Reducing Cardiac Events After Acute Coronary Syndromes

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Coronary heart disease is the number one cause of death in the world and acute coronary syndromes (ACS) continue to be associated with high rates of morbidity. ACS refers to the spectrum of acute myocardial ischemia, including unstable angina, ST segment elevation myocardial infarction (STEMI), and acute MI without ST segment elevation (NSTEMI). Current guidelines indicate both aspirin and glycoprotein IIb/IIIa receptor antagonists (if catheterization/revascularization are planned) as class IA recommendations in ACS. Anticoagulant therapy, in the form of heparin, is a class IA recommendation for the acute hospital phase of ACS. The risk of recurrent thrombotic events following ACS remains high in the post-hospital phase, creating a rationale for the use of oral direct thrombin inhibitors such as ximelagatran, in both the acute and long-term settings. The Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent and Myocardial Damage (ESTEEM) trial, a placebo-controlled, double-blind study of post-MI patients, evaluated 4 dosing regimens of ximelagatran versus placebo in the initial months following an ACS and found an encouraging reduction in the end points of death, MI, and stroke with the use of an oral direct thrombin inhibitor.

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Coronary heart disease (CHD) is the number 1 cause of death in the world.[1] An estimated 700,000 people in the United States had a new CHD event, either myocardial infarction (MI) or CHD death,[2] in 2001 and 500,000 people had a recurrent event. CHD morbidity is closely related to the aging of the population, with 84% of CHD deaths occurring among people aged 65 or older. There are over 2 million annual hospital discharges for CHD,

of which about half are related to acute coronary syndromes (ACS). The total estimated cost of CHD in the United States for 2001 was $133.2 billion.[2]

ACS is a term that refers to the spectrum of acute myocardial ischemia, including unstable angina, ST-segment elevation myocardial infarction (STEMI), and acute myocardial infarction without ST segment elevation (NSTEMI).[3] Just as pathophysiology is similar across the spectrum of ACS, most of the same therapies, including antithrombotic agents, are effective for varying ACS presentations. Over the past decade, there has been a shift in the pattern of ACS, such that a smaller proportion of acute MI is characterized by ST elevation and a larger proportion is non-ST elevated.[4] This may relate to the aging of the population, as ST elevation is less frequent among older patients, as well as to more thorough detection of MI through the use of the biomarker troponin. Whereas patients with STEMI generally have a higher in-hospital rate of mortality, patients presenting with ST depression have higher rates of mortality at 6 months post-event and beyond, which can be attributed to their older age and greater burden of underlying disease.[5]

Though intense antithrombotic treatment is focused on the early in-hospital phase of patient recovery, half of recurrent MIs occur after the first several days. The risk of transition from the acute to the post-hospital phase of management is compounded by the phenomenon of heparin "rebound," an increased risk of reactivation in the hours after discontinuation of antithrombin therapy. Thus, more effective acute and post-discharge antithrombotic therapies are needed to improve the outcome of patients with ACS.[6]

Pathogenesis of Acute Coronary Syndromes

The initiating pathophysiologic event of ACS is instability and rupture of a coronary artery atherosclerotic plaque.[7] Plaque characteristics that are related to high likelihood of disruption and rupture include high lipid content, inflammation (including macrophage and T-lymphocyte activity at the plaque shoulder), metalloproteinase activity, and thinning of the fibrous cap. Growing plaques appear to be more vulnerable than well-established, more severely stenotic lesions.

Although interventional management of ACS focuses on the "culprit" lesion, evidence suggests that plaque instability and atherothrombosis is often a diffuse process that may involve more than 1 location in the coronary system.

Plaque rupture results in turbulence and increased shear forces, exposure of fatty gruel and tissue factor, and activation of platelets and the coagulation cascade with fibrin formation and resulting thrombus formation. The combination of thrombus formation, underlying stenosis, and coronary spasm can result in limitation of myocardial blood flow and myocardial ischemia. Embolization of platelet and fibrin microaggregates from the area of coronary thrombosis has been recognized as an important cause of microvascular dysfunction and ischemia.[8] Serial embolization from active plaques may cause microscopic myocardial necrosis and elevation of troponin, which is both a sensitive marker of necrosis as well as one with a long half-life that allows accumulation of serial releases to rise to detectable levels. Even slight levels of troponin elevation are important in the establishment of diagnosis and prognosis in patients with suspected ACS.[3] This is in part due to troponin's ability to identify patients with true coronary plaque rupture.

