Anticoagulant Therapy for Coronary Heart Disease: Case Studies

Series Editor:
W. Robert Taylor, MD, PhD
Assistant Professor of Medicine, Director, Cardiovascular Disease Fellowship Training Program, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA

Contributing Author:
A. Maziar Zafari, MD, PhD
Assistant Professor of Medicine, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA
Staff Cardiologist, Atlanta Veterans Affairs Medical Center, Decatur, GA

Table of Contents

Introduction .............................................. 2
Anticoagulant Therapy ................................. 2
Case Presentations ..................................... 7
Summary ................................................. 10
References .............................................. 10

Cover Illustration by Scott Holladay
I. INTRODUCTION

Although the rate of cardiovascular mortality during the past 3 decades has decreased substantially, atherosclerotic coronary heart disease (CHD) remains the leading cause of death and disability in the United States.¹ This continuing decrease in CHD mortality is directly related to improved therapies for acute coronary syndromes—unstable angina pectoris, acute myocardial infarction (MI), and chronic manifestations of CHD (stable angina, ischemic congestive heart failure [CHF])—as well as to favorable modifications of major coronary risk factors. Anticoagulant agents can decrease risks of occlusive vascular events by reduction of certain coagulation factors, by inhibition of thrombin formation and activity through activation of antithrombin, and finally by direct inhibition of both free thrombin and thrombin bound to fibrin. Uncertainty remains among health care providers regarding the appropriate uses of these agents in different categories of patients.

This review describes how anticoagulant agents can be used to manage patients with CHD based on data from selected major randomized controlled trials that support recent recommendations of the American College of Cardiology/American Heart Association (ACC/AHA)²⁻⁴ and the American College of Chest Physicians (ACCP).⁵ It also provides clinicians with information for the use of anticoagulant agents in the prevention of CHD. This review does not discuss randomized controlled trials and recommendations regarding the use of anticoagulant agents with percutaneous coronary interventions, which deserve a separate and thorough review. The case studies show how the information discussed in this review translates into day-to-day practice. The first part of this review described antiplatelet agents (“Antiplatelet Agents in Coronary Heart Disease: Case Studies”) and was published in Volume 5, Part 6, of the Hospital Physician Cardiology Board Review Manual.

II. ANTICOAGULANT THERAPY

ANTICOAGULANT AGENTS

Oral anticoagulants produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide through inhibition of vitamin K epoxide reductase and possibly vitamin K reductase. In addition, the vitamin K antagonists impair the function of protein C and protein S, which are
regulatory anticoagulant proteins. Warfarin is the most widely used oral anticoagulant in North America; its antithrombotic effect is achieved by decreasing levels of prothrombin, factor VII, factor IX, and factor X. Bleeding is the major complication of oral anticoagulant therapy. The risk of bleeding is influenced by the intensity of anticoagulant therapy, the patient’s underlying disease, and the concomitant use of aspirin, which impairs platelet function and produces gastric erosions. The most clinically important nonhemorrhagic side effect of warfarin is skin necrosis, which is uncommon and is usually observed on the third to eighth day of therapy.

The anticoagulant effect of heparin, a glycosaminoglycan, is mediated largely through its interaction with antithrombin III (AT-III); this produces a conformational change in AT-III and therefore markedly accelerates its ability to inactivate the coagulation enzymes thrombin (factor IIa), factor Xa, and factor IXa. Of these 3 enzymes, thrombin is the most sensitive to inhibition by heparin/AT-III. In addition to the well-known complication of bleeding (which is common to all anticoagulants), heparin can cause thrombocytopenia and osteoporosis. The low-molecular-weight heparins (LMWHs) are derived from standard heparin by either chemical or enzymatic depolymerization to yield fragments that are approximately one third the size of heparin. Like unfractionated heparin (UFH), LMWHs produce their major anticoagulant effect by activating antithrombin. They bind plasma proteins and endothelial cells less avidly than UFH, resulting in a more predictable degree of anticoagulation. Decreased binding to platelets and platelet factor 4 (PF4) may explain the lower incidence of heparin-induced thrombocytopenia seen with LMWHs. Bleeding is the major complication of therapy with LMWHs. Current trial data support the inference that LMWH does not result in an increased risk of major bleeding compared with UFH.

