The following 2 case presentations illustrate the range of considerations when formulating plans for oral anticoagulation in patients with acute coronary syndromes.

Case A
A 59-year-old patient presented within 5-hours of the onset of an electrocardiographic wave segment (ST) elevation anterior myocardial infarction and was treated with the accelerated dose regimen of alteplase, adjunctive unfractionated heparin, aspirin, and a β-blocker. The maximum isoenzyme of creatine kinase with muscle and brain subunits was >10 times the upper limit of normal. At day 4, echocardiography revealed a mass suggestive of a mural left ventricular thrombus and important apical wall motion abnormalities. ACE inhibition therapy was initiated. To reduce the risk of systemic embolization, heparinization with a target activated partial thromboplastin time of 1.5 to 2.0 times control was started, followed by 6 months of dose-adjusted warfarin, target international normalized ratio (INR) 2.5 to 3.5 (Table 1).

Case B
A 66-year-old diabetic patient, taking aspirin daily because of a prior transient ischemic attack, presented with chest pain at rest and dynamic ST depression >1 mm. He recovered from the acute phase after treatment with low-molecular-weight heparin, nitroglycerine, aspirin, and β-blocker therapy. Cardiac markers remained negative. During the convalescence period, no recurrent chest pain occurred, and exercise testing was negative with respect to symptoms and electrocardiographic signs of ischemia. Before discharge, dose-adjusted medium-intensity oral anticoagulation therapy (target INR, 2 to 3) was started in addition to aspirin (80 mg daily) as a strategy for secondary prevention of death, (re)infarction, and stroke.

Background
Notwithstanding the improvements in the secondary prevention of acute coronary syndromes, death and (re)infarction occur in ~10% to 15% of patients in the 4 to 6 weeks after presentation despite the use of aspirin. Interestingly, increased activity of the coagulation cascade has been reported up to 6 months after the index event. In addition, raised concentrations of factor VII are associated with both initial and recurrent ischemic events. These observations stimulated renewed interest in the potential benefit of oral anticoagulants.

The INR has replaced the nonstandardized prothrombin time and quick tests, and INR monitoring by patients is now a new feature in clinical practice. Several trials have evaluated a combined regimen of aspirin with dose-adjusted coumarins, 2 of which also addressed the direct comparison of both agents alone. In view of these developments, the present report forms an update on the role of oral anticoagulation therapy in acute coronary syndromes with the emphasis on secondary prevention and its additional effect in combination with aspirin.

Pathophysiological Rationale
The process of coronary thrombosis can be divided into 3 major steps: (1) vascular injury with exposure of the thrombogenic subendothelial surface; (2) adhesion and aggregation of platelets; and (3) formation of a fibrin-rich clot.

Exposure of subendothelial collagen not only activates platelets but also the coagulation system (Figure 1). As a result, prothrombin is cleaved into thrombin by prothrombinase (factor Xa, Va, and phospholipids). Thrombin is a potent platelet activator, a process not inhibited by aspirin or clopidogrel. In addition, thrombin activates important cofactors (V and VIII) for coagulation and is the key factor in the process of fibrin clot formation. Not only does it cleave fibrinogen into fibrin, it also activates factor XIII, which...
results in improved clot strength with more resistance to endogenous and exogenous fibrinolysis.

In view of the above, an antithrombotic regimen of both antiplatelet and antithrombin therapy could potentially have an additional impact when compared with a regimen of antiplatelet therapy alone (Figure 1). This favors the combination of aspirin with either unfractionated heparin, low-molecular-weight heparin, or a direct antithrombin in the initial hospital treatment phase in patients with acute coronary syndromes.11–13 After hospital discharge, recurrent ischemic events are not infrequent, and in light of the demonstrated persistent increased coagulant activity, prolonged oral anticoagulation after hospitalization might be beneficial.

**Pharmacology**

Oral anticoagulants such as warfarin act through interference with the vitamin K–dependent production of coagulation factors II, VII, IX, and X, which are produced by the liver (Figure 2). In addition, proteins C and S, regulatory anticoagulants, are also produced in a biologically less-active form (Figure 2). In addition, proteins C and S, regulatory anticoagulants; UFH, unfractionated heparin; and LMWH, low-molecular-weight heparin.