Clot formation is a complex process that involves interaction among the platelet, the coagulation system, and the injured vessel wall. The coagulation cascade is no longer viewed as a simple, sequential, linear process, but rather as a highly complex interactive series of events that includes exposure of tissue factor, binding of tissue factor to Factor VIIa, which leads to the formation of the prothrombinase complex (Factor Xa, Factor Va, calcium, and phospholipid surface) and activates prothrombin to thrombin. Thrombin thereby catalyzes the cleavage of fibrinogen to fibrin. Thrombin is also involved in feedback amplification of the cascade, as well as serving as a potent activator of platelets. Thus, thrombin is a central factor in the generation of thrombus in ACS. Ultimately, clot propagation is a balance of forces that include coagulation, anticoagulation (including endogenous anticoagulant factors C and S), fibrinolysis, and antifibrinolysis.

Although interventional management of ACS focuses on the "culprit" lesion, evidence suggests that plaque instability and atherothrombosis is often a diffuse process that may involve more than 1 location in the coronary system. Studies have found that markers of inflammatory activation are also increased in the venous drainage of the left coronary system, even if the culprit lesion is in the right coronary system.[9] Intravascular ultrasound shows that even among patients with angiographically mild

disease, extensive atherosclerosis is often present.[10] Autopsy studies also show that diffuse disease including multiple areas of coronary thrombosis are common. These findings support management of ACS with systemic therapies, including potent antithrombotic treatments.

Coronary thrombosis can be visualized by angioscopy for weeks following acute MI[11] and the coagulation system remains activated for months following ACS.[12] The epidemiology of recurrence of clinical events is consistent with laboratory evidence, demonstrating that an activated, high-risk state exists for weeks or even months following the acute presentation, especially among patients not undergoing revascularization.[13] Trials have shown that weeks or months of anticoagulant treatment can prevent events during this high-risk period.[13] Even in clinical trials, which tend to select lower-risk patients than seen in general practice, the occurrence of death or (re)infarction within 30 days of presentation occurs in over 14% of patients with the highest risk features.[14] Older patients, those with elevated cardiac markers, and those with ST segment shift on the presenting ECG are at especially high risk for both short- and long-term recurrent events.[3]

There is experimental and clinical evidence of rebound or reactivation of thrombosis upon discontinuation of antithrombin therapy[15] (including heparin, low molecular weight heparin, and direct thrombin inhibitors), supporting the need for effective antithrombotic treatments that can bridge the acute hospital phase with the post-hospital phase of persistent high risk for recurrent thrombosis. Availability of easy-to-use, effective oral anticoagulants could provide an important means to achieve this goal.

Table 1
American College of Cardiology/American Heart Association Guidelines for Hospital Care and Antithrombotic Therapy, Post–Acute Coronary Syndrome (Class I, Level of Evidence A)

Class	I	IIa	IIb	III	
	A				Immediate aspirin; clopidogrel if no aspirin
	A				Aspirin plus clopidogrel, for up to 1 month
	A				Heparin (IV UFH, LMWH)
	A				Any GP IIb/IIIa inhibitor plus aspirin/heparin for all patients, if catheterization/PCI planned

GP, glycoprotein; IV, intravenous; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.
Adapted from Braunwald et al.[3]

Current Recommendations for Antithrombotic Management of ACS

Acute management of ACS includes use of antithrombotic therapy to prevent ongoing and new thrombosis, at least until the time of coronary intervention. Consistent with pathophysiologic evidence of the contribution of both platelets and thrombin, antiplatelet and anticoagulant therapies are effective in improving clinical outcomes.

American College of Cardiology/American Heart Association guidelines[3] (Table 1) call for aspirin in doses of 81 mg to 325 mg daily as a class IA indication for treatment of the entire spectrum of ACS, based on many large, randomized trials. Glycoprotein IIb/IIIa receptor antagonists, which appear to be especially effective at preventing MI before and after procedures in higher-risk, invasively treated patients, are a class IA indication for patients with planned invasive management. The small molecule inhibitors (eptifibatide and tirofiban) are effective as "up-front" treatments, whereas abciximab should be reserved for patients with imminently planned angioplasty. Clopidogrel (when prescribed for 3 to 12 months) has been shown to reduce the incidence of vascular events in a broad population of patients with ACS,[16] including patients undergoing coronary angioplasty and stent placement. Because of increased risk of major bleeding after coronary artery bypass grafting (CABG) among patients who have received clopidogrel in the prior 5 days, many physicians wait until after the diagnostic angiogram (for patients scheduled to undergo angiography in the early phase) before starting clopidogrel, to avoid having to delay surgery for those who need it.