The direct thrombin inhibitors hirudin and hirulog are potent anticoagulants that provide predictable inhibition of thrombin, without the need for a cofactor or a known physiologic inhibitor. Hirudin inhibits the catalytic and anion-binding sites of thrombin; hirulog is a 20–amino acid peptide inhibiting the 2 active sites. Bleeding is the main complication of therapy with direct thrombin inhibitors.

**TREATMENT OF ACUTE CORONARY SYNDROMES**

Studies performed in the 1960s and 1970s showed that oral anticoagulants are effective for the early treatment of patients with acute MI. Specifically, these earlier studies showed that a moderate-intensity warfarin regimen is effective for preventing stroke and venous thromboembolism. Three randomized short-term trials evaluated the efficacy of oral anticoagulants in patients with acute MI. All 3 studies showed a decrease in the incidence of clinically diagnosed pulmonary embolism; in 2 of these studies, the decrease was statistically significant. Two of these studies, the Medical Research Council study and the Veterans Affairs Cooperative study, also showed a significant decrease in stroke. The Bronx Municipal Study was the only study reporting a significant decrease in mortality (Table 1).

Collins and associates summarized the outcomes of short-term trials of heparin therapy in suspected acute MI from 26 unconfounded, properly randomized trials. They showed that in the absence of fibrinolytic therapy, heparin decreases mortality by a statistically significant and clinically important amount (ie, approximately 35 fewer deaths per 1000 patients) (Table 2). The beneficial effects of heparin therapy also include reduction of reinfarction, stroke, and pulmonary embolism. These benefits must be balanced against an increased risk of major hemorrhage, which appears to be confined to the high-dose heparin regimens.

In the overview by Collins and associates of the heparin trials among patients receiving aspirin, 93% of patients also received fibrinolytic agents, which is current standard therapy for suspected acute MI. The addition of heparin to aspirin and fibrinolytic agents was associated with small decreases in mortality, reinfarction, and pulmonary embolism. However, the small mortality benefits observed at 7 days in the International Studies of Infarct Survival (ISIS-3) and Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI-2) trials became less pronounced and lost their statistical significance at 35 days and 6 months of follow-up. Hence, when heparin therapy is considered, a modest early benefit needs to be balanced against the possibility of more major bleeding episodes. These factors suggest that at least among patients receiving streptokinase (SK) or anisoylated plasminogen SK activator complex (APSAC) plus aspirin, heparin is not indicated for routine use. It appears rational to reserve heparin for those patients at high risk of systemic embolization because of large infarction, CHF, or atrial fibrillation and to use heparin as adjunctive therapy for 48 hours among patients receiving recombinant tissue plasminogen activator (rt-PA).

The LMWHs have shown favorable results as adjunctive therapy to thrombolysis in smaller trials of acute MI. In the management of unstable angina and non-Q-wave MI, 4 randomized trials have compared clinical outcomes between treatment with LMWH versus UFH (Table 3). The larger Efficacy and Safety of Enoxaparin...
in Non–Q-Wave Coronary Events (ESSENCE) trial\textsuperscript{14} and the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 11B trial\textsuperscript{15} have shown significantly better results with enoxaparin than with standard heparin. The ESSENCE trial randomly assigned 3171 patients to either enoxaparin or UFH for a minimum of 48 hours and a maximum of 8 days. The rate of death, MI, or recurrent angina at 14 days was lower with enoxaparin than with heparin, 16.6\% versus 19.8\% ($P = 0.019$). The need for a revascularization procedure at 30 days was lower with enoxaparin, 27.1\% versus 32.2\% ($P = 0.001$). The incidence of minor bleeding overall was significantly higher with enoxaparin, 18.4\% versus 14.2\% ($P = 0.001$), primarily because of ecchymoses at injection sites. In the TIMI 11B trial, 3910 patients with unstable angina or non–Q-wave MI were randomly assigned to enoxaparin or UFH in the acute phase and enoxaparin or placebo in the chronic phase. Enoxaparin was superior to UFH in the acute setting, reducing death and myocardial ischemia without increasing the rate of major hemorrhage. This initial benefit was sustained throughout the 43 days of the trial without any additional decrease in events. However, a clinically significant increase in the incidence of major hemorrhage was observed with long-term enoxaparin treatment. It is not currently known how long it is safe to administer enoxaparin.

