves receive optimal anticoagulant therapy throughout the pregnancy period. However, there is a lack of reliable data on the efficacy and safety of anticoagulant therapy in these women. VKA carries the risk for embryopathy especially when it is administered in the early phase of pregnancy. Reported incidences varies between 0 and 67%\(^{17,18}\). VKA-associated embryopathy is thought to occur between 6 and 12 weeks of pregnancy and consists of nasal cartilage deformities. In addition, VKA crosses the placenta and therefore can cause fetal hemorrhage, in particular during delivery. Therefore, it can also not be used in the last 4-6 weeks of pregnancy.

The risk of embryopathy can be prevented when oral anticoagulants are substituted by heparin. Nevertheless, switching to unfractionated heparin during the first trimester can lead to an increased risk of thromboembolism and serious bleeding complications as shown by a study of Salazar et al\(^ {19}\). In their study, an adjusted dose of subcutaneous unfractionated heparin (UFH) was administered in the first trimester and in the last two weeks of gestation. An average dose of 8000 units every 8 hour to maintain the activated partial thromboplastin time between 1.5 and 2.5 times the control level. They followed prospectively 40 pregnancies in 37 women. Pregnancy resulted in live births in 22 cases. Two patients died as a result of valve thrombosis during adequate treatment with heparin. One patient died from a gastrointestinal bleeding while on VKA-therapy. In addition, there was one neonatal death due to cerebral hemorrhage.

Recently, low molecular weight heparin (LMWH) was considered as a potential alternative because it results in stable anticoagulation without the need for monitoring and dose adjustments and it may produce less bleeding than subcutaneous UFH. Although, there is only little evidence regarding the safety of LMWH in terms of prevention of valve thrombosis and embolism the use of LMWH is widespread\(^ {20}\). In conclusion, no method of anticoagulation is free of risk, and anticoagulant strategies must be based on a trade off between risks and benefits and on local experience. A reasonable approach consist of administration of UFH or LMWH in therapeutic dosage in the first trimester, then switch to VKA and followed by reinstitution of UFH or LMWH four weeks before delivery, or in low risk patients by adjusted-dose LMWH therapy throughout pregnancy\(^ {21}\).

Management of anticoagulation during non-cardiac surgery

There is no consensus about the optimal management of anticoagulation during the perioperative period for patients with artificial heart valves receiving VKA. Ideally, randomised controlled trials or large cohort-studies are needed to make guidelines for
daily clinical practice. Since these studies are not available, decisions should be made by quantifying the risk of thrombosis and bleeding of the various anticoagulation-strategies. The opinions from experts are diverse varying from temporary discontinuation of VKA a few days before surgery and reinstitution after surgery to complete coverage with intravenous unfractionated heparin (UFH) only shortly interrupted during the surgical procedure\(^2\). Temporary discontinuation of anticoagulants increases the risk for valve thrombosis and embolism. This risk is unknown because there are no data from patients without long-term anticoagulation, but may be higher than expected since the prothrombotic effect of the surgery itself and the rebound hypercoaguability phenomenon could increase the risk of thromboembolic complications. However, this has not been demonstrated clinically. On the other hand, continuation of anticoagulants perioperatively, or restarting too soon after surgery can cause serious bleeding. The risk for bleeding complications depends on patient-characteristics, type of intervention and the timing of stopping and restarting the heparin infusion.

The use of LMWH as an alternative agent in the perioperative period is now subject of prospective trials. The potential benefit is avoiding hospitalization solely for anticoagulation with intravenous unfractionated heparin. However, the half-life of LMWH is prolonged as compared to UFH and the clearance is not always predictable. This makes it difficult to time the last preoperative injection and therefore this strategy carries a certain risk for perioperative bleeding. Thus although there are no published trials showing that the use of LMWH in this setting is safe in terms of bleeding and thromboembolism, a more aggressive anticoagulant approach may be considered, especially since the case-fatality rate of thromboembolism is high.

**Atrial Fibrillation**

The prevalence of atrial fibrillation (AF) is related to age. In patients older than age 40 the prevalence of AF is 2.3% and in those older than 65 years 5.9%. Approximately 70% of the individuals with AF are between 65 and 85 years of age\(^2\). AF is an independent risk factor for stroke, and mortality in stroke patients with AF is higher than in those without AF\(^2\). The incidence of stroke in patients with AF increases by age, from 1.3% per year in those ages 50 to 59 years, to 5.1% per year by those ages 80 to 89 years\(^2\). The risk for stroke among patients with AF is estimated to be 5 times greater than that for comparable patients in sinus rhythm\(^2\).