Anticoagulant therapy, in the form of either unfractionated or low-molecular-weight heparin, is a class IA recommendation for the acute hospital phase of ACS. Although recent trials have not shown superiority of enoxaparin over unfractionated heparin,[14] an overview of large, randomized trials shows that enoxaparin is modestly more effective than unfractionated heparin in preventing death and recurrent MI at

the cost of a modest increase in bleeding.[17] Even when an early invasive strategy is planned, enoxaparin is a reasonable alternative to unfractionated heparin.

Direct thrombin inhibitors have been shown to be more effective than heparin at inhibiting thrombin activity, as measured by fibrinopeptide A, the peptide cleavage product that results during the formation of fibrin.[18] An overview of all large, randomized, clinical trials, encompassing 36,000 patients, shows that direct thrombin inhibitors, and especially the bivalent hirudin-based inhibitors, are modestly more effective than heparin at reducing MI in the broad spectrum of ACS.[19] There was a 15% relative risk reduction in death or MI during treatment with direct thrombin inhibitors ($P = .001$). These findings support the concept that direct thrombin inhibition in ACS is a clinically effective approach. For patients with suspected or documented heparin-induced thrombocytopenia, lepirudin or bivalirudin are reasonable alternatives.

The longer-term benefits of anticoagulation therapy following acute MI have been demonstrated with the vitamin K antagonist warfarin.

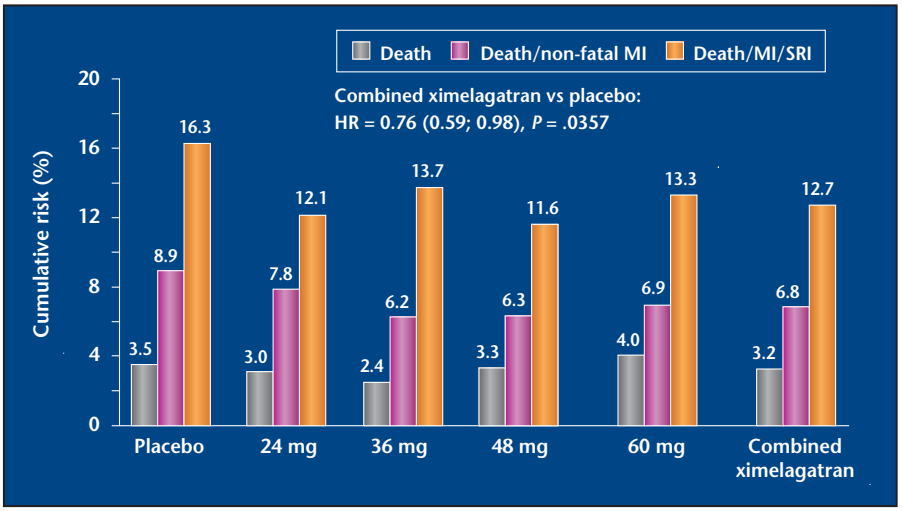


Figure 1. *Combined endpoint efficacy results for ximelagatran versus placebo in the ESTEEM trial. MI, myocardial infarction; SRI, severe recurrent ischemia. Data from Wallentin et al.*[21]

Direct thrombin inhibitors have been shown to be more effective than heparin at inhibiting thrombin activity, as measured by fibrinopeptide A, the peptide cleavage product that results during the formation of fibrin.

In the Warfarin, Aspirin, Reinfarction Study II (WARIS-II), there was a 20% to 30% relative risk reduction in the primary end point of death, MI, and stroke with warfarin either instead of (target INR 2.8-4.2) or in addition to (target INR 2.0-2.5) low-dose aspirin.[20] The absolute rates of the primary end point were 20.0%, 16.7%, and 15.0% with aspirin alone, warfarin alone, and warfarin plus aspirin, respectively. Warfarin was accompanied by only a modest increase in risk of bleeding. However, it has not become a mainstay in treatment, partly because of the inconvenience and difficulty of adequately monitoring treatment and the concern over major bleeding.