Early-phase trials for acute MI and unstable angina using hirudin and hirulog (2 direct thrombin inhibitors) have been promising. Large-scale trials were initiated but had to be reconfigured owing to an excessive rate of intracerebral hemorrhage in patients treated with fibrinolytic agents.\textsuperscript{16,17} The Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot study tested a low dose versus a moderate dose of r-hirudin versus heparin in 909 patients with unstable angina or suspected acute MI without ST-segment elevation.\textsuperscript{18} Moderate-dose hirudin was superior to the other treatments with respect to rates of cardiovascular death, new MI, or refractory angina ($P = 0.047$ for heparin versus moderate-dose hirudin). OASIS-2, a recently completed large phase III trial comparing heparin with hirudin in 10,141 patients with unstable angina or non–Q-wave MI, demonstrated a 17\% risk reduction with hirudin in the composite end point of cardiovascular death or new MI at 7 days.\textsuperscript{19} Hirudin therapy was not associated with an increased risk of stroke, but it was associated with a small and significant increase in major bleeding events (0.7\% versus 1.2\% for the heparin and hirudin groups, respectively).

### SECONDARY PREVENTION

The early evidence that oral anticoagulants are effective in the long-term management of acute MI comes from analysis of pooled data from 7 randomized trials published between 1964 and 1980. These studies showed that oral anticoagulant therapy during a 1- to 6-year treatment period decreased the combined end point of mortality and nonfatal reinfarction by approximately 20\%.\textsuperscript{20} Four of these studies are described in the following paragraphs.
In the Warfarin and Reinfarction Study (WARIS), the effect of long-term warfarin therapy (international normalized ratio [INR], 2.8–4.8) was compared with placebo in 1214 patients who had recently sustained acute MI (a mean of 27 days earlier). Aspirin use was not recommended during the trial. At 3-year mean follow-up, warfarin anticoagulation significantly decreased mortality (24%), nonfatal reinfarction (34%), and fatal reinfarction and fatal stroke (55%). In a post hoc subgroup analysis of WARIS, mortality and recurrent MI were not significantly decreased in patients with previous MI or diabetes mellitus, and a trend to an attenuated benefit was observed among the oldest patients.

The Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial studied 3404 patients who had sustained an acute MI within 6 weeks of hospital discharge in 60 Dutch hospitals. These patients were randomly assigned to oral anticoagulant therapy with phenprocoumon or nicoumalone versus placebo and were followed for an average of 37 months. There was a significant 53% decrease in recurrent MI, a significant 42% reduction in stroke, and a favorable trend for but nonsignificant reduction in mortality (10%) in both anticoagulant treatment groups when compared with placebo. Major bleeding complications were 4 times greater with anticoagulant therapies than with placebo.

In the Sixty Plus Reinfarction Study, 878 patients older than 60 years who had received anticoagulant therapy after a transmural MI that had occurred at least 6 months earlier were randomly assigned to continued anticoagulant therapy or placebo. After 2 years, anticoagulant therapy was associated with lower rates of mortality (7.6% versus 13.4%, \( P = 0.017 \)) and reinfarction (5.7% versus 15.9%, \( P = 0.0001 \)) when compared with placebo. However, the findings were limited by the study’s lack of generalizability as a “stopping trial” in a select age group (Table 4).

In the multicenter Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT) trial, 300 patients with a patent infarction-related artery less than 48 hours after acute MI were randomly assigned to 325 mg of aspirin daily or heparin followed by warfarin (INR, 2.8–4.0) versus placebo. At 3 months, coronary reocclusion was comparable in all 3 groups. Aspirin decreased the reinfarction and revascularization rates and increased event-free survival more than placebo; the beneficial effect of warfarin on these end points was less than that of aspirin.

All 4 contemporary studies (WARIS, ASPECT, Sixty Plus, and APRICOT) used high-intensity regimens (INR, 2.7–4.8) and reported an increased incidence of bleeding with anticoagulant agents. The efficacy of oral anticoagulants in patients with CHD was indirectly shown in a randomized trial of patients with peripheral arterial disease; compared with an untreated control group, a high-intensity oral anticoagulant regimen (INR, 2.6–4.5) produced a 50% decrease in the mortality rate.