**Clinical Efficacy**

**Primary Prevention**

Dose-adjusted low-intensity warfarin (target INR, 1.3 to 1.8) has been shown to reduce the risk of ischemic heart disease to

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**TABLE 1. Established Indications for Oral Anticoagulant Therapy and Recommended Therapeutic Range**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Target INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis</td>
<td>INR 2.0–3.0</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction*</td>
<td>INR 2.5–3.5</td>
</tr>
<tr>
<td>Mechanical prosthetic valve (high risk)</td>
<td>INR 2.0–3.0</td>
</tr>
<tr>
<td>Bileaflet mechanical valve in aortic position</td>
<td>INR 2.0–3.0</td>
</tr>
</tbody>
</table>


*As demonstrated in case A.
an extent similar to 75 mg of aspirin. Interestingly, warfarin (mean INR, 1.5) primarily reduced fatal events and aspirin primarily reduced nonfatal myocardial infarction. The combination of warfarin and aspirin had additional beneficial impact but increased fatal strokes and minor bleeding. The use of either agent alone was associated only with more minor bleeding. Similar to primary prevention studies with aspirin, the benefit of oral anticoagulant therapy in primary prevention is confined to high-risk men, with little data available for women.

Secondary Prevention

Monotherapy Versus Control

Oral anticoagulation is one of the oldest strategies for secondary prevention of ischemic heart disease. After a large number of controlled trials in the 1960s, 2 large double-blind placebo-controlled randomized trials in the early 1990s unequivocally demonstrated the efficacy of full-intensity anticoagulation (INR, 2.8 to 4.2) at the cost of a 4-fold increased risk of major bleeding.17,20,21

Monotherapy Versus Aspirin

Given its ease of administration and favorable safety profile, aspirin has become the initial antithrombotic agent of choice in acute coronary syndromes. Meta-analysis of the few small trials comparing moderate-to-high intensity anticoagulation versus aspirin did not demonstrate a difference in efficacy, whereas bleeding was lower with aspirin.17 Interestingly, the ASPECT-2 (target INR, 3 to 4) and WARIS-2 (target INR, 2.8 to 4.2) trials both reported that full-intensity anticoagulation as monotherapy was superior to aspirin alone in the secondary prevention of death, (re)infarction, and stroke.9,10 Thus, high-intensity oral anticoagulation seems an effective alternative for aspirin in the setting of well-organized frequent INR monitoring.

Combination Therapy Versus Aspirin Alone

Oral anticoagulation therapy at medium-high and low intensity combined with aspirin has been tested (Table 2). A combination of medium-high intensity oral anticoagulation plus aspirin seems promising17 whereas fixed-dose, low intensity does not improve clinical outcome.22 Since the start of the new millennium, 4 trials with a target INR >2 have been completed, 3 involving patients with myocardial infarction8–10 and 1 that primarily included patients with unstable angina.6 APRICOT-2 and ASPECT-2 were performed in the Netherlands8,9 and WARIS-2 was performed in Norway,10 countries that are known for the high quality of their anticoagulation clinics. ASPECT-2 was unfortunately prematurely discontinued because of slow recruitment. Although underpowered, a significant clinical benefit for the combined antithrombotic regimen (INR, 2.4) was observed when compared with aspirin alone.

