Long-term anticoagulant therapy in patients with coronary artery disease

S.E. Husted¹*, B.K. Ziegler², and A. Kher³

¹Department of Medicine and Cardiology, University Hospital of Aarhus, Tage Hansens Gade 2, DK-8000 Aarhus C, Denmark; ²Department of Clinical Pharmacology, University Hospital of Aarhus, Bartholinbygningen University of Aarhus, DK-8000 Aarhus C, Denmark; and ³Euthe´mis, 5-7 Av. du Générale de Gaulle, F-94160 Saint-Mandé, France

Received 7 January 2005; revised 12 December 2005; accepted 15 December 2005; online publish-ahead-of-print 9 January 2006

Secondary prevention of coronary events in coronary artery disease (CAD) patients with aspirin is generally accepted because of ease of administration, predictable safety, and proven efficacy. The use of long-term anticoagulant therapy with heparins, vitamin-K antagonists (VKAs), or thrombin inhibitors is, however, more controversial. During the last 40 years, several trials have been conducted in order to evaluate the role of anticoagulant therapy in patients with CAD as a protection against subsequent death and thrombo-embolic complications. The conducted trials are heterogeneous in many ways, concerning comparative medications, patient populations, endpoints and follow-up, which makes a standardized recommendation on the basis of these studies difficult. This review is an overview of the largest and best studies on this topic and discusses the scientific background for a possible use of VKA or an alternative anticoagulant treatment in CAD patients, looking at both the beneficial effects and the risk of bleeding.

KEYWORDS
Anticoagulation; Warfarin; Coronary artery disease; Prophylaxis; AMI

Introduction

Secondary prevention of cardiovascular events in coronary artery disease (CAD) patients with aspirin is generally accepted and used in contrast to long-term anticoagulant therapy, where the evidence is more heterogeneous and the use more controversial. The drugs used to assess this question are mainly vitamin-K antagonist (VKA), oral thrombin inhibitors, unfractionated heparin (UFH), and low-molecular-weight heparin (LMWH).

The VKAs exert their anticoagulant effect by interfering with the γ-carboxylation and thereby activation of the vitamin K-dependent coagulation factors II, VII, IX, and X.¹ UFH is a heterogeneous mixture of glycosaminoglycans. The anticoagulant effect is mediated by the binding of UFH to antithrombin (AT), which converts AT from a slow to a very rapid inhibitor of activated coagulation factors. The binding to AT is through a unique glucosamine unit, which is contained within a pentasaccharide sequence. LMWHs are derived from UFH by chemical or enzymatic depolymerization.² As the inactivation of factor Xa only requires the presence of the high-affinity pentasaccharide, whereas at least 18 saccharides are required for thrombin inhibition, the LMWHs have reduced AT activity relative to anti-Xa activity. Furthermore, when compared with UFH, the LMWHs have longer half-lives and a better bioavailability after subcutaneous injection.

The oral thrombin inhibitors are, unlike heparin, not bound to plasma proteins and can inactivate both fibrin-bound thrombin and fluid-phase thrombin.³ Over the past 40 years, many clinical trials have been conducted to demonstrate the effectiveness of VKA therapy in patients with CAD.⁴ Despite the fact that a beneficial effect of VKA compared with placebo has been demonstrated, the role of these anticoagulant agents remains controversial because of several reasons. First, VKA is, compared with aspirin, inconvenient to use because of a narrow therapeutic window and concerns regarding major bleeding. Second, the published studies have randomized different subpopulations of patients with acute coronary syndromes (ACSs), i.e. ST-segment elevation acute myocardial infarction (STEMI), non-ST-segment elevation acute myocardial infarction (NSTEMI), and unstable angina pectoris (UAP), and therefore, the target population for anticoagulant therapy may be difficult to identify. Third, none of the investigations so far has studied the patient populations identified on the basis of the new diagnostic standard for myocardial infarction (MI), which is based on a rise in biochemical markers for myocyte necrosis.⁵ Given the fact that both platelet activation and thrombin generation are involved in the pathogenesis of intracoronary thrombi, a number of studies have assessed the clinical benefit of combined VKA and aspirin in patients with CAD. Moreover, the complexity of VKA therapy has called for more simple treatment regimens, and this has lead to the introduction of oral direct thrombin inhibitors as a possible...
alternative for patients with thrombo-embolic diseases including ACS. Both the oral thrombin inhibitors UFH and LMWH have been assessed in this review to complete the picture.