Recently, the Coumadin Aspirin Reinfarction Study (CARS) showed that low fixed-dose warfarin therapy (INR, < 1.5) plus 80 mg aspirin is no more effective than 160 mg aspirin in the long-term treatment of acute MI. The results of CARS appear to be at odds with the results of the Thrombosis Prevention Trial (TPT). However, fixed-dose warfarin therapy was used in CARS, whereas in the TPT trial, the warfarin dose was adjusted and varied over a wide range (from 0.5 to 12.5 mg/day). The
Combination Hemotherapy and Mortality Prevention (CHAMP) trial, a randomized clinical trial currently in progress, is comparing warfarin with aspirin and combination therapy in survivors of acute MI.\textsuperscript{28}

The Post Coronary Artery Bypass Graft (POST-CABG) trial studied the efficacy of combined low-level anticoagulation with warfarin and aspirin in the prevention of graft failure in patients who had undergone coronary artery bypass grafting (CABG).\textsuperscript{29} Low-dose warfarin therapy had no additive benefit when combined with aspirin. CARS and POSTCABG demonstrated the safety of combination hemotherapy using low-intensity warfarin therapy but failed to establish clinical efficacy of this regimen in secondary prevention after acute MI and graft failure in patients who had had CABG surgery.

Serneri and colleagues\textsuperscript{30} evaluated heparin (12,500 U subcutaneously once daily) among patients who had sustained Q-wave MI 6 to 18 months previously and found a significant reduction in reinfarction with favorable trends for the reduction of all-cause and cardiovascular mortality. No major hemorrhages occurred, and no evidence of osteoporosis was found.

Until new information is available, patients with CHD should be treated with 160 to 325 mg of aspirin daily. Oral anticoagulants are favored for CHD patients with aspirin intolerance, for those at risk of left ventricular (LV) embolism (ie, with mural thrombi) or left atrial embolism (ie, atrial fibrillation), and for those with previous thromboembolism.\textsuperscript{2} Despite a lack of randomized controlled trials, warfarin may be used in patients with large anterior infarction because a number of small observational studies demonstrated a higher risk of embolic stroke in such patients and a better outcome when these patients were treated with warfarin after demonstration of LV mural thrombus by echocardiography.\textsuperscript{31}

### PRIMARY PREVENTION

The TPT trial evaluated warfarin and aspirin therapy in 5499 men between the ages of 45 and 69 years with risk factors for atherosclerosis but without symptoms of angina.\textsuperscript{27} The main outcome was the primary prevention of acute coronary events defined as the composite of coronary death, fatal MI, and nonfatal MI. The target INR was 1.3 to 1.8, and the mean warfarin dose was 4.1 mg/day. The annual incidence of acute ischemic coronary events was 1.4% per year in the placebo group. Warfarin and aspirin produced similar and non-significant reductions in acute ischemic events of 22% and 23%, respectively, whereas the combination of warfarin and aspirin produced a significant reduction of 34% ($P = 0.006$). However, the more effective combined treatment was associated with an increased risk of hemorrhagic stroke. The results show that a targeted INR of 1.3 to 1.8 is effective in preventing acute ischemic events, particularly fatal events. The results also showed that the combination of low-intensity warfarin therapy and low-dose aspirin therapy is more effective than either agent used alone, but that the combination increases the risk of bleeding.

Low-intensity warfarin therapy (target INR, 1.5) may be considered as an alternative to aspirin for men at high risk of cardiovascular events for the prevention of those events and for reduction in all-cause mortality, based on 1 large randomized controlled trial.\textsuperscript{27} Furthermore, a combination of low-dose aspirin and low-intensity warfarin may be considered as an alternative to

### Table 3. Trials of Low-Molecular-Weight Heparin Versus Unfractioned Heparin in Unstable Angina/Non–Q-Wave Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>LMWH</th>
<th>Patients, ( n )</th>
<th>Follow-up</th>
<th>Death/MI</th>
<th>Death/MI</th>
<th>Refractory UA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LMWH, %</td>
<td>UFH, %</td>
<td>( P ) Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LMWH, %</td>
<td>UFH, %</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Gurfinkel et al\textsuperscript{40}</td>
<td>Nadroparin vs UFH for 5–7 d</td>
<td>138</td>
<td>In-hospital</td>
<td>0</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>FRIC\textsuperscript{26}</td>
<td>Dalteparin vs UFH for 6–45 d</td>
<td>1482</td>
<td>6 d</td>
<td>3.9</td>
<td>3.6</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Dalteparin vs placebo 6–45 d</td>
<td>1132</td>
<td>6–45 d</td>
<td>4.3</td>
<td>4.7</td>
<td>NS</td>
</tr>
<tr>
<td>ESSENCE\textsuperscript{14}</td>
<td>Enoxaparin vs UFH for 2.6 d</td>
<td>3171</td>
<td>14 d</td>
<td>4.9</td>
<td>6.1</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 d</td>
<td></td>
<td>6.2</td>
<td>7.7</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.6</td>
<td>19.8</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.8</td>
<td>23.3</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ESSENCE = Efficacy and Safety of Enoxaparin in Non–Q-wave Coronary Events; FRIC = Fragmin in Unstable Coronary Heart Disease; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NS = not significant; UA = unstable angina; UFH = unfractioned heparin.