Atrial fibrillation leads the loss of atrial contraction and to stasis of blood, which is most marked in the left atrial appendage. The rate of thromboembolism, especially stroke, is related to several clinical factors. Pooled data from large randomised trials give insight in these risk factors which are summarised in Table II\(^2\). The independent
clinical risk factors identified with multivariate analysis were age above 65 years, a previous thromboembolism, a history of hypertension and diabetes mellitus. Two transthoracic echocardiographic predictors of increased risk can be identified, i.e. an increased left atrial diameter and left ventricular dysfunction. Additional echocardiographic evaluation is useful, since almost 40% of patients with AF classified at low risk using clinical variables were found to be at higher risk on the basis of additional echocardiographic information\textsuperscript{28}. On the basis of these results, subgroups of patients with low risk for thromboembolism can be identified in whom a less intense anticoagulant strategy, with lower risk for bleeding but with optimal prevention of thromboembolic events, may be effective.

**Table II.** Risk factors for thromboembolism in patients with atrial fibrillation\textsuperscript{27,29,30}

<table>
<thead>
<tr>
<th>Risk factors for thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous thromboembolism</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Heartfailure</td>
</tr>
<tr>
<td>Age above 65 year</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
</tr>
<tr>
<td>Left atrium enlargement</td>
</tr>
</tbody>
</table>

**Trials of anticoagulation**

Several randomised controlled trials have been performed to evaluate the efficacy and safety of VKA and antiplatelets agents for the prevention of thromboembolism, especially stroke, in patients with AF. In 1994, data from five randomised trials comparing VKA or aspirin versus no treatment trials were pooled\textsuperscript{29}. Only 6% of the study population had a history of thromboembolism, therefore the results of this meta-analysis can be translated to recommendations for the primary prevention. The incidence of ischemic stroke in the placebo group was 4.5% per year as compared to 1.3% per year for patients treated with VKA. Overall, VKA decreased the frequency of ischemic stroke with 68%. A majority of the patients in the VKA group with ischemic stroke were not taking VKA at the time of the event or had an subtherapeutic INR. The relative risk reduction for patients taking aspirin is 38% as compared to the placebo group. Unfortunately, a direct comparison of the efficacy between VKA and aspirin was not performed. The annual frequency of major bleeding events was 1.3% in VKA-treated
patients, 1.0% in patients treated with aspirin and 1.0% in patients receiving placebo or no treatment.

One large trial for the secondary prevention of atrial fibrillation was performed (Table III). In the EAFT-trial, 1007 patients with a recent transient ischemic attack or stroke were randomised to VKA, aspirin or placebo\textsuperscript{31}. When patients had an absolute contraindication for VKA, they were randomised for aspirin or placebo. The incidence of ischemic and hemorrhagic stroke was 4% in the VKA-treated group versus 12% in the placebo group. Aspirin was more effective than placebo in the prevention of all strokes, although the difference was not statistically different (10%/year versus 12%/year, \( p=0.31 \)). In a direct comparison between VKA and aspirin, VKA were more effective than aspirin in the prevention of all strokes (hazard ratio 0.38, \( p<0.001 \)). However, patients with major stroke were excluded from the study, and it is possible that they are prone to hemorrhagic transformation after ischemic stroke when treated with anticoagulants.

Table III. Primary and secondary prevention of (ischemic) stroke in patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients (n)</th>
<th>RRR (%)</th>
<th>NNT (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention\textsuperscript{29*}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA vs placebo</td>
<td>2461</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>aspirin vs placebo</td>
<td>2036</td>
<td>36</td>
<td>- §</td>
</tr>
<tr>
<td>Secondary prevention\textsuperscript{31 †}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA vs placebo</td>
<td>439</td>
<td>68</td>
<td>12</td>
</tr>
<tr>
<td>aspirin vs placebo</td>
<td>782</td>
<td>11</td>
<td>53</td>
</tr>
<tr>
<td>VKA vs aspirin</td>
<td>455</td>
<td>67</td>
<td>14</td>
</tr>
</tbody>
</table>

RRR = relative risk reduction of a (ischemic) stroke; NNT = number needed to treat to prevent one (ischemic) stroke
* primary outcome ischemic stroke; † primary outcome ischemic and hemorrhagic stroke; § Not specified