The aims of this paper are to determine the therapeutic impact of anticoagulant therapy administered for at least 3 months with or without aspirin in patients with established CAD in the light of the existing data.

Studies and meta-analysis have been selected by an extensive search in EMBASE and Medline using the following keywords: anticoagulation, vitamin-K antagonist, oral thrombin inhibitor, unfractionated heparin, coronary artery disease, acute coronary syndrome, unstable angina, and acute myocardial infarction.

Bibliographies of the obtained studies were cross-checked where necessary. Only studies where a controlled, randomized design was used were included.

**Anticoagulant agents vs. control**

**MI and anticoagulant agents**

**Unfractionated heparin**

Only one trial was performed using low-dose UFH. A total of 728 patients was recruited 6–18 months after MI and randomly assigned to 12 500 IU daily subcutaneously or no treatment for an average of 23 months. The re-infarction rate was significantly lower in the UFH group (1.3%) when compared with the control group (3.5%), and mortality was reduced by 48% on drug-efficacy analysis ($P < 0.05$) and by 34% on intention-to-treat analysis (NS). Cardiovascular mortality was reduced by 33% and not statistically significant (NS). Only minor adverse events were observed.

**Vitamin-K antagonists**

A large number of clinical trials have been conducted over the past four decades using long-term VKA treatment after MI. From 1962 to 1980, 15 controlled clinical studies have been performed, but many of these trials were poorly designed and of insufficient sample size. However, pooled data from nine studies suggested that VKA reduces the mortality rate from 0.79 deaths/100 man-months to 0.63 deaths/100 man-months, which was considered to be significant. From the beginning of the 80s, three randomized, double-blind, placebo-controlled trials were published. These studies were performed according to more stringent methodological requirements. The main results of these trials are summarized in Table 1.

(i) The Sixty Plus Trial entered patients older than 60 years (85% males) and treated with VKA therapy for at least 6 months. The patients were randomly allocated in a double-blind manner to either continued active treatment or matching placebo. All patients were followed for 2 years. The total mortality was not significantly reduced, but the incidence of recurrent MI was more than halved in the treated group ($P = 0.0005$). Haemorrhagic events occurred in 35 and four patients retrospectively in the VKA and placebo group, with four and one fatal intracranial bleeding in the two groups (NS), respectively.

(ii) The Warfarin, Aspirin Reinfarction Study (WARIS) trial was a multicentre, double-blind study, randomizing patients to either warfarin or placebo after a mean of 27 days after their MI. Follow-up was 37 months. All-cause mortality, total re-infarction, and total stroke rates were significantly reduced with the warfarin treatment. Eight major bleeding complications and three fatal intracranial haemorrhages occurred in the warfarin-treated group. Thus, serious bleeding was noted in 0.6% of the warfarin-treated patients per year and in none of the patients in the placebo group, but it is not stated in the paper whether it was significant.

(iii) In the Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial, patients were randomly assigned in a double-blind manner to VKA or placebo within 6 weeks of discharge after an MI. The mean follow-up was 37 months. There were fewer deaths among patients treated with VKA, but the difference was not statistically significant. However, VKA treatment led to significant reductions in recurrent MI and cerebrovascular events. Major bleeding complications were significantly increased in the VKA group when compared with that in the placebo group (1.5 vs. 0.2%, Hazard ratio 9.05, 95% CI 3.9–21.0).