---

\[ \text{Anticoagulant Therapy for CHD} \]
aspirin or to warfarin alone for men at very high risk of cardiovascular events, for the prevention of these events, and for reduction in all-cause mortality.27

III. CASE PRESENTATIONS

CASE PATIENT 1 PRESENTATION

Patient 1 is a 51-year-old man who suddenly develops severe substernal chest pain associated with dyspnea, diaphoresis, nausea, and vomiting. Three hours after the onset of chest pain, he presents to the emergency department, where his blood pressure is 145/85 mm Hg and his heart rate is 80 bpm. His initial electrocardiogram (ECG) is shown in Figure 1.

• Of the following options, what is the best next step in the management of patient 1?
  A) Give sublingual nitroglycerin and supplemental oxygen
  B) Have the patient crush or chew and swallow a 325-mg aspirin tablet
  C) Repeat ECG in 15 minutes
  D) Await the results of cardiac enzymes testing
  E) Call an ambulance to transport the patient to a facility with interventional cardiology, 3 hours away

The correct answer is B. The ISIS-2 study has shown conclusively the efficacy of aspirin alone for treatment of evolving acute MI, with a 35-day mortality reduction of 23%.32 A meta-analysis demonstrated that aspirin decreased coronary reocclusion and recurrent ischemic events after thrombolytic therapy with either streptokinase or alteplase.33 In a dose of 160 mg or more, aspirin produces a rapid clinical antithrombotic effect caused by immediate inhibition of thromboxane A2 production. Based on the ACC/AHA guidelines for the management of patients with acute MI, aspirin is part of the early management of all patients with suspected acute MI and should be given promptly (certainly within the first 24 hours) at a dose between 160 and 325 mg and continued daily indefinitely.2 Data support the contention that in the early hours after infarction, a chewed aspirin is absorbed more quickly than one swallowed whole, particularly after opiate therapy. In patients with true salicylate allergy, antiplatelet agents such as ticlopidine or clopidogrel should be used.

FURTHER PRESENTATION OF CASE PATIENT 1

Patient 1 receives 325 mg of aspirin and begins therapy with intravenous (IV) nitroglycerin, oral metoprolol, and IV UFH. He has no contraindications to fibrinolysis, and he receives rt-PA within 30 minutes of arrival in the emergency department. His cardiac enzyme measurements peak with troponin I at
2270 ng/mL, creatine kinase at 6127 U/L, and creatine kinase-MB at 991 ng/mL.

Patient 1 has no complications after his MI, and IV UFH is continued for 48 hours. During his hospitalization, a transthoracic echocardiogram shows anteroseptal and anteroapical akinesis with a mural thrombus, and his LV ejection fraction is decreased to 30%. A symptom-limited standard exercise test with nuclear images reveals a large scar in the anterior myocardium without viability on late imaging.

- Which of the following antithrombotic regimens should NOT be recommended to patient 1?

A) Lifelong aspirin 160 to 325 mg daily
B) Clopidogrel 75 mg daily
C) Warfarin with target INR of 2.5 (range, 2.0 to 3.0) for at least 3 months
D) Combination hemotherapy with 3 mg warfarin and 80 mg aspirin

**DISCUSSION**

The correct answer is D. The indications for long-term anticoagulation after acute MI remain controversial. A series of studies comparing warfarin with conventional therapy has demonstrated a reduction in risk of death of 13% and a reduction in relative risk of both stroke and reinfarction of 41% with warfarin therapy. The lack of aspirin use in the control groups in these trials has made it difficult to assess the relative merits of aspirin alone versus warfarin alone. The cost-effectiveness of aspirin makes aspirin alone the current standard antithrombotic regimen for secondary prevention of MI. In theory, aspirin and warfarin can be used in combination as a secondary preventive strategy. However, a recent report evaluating 3 different regimens—(1) 160 mg aspirin alone, (2) 80 mg aspirin plus 3 mg warfarin, or (3) 80 mg aspirin plus 1 mg warfarin—showed that combination hemotherapy did not decrease subsequent events in 8803 patients after MI. Combination therapy did not provide clinical benefit beyond that achievable with 160 mg of aspirin alone.