Low risk and high risk patients

Patients with atrial fibrillation without one of the risk factors for stroke have an annual risk for stroke of 1.0\%\textsuperscript{29}. The SPAF-III-investigators have attempted to identify groups of patients who have a low risk of thromboembolism and who could be satisfactorily managed with aspirin in stead of VKA\textsuperscript{32,33}. Risk stratification was based on the results of the SPAF-I and SPAF-II-studies\textsuperscript{34,35}. Patients were classified as low risk patients based on the absence of four predefined thromboembolic risk factors: recent congestive heart failure, previous thromboembolism, systolic blood pressure greater than 160 mmHg, or female sex at age older than 75 years. These low-risk patients were treated with aspirin.
325mg per day. Patients with one or more risk factors were treated with adjusted-dose VKA (INR 2.0-3.0) or low intensity, fixed-dose VKA plus aspirin. The annual incidence of thromboembolism (ischemic stroke and systemic embolism) was 2.2% for low risk patients with aspirin, 1.9% for high risk patients with VKA and 7.9% for high risk patients with low dose VKA and aspirin. On the basis of these findings, it can be concluded that in patients with a low risk for thromboembolism treatment with aspirin is relatively safe and can be considered.

The SPAF-III study also identified patients with a high intrinsic risk for thromboembolism, with one of the above mentioned risk factors. A transoesophageal echocardiography (TEE) was performed in order to identify other mechanisms which may contribute to stroke in patients with atrial fibrillation. TEE was done within 3 months after these high risk patients were randomly assigned to adjusted dose VKA (INR 2.0-3.0) or combination therapy with low-dose VKA (INR 1.2-1.5) and aspirin.

Patients with dense spontaneous echocardiographic contrast assigned to combination therapy had an event rate of 18.2% per year and a relative risk of 2.7 compared with patients without dense contrast. Patients in the VKA group who had dense echocardiographic contrast had an event rate of 4.5% per year. The relative risk reduction was 75% compared with the combination therapy group. Complex aortic plaque was strongly associated with an increased risk for thromboembolism in patients assigned to low dose VKA and aspirin; the event rate was 15.8% per year in these patients compared with 4.0% per year in patients with VKA. In addition, the trial was stopped after an observation period of 1 year because the lack of efficacy of the low dose VKA and aspirin regimen.

**Intensity of anticoagulation in AF**

The optimal intensity of oral anticoagulation, defined as the intensity at which the incidence of both thromboembolic and bleeding complications is lowest, is a delicate equilibrium. Only one study has compared different intensities of oral anticoagulation in a randomised fashion. A target INR between 2.5 and 3.5 was compared with low intensity VKA therapy (INR 1.1-1.6) for the primary prevention of thromboembolism in patients with AF in general practice. The incidence of thromboembolism and major bleeding did not differ between the two groups. The small number of participants in the study and the low overall event rate limits the power to detect a difference. The EAFIT-investigators calculated INR-specific incidence rates for both ischemic and hemorrhagic events occurring in 214 patients. The authors conclude that the optimal level of anticoagulation lies between 2.0 and 3.9. However, a more precise analysis of the results shows that the lowest number of ischemic and hemorrhagic events occur at a INR-level between 2.0 and 2.9. Hylek et al. performed a case-control study of the lowest effective intensity of VKA. Seventy-four patients with AF and ischemic stroke were
identified and matched with 222 controls. An increase in the risk of stroke was observed below INR-values of 2.0. In contrast, an INR of 2.0 or greater not only reduces the frequency of stroke, but also its severity and the risk of death from stroke\(^\text{40}\). These findings provide evidence against the use of low intensity VKA and supports maximal protection with an INR between 2.0 and 3.0.

**Elderly patients with AF**

Despite the proven effectiveness and safety of oral anticoagulation for thromboembolism prophylaxis in AF, VKA remains underused, especially among the elderly (75 years and older), who are at the greatest risk of stroke and would likely benefit most from prophylactic anticoagulation. Due to the fear of the risk of bleeding, many physicians are reluctant to prescribe VKA therapy for patients with increasing age. VKA is used in only a minority of the patients. Physicians continue to prescribe aspirin, despite the lack of efficacy in this age group. An analysis of pooled data from 3 randomised trials did not show a benefit of aspirin compared to placebo in the age group above 75 year\(^\text{41}\). The rate of major bleeding while receiving VKA was 2.3% per year versus 1.1% per year for patients receiving aspirin\(^\text{42}\). But higher bleeding rates may occur in clinical practice, when there is less restrictive patient selection and less intense anticoagulation monitoring, although a recently published clinical review showed similar rates of stroke and major bleeding in patients in actual clinical practice compared to those treated with VKA in a randomised clinical trial setting\(^\text{43}\). Attempts to reduce the risk of bleeding by using low-intensity VKA plus aspirin have been associated with a four-fold increase in stroke compared to adjusted-dose VKA, without a decrease in the risk for bleeding\(^\text{33}\).