**Unstable CAD and anticoagulant agents**

Anticoagulant therapy has not been tested extensively for secondary prevention after an episode of unstable CAD. Two trials have been carried out with VKA and one with LMWH.

(i) In the Combined Antithrombotic Therapy in Unstable Rest Angina and Non-Q-wave Infarction in Nonprior Aspirin Users (ATACS) trial, patients received aspirin alone or aspirin + iv UFH for 3–4 days, followed by warfarin (INR = 2–3) for 12 weeks. At day 14, there was a significant reduction in the incidence of death, MI, or recurrent angina in the combination group when compared with the aspirin group, 10.5 vs. 27.5%
The main objective of the Organization to Assess Strategies for Ischemic Syndromes-2 (OASIS-2) trial was to test hirudin against UFH for 7 days in 10,141 patients with NSTE MI and UAP, who were receiving aspirin. In a predefined substudy, 3712 patients were randomized 12–48 h after inclusion to VKA (INR = 2–2.5) + aspirin or aspirin alone for 5 months. The incidence of cardiovascular death, MI, and stroke was 7.6% in the VKA + aspirin group and 8.3% in the aspirin group (NS). There was a significant increase in the risk of major and minor bleedings with VKA (P < 0.05). In a second step, countries participating in the trial were divided into good or poor compliers, on the basis of more or less than 70% of patients still receiving the study drug at 35 days. There was a significant reduction in the earlier composite endpoint with VKA in the good-complier countries (6.1 vs. 8.9%, P = 0.02) and little difference in the poor-complier countries (7.8 vs. 9.0%, ns).

The Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease (FRISC II) study was a prospective, randomized, parallel-group, multicentre trial. A factorial design was applied to compare invasive vs. non-invasive management and extended vs. acute-phase dalteparin treatment. All patients received aspirin. In all, 2267 subjects were included in the non-invasive arm of the trial. At day 30, the incidence of death or MI was 3.1% in the dalteparin group when compared with 5.9% in the placebo group, giving a significant relative-risk (RR) reduction of 47% (P = 0.002). The results at 3 months demonstrated a 19% RR and 1.3% absolute-risk reduction in death or MI in the dalteparin group, which was not statistically significant. However, there was a significant absolute-risk reduction in death, MI, or revascularization of 4.3% (P = 0.031). An increased risk of bleeding complications with extended dalteparin treatment (2.2 vs. 1.2%) was considered acceptable in view of the clinical benefits. No additional beneficial effect was noticed during 3 months of dalteparin treatment in patients undergoing early revascularization.

Combination of VKA and aspirin

Several studies have compared combined VKA + aspirin with aspirin alone. These studies were based on the assumption that the anticoagulant effect of VKA combined with the antiplatelet effect of aspirin may enhance antithrombotic efficacy when compared with either drug alone. The main results from these trials are summarized in Table 2.

Combination therapy with low-dose aspirin + low-intensity VKA vs. low-dose aspirin alone

(i) The Coumadin Aspirin Reinfarction Study (CARS) compared aspirin alone (160 mg/day) with warfarin (fixed dose 3 mg/day) + aspirin (80 mg/day) and warfarin (fixed dose 1 mg/day) + aspirin (80 mg/day) in a double-blind fashion. In this trial, patients with a mean age of 59 years were included 3–21 days after an MI. The study was prematurely stopped, as the Data and Safety Monitoring Committee decided that a statistically significant difference would not emerge between the treatment groups with additional recruitment or follow-up. The median follow-up was 14 months.

(ii) The Combined Hemotherapy and Mortality Prevention (CHAMP) study was an open-label study comparing aspirin alone (162 mg/day) with aspirin (81 mg/day) + warfarin. The study enrolled patients within 14 days of an acute MI with a median age of 62 years. The study demonstrated that in post-MI patients, warfarin therapy at a mean INR of 1.8 combined with low-dose aspirin did not add additional clinical benefit when compared with aspirin monotherapy.