A small number of observational studies have demonstrated a higher risk of embolic stroke in patients with large anterior infarction and a better outcome in patients treated with warfarin after demonstration of LV mural thrombus by echocardiography. However, randomized controlled trials are not available to support this treatment regimen. A firm recommendation based on empirical information cannot be made because patients at lower risk may have been treated in the observational studies. Based on the ACC/AHA guidelines for the management of patients with acute MI, long-term
anticoagulation with warfarin is recommended in patients with persistent atrial fibrillation after MI, for secondary prevention of MI in patients unable to take daily aspirin, and in patients with LV thrombus. In post-MI patients with extensive wall motion abnormalities or in patients with paroxysmal atrial fibrillation, current evidence and opinion suggest that warfarin may be useful and efficacious. However, in post-MI patients with severe LV systolic dysfunction with or without CHF, warfarin is not currently recommended.

CASE PATIENT 2 PRESENTATION

Patient 2 is a 65-year-old woman who presents to the emergency department with 4 hours of new-onset chest pain at rest. Her medical history is pertinent for essential hypertension for 10 years. She is hemodynamically stable, and her chest pain resolves quickly with 2 sublingual nitroglycerin tablets. She receives 325 mg of aspirin. Her initial ECG shows 1-mm ST depressions in leads I, aVL, and V4–V6.

- Of the following options, what is the next best step in the anticoagulant management of patient 2?
  A) Start warfarin, 5 mg daily
  B) No anticoagulant therapy
  C) Start enoxaparin (1 mg/kg every 12 hours for at least 48 hours) and daily aspirin
  D) Start UFH (IV dose-adjusted for at least 48 hours) and daily aspirin
  E) Start dalteparin (120 U/kg every 12 hours for 5 days) and daily aspirin

DISCUSSION

The correct answer is C. Enoxaparin for the acute management of patients with unstable angina or non-Q-wave MI has been shown to be superior to UFH for decreasing mortality and for reducing serious cardiac ischemic events. This superiority is achieved without an increase in the rate of either spontaneous or instrumented major hemorrhage.

In the ESSENCE study, the rate of end point events was significantly reduced in the enoxaparin group compared with UFH (16.6% versus 19.8% for the enoxaparin and UFH groups, respectively; \( P = 0.019 \)). The enoxaparin group continued to have fewer events than the UFH group through 30 days, at which time a primary end point event had occurred in 19.8% of the enoxaparin group and in 23.3% of the UFH group (\( P = 0.016 \)). At 48 hours, a statistically significant relative risk reduction of 24% was observed with enoxaparin (7.3% in the UFH group versus 5.5% in the enoxaparin group). By 14 days, the rate of death/MI/urgent revascularization was 16.7% in the UFH group compared with 14.2% in the enoxaparin group, yielding a relative risk reduction of 15% (\( P = 0.03 \)).

The initial benefit observed with enoxaparin in the TIMI-11B trial was sustained through day 43; however, no further relative decrease in events was observed in the chronic phase. An increase in the rate of major hemorrhage (both spontaneous and instrumented) occurred with long-term enoxaparin treatment.

In the Fragmin during Instability in Coronary Artery Disease (FRISC) trial, dalteparin-treated patients experienced a 63% reduction in death and nonfatal MI at the 6-day evaluation. However with longer-term follow-up, event rates for the 2 groups began to converge, and a non-significant trend toward improved outcome was observed in the dalteparin group by 40 days. By 150 days, no significant difference was noted between the 2 groups. The occurrence of the composite outcome of death, MI, or recurrent angina was similar for the UFH and dalteparin groups during the 6-day acute period. Similarly, after 45 days, the incidence of death, MI, or recurrent angina was 12.3% for both groups.

In the Fragmin in Unstable Coronary Heart Disease (FRIC) study, the occurrence of the composite outcome of death, MI, or recurrent angina was similar for the UFH and dalteparin groups during the 6-day acute period (7.6% versus 9.3% for the UFH and dalteparin groups, respectively). Similarly, after 45 days, the incidence of death, MI, or recurrent angina was 12.3% for both groups.