### TABLE 2. Randomized Aspirin-Controlled Studies of Oral Anticoagulation in Addition to Aspirin After Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>INR Target</th>
<th>INR Reached</th>
<th>ASA Dose, mg</th>
<th>1° End Point</th>
<th>RR</th>
<th>P</th>
<th>Fup, mo</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Angiographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams23</td>
<td>1997</td>
<td>57</td>
<td>2.0–2.5</td>
<td>2.0</td>
<td>150</td>
<td>4%</td>
<td>33%</td>
<td>NA</td>
<td>0.02*</td>
</tr>
<tr>
<td>APRICOT-2a</td>
<td>2000</td>
<td>308</td>
<td>2.0–3.0</td>
<td>2.6</td>
<td>80</td>
<td>18%</td>
<td>30%</td>
<td>0.60 (0.39–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARSA22</td>
<td>1997</td>
<td>8803</td>
<td>1 mg QD</td>
<td>80 vs 160</td>
<td>8.8%</td>
<td>8.6%</td>
<td>1.03 (0.87–1.22)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 mg QD</td>
<td>8.4%</td>
<td>0.95 (0.81–1.12)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>CHAMP7</td>
<td>1999</td>
<td>5059</td>
<td>1.5–2.5</td>
<td>1.8</td>
<td>80 vs 160</td>
<td>17.6%†</td>
<td>17.3%†</td>
<td>0.98 (0.87–1.11)</td>
<td>0.76</td>
</tr>
<tr>
<td>ASPECT-29</td>
<td>2000</td>
<td>668</td>
<td>2.0–2.5</td>
<td>2.4</td>
<td>80</td>
<td>5.1%</td>
<td>9.2%</td>
<td>0.55 (0.31–0.98)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OASIS-2a</td>
<td>2001</td>
<td>3712</td>
<td>2.0–2.5</td>
<td>NP</td>
<td>Not specified</td>
<td>7.6%</td>
<td>8.3%</td>
<td>0.90 (0.72–1.14)</td>
<td>0.40</td>
</tr>
<tr>
<td>Good compliers</td>
<td>1821</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.1%</td>
<td>8.9%</td>
<td>0.68 (0.48–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Poor compliers</td>
<td>1891</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.0%</td>
<td>7.8%</td>
<td>1.17 (0.86–1.60)</td>
<td>0.33</td>
</tr>
<tr>
<td>WARIS-215</td>
<td>2001</td>
<td>2414</td>
<td>2.0–2.5</td>
<td>2.2</td>
<td>75 vs 160</td>
<td>15.0%</td>
<td>20.0%</td>
<td>0.71 (0.58–0.86)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Unpublished data are shown as presented at the respective congresses (see References) and are preliminary results. See References for full trial names. n indicates number of patients randomized; INR, international normalized ratio; ASA, aspirin; OAC, oral anticoagulation; 1° End Point, primary end point; RR, relative risk; Fup, follow-up period; Good/poor compliers, oral anticoagulation use in > or <70% patients at 35 days; NA, not applicable; and NP, not published.

*P value by Fisher exact test.
†Mortality, primary end point.
pared with aspirin alone. In APRICOT-2, designed and powered as angiographic follow-up trial, the combined anti-thrombotic regimen (INR, 2.6) produced a 40% reduction in 3-month reocclusion after successful fibrinolytic therapy. Similar findings were observed in a smaller, more heterogeneous group of patients after acute coronary syndromes. Clinical outcome, the secondary end point, was also significantly improved. The larger WARIS-2 trial (INR, 2.2) confirmed these observations over a 4-year follow-up period, with a reduction in the combined end point of death, reinfarction, and stroke from 20% to 15%. OASIS-2 was performed worldwide and showed a nonsignificant 10% reduction for the combined strategy. When OASIS-2 was reanalyzed, stratified by countries with good compliance to anticoagulation therapy, a marked clinical benefit was apparent (Table 2). The largest worldwide trial after myocardial infarction to date, CHAMP, was aimed at a target INR of 1.5 to 2.5 and was neutral. In this trial, with a mean INR of 1.8, most patients had an INR near the lowest intensity.

In aggregate, the available data suggest that in a setting of good compliance and well-organized INR monitoring, addition of oral anticoagulation (INR, >2.0) to aspirin seems beneficial. More insight into the efficacy and safety of a regimen with a target of 1.5 to 2.5 will be provided by the LOWASA study, which is enrolling >5000 patients in Sweden.

**Clinically Observed Mechanism of Benefit**

The controlled trials of warfarin as a single agent showed marked reductions in death, (re)infarction, and stroke, respectively. As for the direct comparison with aspirin, or a specification of the efficacy of the combined regimen, an updated meta-analysis including final data of the unpublished trials is warranted. The fact that oral anticoagulants take 2 to 4 days to become therapeutically effective is an important clinical consideration. Timing of initiation of oral anticoagulation and the antithrombotic regimen administered during the acute phase therefore must take into account such pharmacological factors.