(iii) In the Fixed Low-dose Warfarin added to Aspirin in the Long-term after Acute Myocardial Infarction (LoWASA), patients with MI were randomized to receive 1.25 mg of warfarin + 75 mg of aspirin daily or 75 mg of aspirin
Combined therapy of low-dose aspirin + moderate-intensity VKA vs. high-intensity VKA alone vs. aspirin alone

In three randomized, open-label studies on post-MI patients, three groups of patients were allocated to low-dose aspirin or high-intensity VKA or low-dose aspirin + moderate-intensity VKA.

The primary efficacy endpoint in two of the studies was a composite of death, non-fatal re-infarction, or non-fatal stroke, and the main results are summarized in Table 3.

(i) The ASPECT-2 trial randomly allocated patients (87% with MI and 13% with UAP) to low-dose aspirin alone (80 mg/day) or low-dose aspirin (80 mg/day) + moderate-intensity VKA or high-intensity VKA at a median time of 7 days from the index coronary event. The study was terminated early because of slow recruitment of patients. Significantly fewer patients in the VKA and combination group reached the primary endpoint of MI, stroke, or death than in the aspirin group with hazard rates of 0.55 (95% CI 0.33–0.80), 0.50 (95% CI 0.27–0.92), respectively, both with P-value of 0.03. The incidence of major bleeding was not significantly different between the three groups.

(ii) The WARIS II enrolled patients with mean time from onset of MI of 6 days and a mean age of 60 years. Patients were randomly assigned to receive warfarin or aspirin (160 mg/day) or aspirin (75 mg/day) + warfarin. STEMI was present in 60% of the patients, and one-third of the patients underwent CABG or PCI. In both groups receiving warfarin, the incidence of the primary endpoint (death, non-fatal re-infarction, or thrombo-embolic stroke) was significantly reduced. There was a significant 44% RR reduction (P < 0.001) in re-infarction rate and 48% (P < 0.03) in thrombo-embolic stroke rate, but no difference in death rate in the combination group when compared with the aspirin alone group. There was a significantly higher risk of major bleeding complications in the two groups receiving warfarin than in the group receiving aspirin alone (P < 0.001).

(iii) In the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis-2 (APRICOT-2) trial, 308 patients with a MI had an angiogram performed within 48 h after the thrombolytic therapy. Patients with an open infarct-related artery were randomly assigned to aspirin alone or to a 3-month combination of aspirin with moderate-intensity VKA (INR 2.0–3.0). Angiographic and clinical follow-ups were assessed at 3 months. Reocclusion was the primary endpoint, and this (≤ TIMI grade 2 flow) was observed in 15% of patients receiving aspirin and coumarin when compared with 28% of patients receiving aspirin alone (RR 0.55, 95% CI 0.33–0.90, P < 0.02). Survival rates free from re-infarction and revascularization were 86 and 66%, respectively (P < 0.01). Bleeding (both major and minor) was infrequent: 5 vs. 3% (NS).

Low-dose aspirin in combination with an oral direct thrombin inhibitor (Ximelagatran) vs. low-dose aspirin alone

The direct thrombin inhibitor Ximelagatran, which is a prodrug, can be administered orally in a fixed daily dose without monitoring of the anticoagulant response. The active metabolite melagatran reversibly and directly inhibits thrombin.

(i) The Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Infarction (ESTEEM) trial was a placebo-controlled, double-blind, multicentre, dose-guiding study enrolling 1883 patients within 14 days of a MI. About 50% had Q-wave MI. All patients received aspirin 160 mg/day, and they were randomized to oral
Ximelagatran at doses of 24, 36, 48, or 60 mg twice daily or placebo for 6 months. The primary efficacy outcome was the occurrence of all-cause mortality, non-fatal MI, or recurrent myocardial ischaemia. The mean age of the patients was 69 years. Ximelagatran reduced the risk for the primary endpoint from 16.3 to 12.7% (P = 0.04) with no efficacy difference between the individual doses. Major bleeding was rare in all groups with an overall occurrence of 1.8% in Ximelagatran-treated patients when compared with 0.9% in the placebo group (NS). A dose-related increase in the concentration of alanine transaminase, which was reversible after discontinuation of therapy, was noticed in 6.5–13% of patients during Ximelagatran treatment.