FURTHER PRESENTATION OF CASE PATIENT 2

Patient 2 receives weight-adjusted UFH. Five days after initiation of anticoagulant therapy with UFH, she develops a more than 50% decrease in her platelet count and a small stroke. A diagnosis of the immune form of heparin-induced thrombocytopenia (HIT) is made, and treatment with UFH is stopped.

- Of the following options, what is the appropriate step in the anticoagulant management of patient 2?
  A) Start oral anticoagulation with warfarin
  B) Initiate treatment with IV lepirudin
  C) Switch to LMWH
  D) Initiate therapy with danaparoid sodium

DISCUSSION

The correct answer is B. Warfarin should not be given alone to patients with acute HIT. However, warfarin appears to be safe in acute HIT when it is given to a patient who is adequately anticoagulated with a drug that decreases thrombin generation in HIT (such as dana-
paroid sodium or lepirudin), although warfarin therapy should be delayed until the platelet count has risen to more than $100 \times 10^9/L$. Only lepirudin has been approved by the Food and Drug Administration for the treatment of HIT complicated by thrombosis. The efficacy and safety of lepirudin (a hirudin derivative that directly inactivates thrombin) in patients with HIT-associated thrombosis was compared with historical controls in 2 trials. Lepirudin was associated with a lower composite event rate (new thrombosis, limb amputation, death) in patients with serologically confirmed HIT compared with historical control subjects: 10% versus 23% at day 7 follow-up, and 25% versus 52% at day 35 follow-up, respectively (adjusted risk ratio, 0.525; $P < 0.001$).

Danaparoid sodium is a mixture of anticoagulant glycosaminoglycans with predominant antifactor Xa activity and is the only agent that has been evaluated for HIT in a randomized clinical trial, where it was reported to be significantly better than the control agent, dextran. High success rates have also been reported in retrospective studies. In the United States, danaparoid has been approved for deep venous thrombosis prophylaxis but is often used “off label” for the treatment of suspected or proven HIT. The half-life of danaparoid’s antifactor Xa activity is approximately 25 hours, which can be a disadvantage in patients in whom surgery or invasive procedures are planned or who develop bleeding.

LMWH is less likely to trigger formation of HIT antibodies than is UFH. However, sensitive functional assays revealed that LMWH is just as effective at triggering platelet activation by HIT antibodies as is UFH. LMWH is not recommended for treatment of HIT because of the high rate of in vitro cross-reactivity indistinguishable from UFH, the apparently high associated risk for clinically significant in vivo cross-reactivity, and the availability of alternate agents that are likely to be more effective.

**IV. SUMMARY**

The common factor precipitating acute cardiac events in patients with CHD is endovascular thrombus formation; the common precipitant of such thrombosis is the rupture of an underlying atherosclerotic plaque. The rupture exposes subendothelial proaggregant and procoagulant substances to the circulating blood. The separation of platelet adhesion and the complex formation between tissue factor and factor VIIa trigger the intrinsic and extrinsic pathways of the coagulation cascade leading to factor X activation and the generation of thrombin, a potent platelet agonist.

Anticoagulant strategies to inhibit arterial thrombosis have focused on inhibiting thrombin or preventing thrombin generation. Randomized clinical trials using anticoagulant agents in patients with CHD have provided convincing evidence that these agents are beneficial in decreasing all-cause mortality and decreasing cardiovascular morbidity and mortality in patients with acute MI and unstable angina as well as in primary and secondary prevention of CHD.

The combination of heparin and aspirin has been the antithrombotic treatment of choice in patients with unstable angina and non–Q-wave MI. The increased convenience and recent success of LMWHs for the treatment of acute coronary syndromes has led to the widespread use of these anticoagulant agents in the management of such patients. In the recent “1999 Update: ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction,” either LMWH or UFH is recommended to be used for patients with non–ST-elevation MI and for all patients not treated with fibrinolytic therapy who do not have a contraindication to heparin. For secondary prevention, reports suggest that warfarin is effective only at INRs ranging from 2 to 3.5.

Ongoing research is studying the possible role for parenteral and oral thrombin inhibitors in the management of patients with CHD. Until conclusive data have been produced, these agents are not indicated for the management of patients with acute coronary syndromes. Nevertheless, the intensity of research in this area and the expanding numbers of antithrombotic agents have furthered our knowledge of arterial thrombosis and highlighted the critical role of platelets and thrombin in this process.

**REFERENCES**


Anticoagulant Therapy for CHD


15. Antman EM: Final results of TIMI 11B. Slide presentation at American Heart Association; November 1998; Dallas, TX.