**Adverse Events**

In patients taking oral anticoagulants, the initiation or withdrawal of concurrent medications must be reviewed by a health care professional, preferably a member of a dedicated anticoagulation service committed to close communication with the patient. The most frequent complication is bleeding, which is related to the intensity of anticoagulation and is more frequent when oral anticoagulation is used in patients with cerebrovascular or peripheral disease. High-risk subgroups are those with a history of gastrointestinal bleeding, stroke, hypertension, impaired renal function, and anemia. Whether increased age is an independent risk factor or whether bleeding is primarily a result of comorbid factors remains an issue of controversy. Irrespective of age, bleeding episodes should trigger a search for a possible underlying occult lesion, which may be malignant. With respect to the safety of a combined regimen of aspirin and dose-adjusted oral anticoagulation therapy, the different studies report a 2- to 3-fold increased risk of minor and major bleeding, without an increased risk of intracerebral hemorrhage. 

A less frequently observed side effect is skin necrosis attributable to thrombosis of the venules and capillaries within the subcutaneous fat. An abrupt drop in protein C levels or a preexisting deficiency is responsible for the procoagulant response seen in the first 3 to 8 days after initiation of therapy. It should be noted that oral anticoagulants are associated with an increased risk of fetal central nervous system and bone abnormalities, bleeding, and fetal death. For most pregnant women requiring anticoagulant therapy, unfractionated heparin and subcutaneous low-molecular-weight heparin are safe alternatives.

**Recommendations**

Irrespective of the indication, dose-adjusted, frequently monitored, and individually tailored therapy is a prerequisite for optimal oral anticoagulation. Primary prevention can be considered in high-risk patients with nonmodifiable risk factors or risk factors that are not easily controlled, aiming at a target INR of 1.5. In patients with an acute coronary syndrome, oral anticoagulation should be prescribed for established indications (eg, case A, Table 1) in the absence of contraindications.

Secondary prevention of coronary events attributable to recurrent thrombosis is a major component of management of patients after presentation with an acute coronary syndrome. Given its ease of administration, predictable safety, and proven efficacy, aspirin should be the preferred agent for this indication. In clinical settings with a good infrastructure, full-intensity oral anticoagulation (target INR, 2.8 to 4.2) is an effective alternative, with ample evidence-based support. If aspirin is contraindicated, oral anticoagulation is the only effective alternative long-term antithrombotic regimen evaluated to date in patients after ST elevation myocardial infarction. Although both low-molecular-weight heparin and clopidogrel in addition to aspirin have been proven safe in the long-term treatment of patients after a non-ST elevation acute coronary syndrome, only clopidogrel proved to be of additional benefit. In cases of aspirin intolerance, 75 mg clopidogrel once daily seems a practical long-term alternative. With respect to the long-term benefits of clopidogrel, direct comparisons with oral anticoagulation, both as single agents and in addition to aspirin, have not been performed to date. We believe this is an important area for future trials.

Data on the combination of moderate intensity anticoagulation (target INR, 2 to 3) with aspirin seem promising, but routine implementation in general cannot yet be recommended in uncomplicated patients (eg, case B). Combination therapy can certainly be considered in individual (high-risk) cases; in that case, the recommended aspirin dose is 80 mg daily to be taken along with moderate-intensity oral anticoagulation. Definition of the optimal duration of therapy and identification of subsets of patients with the optimal risk-benefit profile are relevant clinical issues. A practical aspect of concern is the fact that even in countries with an established good quality anticoagulation service infrastructure and high short-term compliance, ~20% to 25% of
patients discontinue therapy within 6 months, and only a minority do so as a result of bleeding.6,9

Conceptually, the observed benefits of anticoagulant therapy in addition to an antiplatelet regimen call for the search of a less cumbersome long-term alternative that is at least as effective as warfarin but with less intraindividual and interindividual variability. For patients after ST elevation myocardial infarction, data on low-molecular-weight heparin seem promising when administered in hospital,28 and consideration should be given to trials of long-term therapy in that patient subset. For the entire spectrum of patients recovering from an acute coronary syndrome, agents without the need for hematology monitoring, such as Xa inhibitors29,30 and oral direct thrombin inhibitors, seem appealing candidates for additional study.

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Marc A. Brouwer and Freek W.A. Verheugt

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