Combination of VKA and aspirin in patients undergoing coronary intervention

In the FRISC-II, a double-blind trial, patients with unstable CAD and early intervention were randomized to receive either dalteparin in a weight-adjusted dose subcutaneous for 3 months in combination with aspirin or aspirin alone. Dalteparin did not reduce ischaemic events following revascularization.

Only one major study has randomized patients with CAD undergoing PCI to assess the therapeutic effect of VKA combined with aspirin in this setting.

(i) The Balloon Angioplasty and Anticoagulation Study (BAAS) was an open, randomized trial with 1058 patients, designed to evaluate the effect of VKA (INR = 2.1–4.8) in addition to aspirin (100 mg/day) on the incidence of early- and late-cardiovascular events in patients with symptomatic CAD planned to undergo PCI. The VKA treatment was started before the PCI (in >80%, VKA was started ≥3 days before the procedure) and continued for 6 months. The primary efficacy endpoint was the composite of death, MI, target-vessel revascularization, and stroke at 1 year. At 30 days, the incidence was 3.4% in the combination group and 6.4% in the aspirin group (P = 0.04). At 1 year, the incidence was 14.3 and 20.3%, respectively (P = 0.01). The incidence of major bleeding during hospitalization was 1.3 and 0.2%, respectively (NS). At the start of PCI, the mean INR was 2.7 ± 1.1, and it was 3.0 ± 1.1 during follow-up in the VKA-treated patients. In patients receiving a stent, VKA was discontinued and treatment with ticlopidine was initiated.

Discussion

Despite several large randomized trials demonstrating the beneficial effect of VKA in CAD, the target patient population and the optimal treatment regimen are still a subject of debate. Thus, definition of the optimal duration of therapy and identification of subsets of patients with the optimal risk–benefit profile are relevant clinical issues.

The scientific basis for VKA therapy in secondary CAD prevention is the direct involvement of coagulation proteases in thrombotic, inflammatory, and cellular regulatory processes in atherothrombosis. Arterial thrombosis, though traditionally viewed as a platelet-dependent process, occurs also through a variety of other activated cell surfaces including endothelial cells and monocytes, which are tissue-factor expressing cells. Leucocytes can adhere to activated endothelial cells and can travel through several pathways also promote thrombosis.

Secondary prevention of coronary events in CAD patients with aspirin is generally accepted because of ease of administration, predictable safety, and proven efficacy. Patients with CAD may be ‘aspirin resistant’ and may need additional antithrombotic therapy. These patients cannot be identified by routine laboratory tests, but it has been demonstrated that aspirin users compared with non-aspirin users among patients with ACS have a higher incidence of death and MI at 30 days and at 6 months. This may be one of the explanations for the additional beneficial effect of anticoagulant treatment in combination with aspirin.

Adding clopidogrel to aspirin treatment in patients with non-ST-segment ACS was shown to reduce ischaemic events in a mean treatment period of 9 months, and the effect could be demonstrated both in patients with a low- and high-risk profile and in those treated with coronary intervention. Clopidogrel in combination with aspirin has not yet been tested against VKA in patients with CAD.

Anticoagulant therapy in CAD was evaluated in 1999 in the meta-analysis by Anand and Yusuf, who concluded, especially on the basis of the two major trials WARIS and ASPECT, that high- and moderate-intensity VKA therapies are effective in reducing MI and stroke but increase the risk of bleeding. In addition, the analysis indicated that in the presence of aspirin, low-intensity VKA therapy does not appear to be superior to aspirin alone. This was later confirmed in the major CHAMP and LoWASA trials.