There are no clinical trials comparing VKA with aspirin in older patients. However a subgroup analysis of the SPAF-II study compared the efficacy of aspirin with VKA (mean INR 2.6) in 385 patients older than 75 years of age\(^\text{35}\). The mean age was 80 years with a mean follow up of 2 years. A history of hypertension was present in 52% of the patients. The VKA-assigned patients had a 1.2% lower rate of thromboembolism than the aspirin-assigned patients. (3.6% versus 4.8%). The total number of thromboembolism and intracranial bleeding was decreased in the VKA-group, although not significantly. Ezekowitz et al showed in their randomised trial comparing VKA (INR 1.4-2.8) with placebo, that in a subgroup of patients over 70 years of age, VKA prevented cerebral infarction without producing an excess of major bleeding\(^\text{44}\). Thus, although VKA is associated with a greater risk for bleeding, the risks do not offset the benefits in these older patients if VKA are carefully administered.
New anticoagulants

Clopidogrel is an ADP receptor antagonist that in combination with aspirin is indicated for the secondary prevention of cardiovascular events after acute coronary syndromes or percutaneous coronary interventions. In the CURE-study, the addition of clopidogrel to aspirin resulted in a 21% reduction of thromboembolic events\(^45\). In addition, there was a reduction in stroke in clopidogrel-treated patients. Although the pathological mechanism of stroke may differ in patients with AF, there is rationale that a combination of aspirin with clopidogrel conferred protection against thromboembolism. However this has not been evaluated in a randomised fashion.

The oral direct thrombin inhibitor ximelagatran inhibits the conversion of fibrinogen to insoluble fibrin. There is no need for dose titration or coagulation monitoring, which is an advantage and may increase the compliance. A recently published phase II study compared 3 dosages of ximelagatran (20, 40 or 60 mg twice daily) with VKA (INR 2.0-3.0) for the prevention of ischemic stroke in 257 patients with atrial fibrillation\(^46\). The aim of the study was to investigate the safety and tolerability and the treatment duration was 12 weeks. The total number of bleeding was low and comparable in all treatment groups. One ischemic stroke and one TIA occured in the ximelagatran group. One major bleed was observed in a VKA-treated patient. In the SPORTIF III trial ximelagatran 36 mg twice daily was compared with VKA (INR 2.0-3.0)\(^47\). This phase III study was conducted in 3407 patients with non-valvular atrial fibrillation. Patients were treated for between 12 and 26 months. The combined rates of thromboembolism, major bleeding and death was 4.6% in the ximelagatran group compared with 6.1% in the VKA group. Furthermore, the combined rate of major and minor bleeding was also significantly lower for ximelagatran compared with VKA (p=0.007).

Low molecular weight heparin (LMWH) has been evaluated for the treatment of acute stroke in patients with atrial fibrillation. In the HAEST-trial, LMWH (dalteparin 100 IU/kg, twice daily) was compared with aspirin 160 mg/day for the treatment of acute ischemic stroke in 449 patients\(^48\). The aim of the study was to investigate whether LMWH was superior to aspirin for the prevention of early recurrent stroke during the first 14 days. The frequency of recurrent ischemic stroke was 8.5 % in the LMWH group versus 7.5 % in aspirin allocated patients during the first 14 days. Other endpoints (cerebral hemorrhage, progression of symptoms within 48 hrs and death) also revealed no benefit of LMWH.

**CONCLUSION**

Lifelong anticoagulation with VKA is recommended in patients with mechanical heart valves. However, the optimal anticoagulant level is an ongoing matter of debate. On the
basis of several studies, recommendations for daily clinical practice can be made. These recommendations vary among Europe and United States. Guidelines for the prevention of thromboembolic complications in patients with atrial fibrillation are more stringent and evidence based. VKA with a target INR between 2.0 and 3.0 is more effective in the prevention of stroke than aspirin, especially in the presence of risk factors for thromboembolism (age above 65, previous thromboembolism, history of hypertension and diabetes, enlarged left atrial diameter and left ventricular dysfunction). In the absence of clinical or echocardiographical risk factors for thromboembolism, patients may be safely treated with aspirin.

**REFERENCE LIST**