The two large, newer trials, WARIS-II with target INR 2.8–4.2 and ASPECT-2 with target INR 3–4, showed that monotherapy with VKA is superior to aspirin alone in the

Table 3 Results of trials comparing moderate-intensity VKA + aspirin vs. aspirin alone vs. high-intensity VKA after MI

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Aspirin (160 mg)</th>
<th>Warfarin (INR 2–2.5) + Aspirin (75 mg)</th>
<th>Warfarin (INR 3–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WARIS-II (n = 3630)</td>
<td>4 years</td>
<td>20</td>
<td>15</td>
<td>16.7</td>
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<tr>
<td></td>
<td></td>
<td>0.15</td>
<td>0.52</td>
<td>0.58</td>
</tr>
<tr>
<td>ASPECT-2 (n = 999)</td>
<td>1 year</td>
<td>9</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
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</tbody>
</table>

ASA, acetylsalicylic acid.

*13% of the patients in ASPECT-2 had unstable angina.
prevention of death, (re)infarction, and stroke. In WARIS-II with about 1200 patients in each group, the risk of major bleeding complications was increased from 0.17 to 0.68% per treatment-year (P < 0.001).

In both WARIS-II and ASPECT-2, VKA (INR = 2–2.5) in combination with aspirin was also evaluated and was in both studies superior to aspirin alone but with a higher rate of major bleeding complications—in WARIS-II 0.57% per treatment-year.

Although these two studies included both patients with Q-wave and non-Q-wave MI as well as UA (only in ASPECT-2), the studies do not allow for separate analyses of these subgroups of ACS patients. Only in the OASIS-2 study,12 long-term treatment with VKA (INR = 2–2.5) in combination with aspirin has been evaluated against aspirin alone in patients with UA and NSTEMI, and no difference could be demonstrated.

In the recent phase 2 ESTEEM study, Ximelagatran significantly reduced ischaemic events when compared with placebo in patients with recent MI.25 In this trial, the recent recommendations from The Joint Committee of the European Society of Cardiology and American College of Cardiology were used, stating that all patients, who have detectable levels of cardiac troponin as a result of myocardial ischaemia, should be diagnosed as having an MI. This definition of MI has not been used in any VKA trial.

In recent years, more and more patients with ACS have a coronary intervention immediately or early in the course of the disease. In the FRISC II study, extended anticoagulant treatment with dalteparin for 3 months following early coronary intervention in patients with UA or NSTEMI did not show additional benefit.15 Patients treated with a stent received either ticlopidine or clopidogrel. In the BAAS trial, VKA treatment in combination with aspirin was superior to aspirin alone in CAD patients treated with PCI and with pre-procedural initiation of the antithrombotic therapy.26 Concomitant treatment with ticlopidine or clopidogrel was not allowed. It is unsettled whether or not VKA treatment is effective and safe in ACS patients receiving a modern invasive and antithrombotic regimen.

In conclusion, current evidence does not support the routine use of moderate- to high-intensity VKA as an alternative or supplement to aspirin in high-risk ACS patients in order to prevent ischaemic events at the cost of increased risk of bleeding. None of the studies published so far has evaluated VKA when compared with newer antiplatelet agents such as clopidogrel, and VKA in combination with such effective antiplatelet drugs needs to be examined in order to define effectiveness in relation to bleeding risk, before these drugs can be combined routinely.

The use of VKA in ACS patients treated immediately or early with coronary intervention and modern antithrombotic treatment regimens need evaluation before any recommendations can be given in this setting, which is becoming more and more routinely used. Furthermore, the effect of VKA in different subgroups of ACS patients is not clear from the available data in the literature and the impact of a change in the definition of MI on VKA treatment effect and risk is unknown.

Because of these shortcomings, the use of VKA in CAD patients is still limited and well-designed clinical trials including ACS patients receiving modern-treatment regimens like intervention and clopidogrel are highly needed. If Ximelagatran or other oral direct inhibitors of coagulation are proved to be safe and effective in phase III trials, they (it) may replace VKA.

**Conflict of interest:** none declared.

**References**