Ximelagatran in Acute Coronary Syndromes

The rationale for the use of oral direct thrombin inhibitors following ACS is based on the observation that, in spite of available antithrombotic therapies, the risk of recurrent thrombotic events following ACS remains high, both early and late after presentation, when the coagulation system remains activated. As anticoagulants, direct thrombin inhibitors have advantages over heparin in that they are more predictable, potent agents that can inhibit clot-bound as well as free thrombin, are neutralized by circulating proteins such as platelet factor 4, and are not dependent on anti-thrombin III.

Ximelagatran, the first in a new class of oral direct thrombin inhibitors, has the additional advantage of allowing the extension of treatment into the high risk, post-hospital phase, thereby avoiding the attendant risk of rebound reactivation during the early high-risk period. Ximelagatran is bioconverted to its active form, melagatran, which is primarily renally excreted. Ximelagatran's rapid onset of action, predictable pharmacokinetic profile, and 4 to 5 hour half-life allow twice-daily dosing with dependable anticoagulant effect.

ESTEEM Trial

Ximelagatran's anticoagulant efficacy and safety have been well studied in atrial fibrillation and in prevention of thromboembolism following orthopedic surgery. The Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patiEnts with rEcent and Myocardial damage (ESTEEM) phase II trial provides the first clinical outcome data for ximelagatran in ACS.[21]

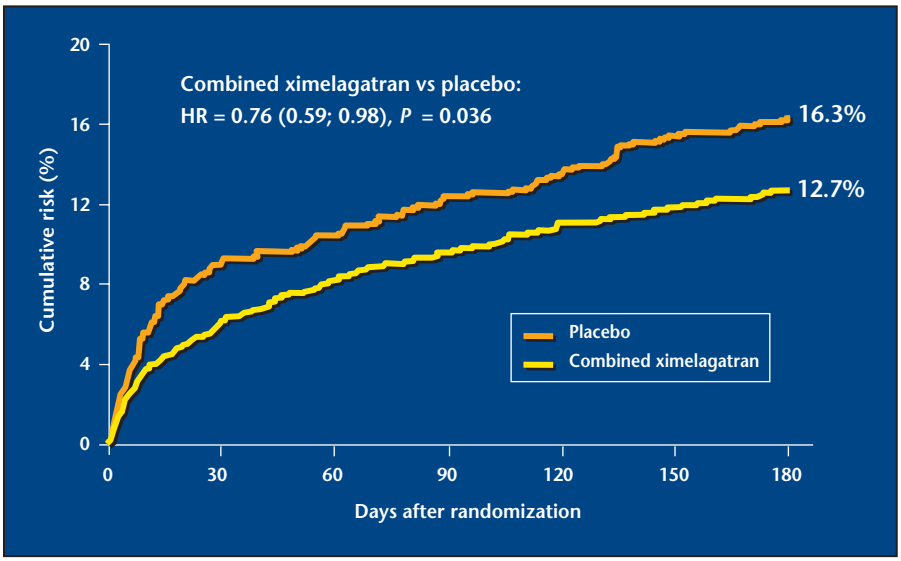


Figure 2. *Rates of combined endpoints (death/nonfatal myocardial infarction/severe recurrent ischemia) over a 6-month period in the placebo versus combined ximelagatran groups in the ESTEEM Trial. Reproduced with permission from Wallentin et al.*[21]

ESTEEM Design

ESTEEM was a placebo-controlled, double-blind, international study of 1883 post-MI patients, evaluating 4 dosage regimens of ximelagatran (Figure 1). The objective was to determine the efficacy of ximelagatran in addition to aspirin for prevention of death, non-fatal recurrent MI, and severe recurrent ischemia in high-risk patients who were unlikely to undergo urgent coronary intervention. Other important end points included stroke, bleeding, and blood tests, including those for liver function abnormalities.

Eligible patients had experienced MI within the previous 2 weeks, either with or without ST elevation, and were also considered at high risk for a recurrent event based on 1 of the following criteria: older age (≥ 65 years), diabetes, prior vascular disease (MI, stroke, multivessel coronary disease), heart failure, new left bundle branch block or ST depression, or history of hypertension. Patients with recent prior or with planned revascularization within 60 days, known liver disease, or who were at high risk of bleeding were excluded. Because ximelagatran is renally excreted, patients with severe renal dysfunction (creatinine clearance < 30 ml/min) were also excluded.

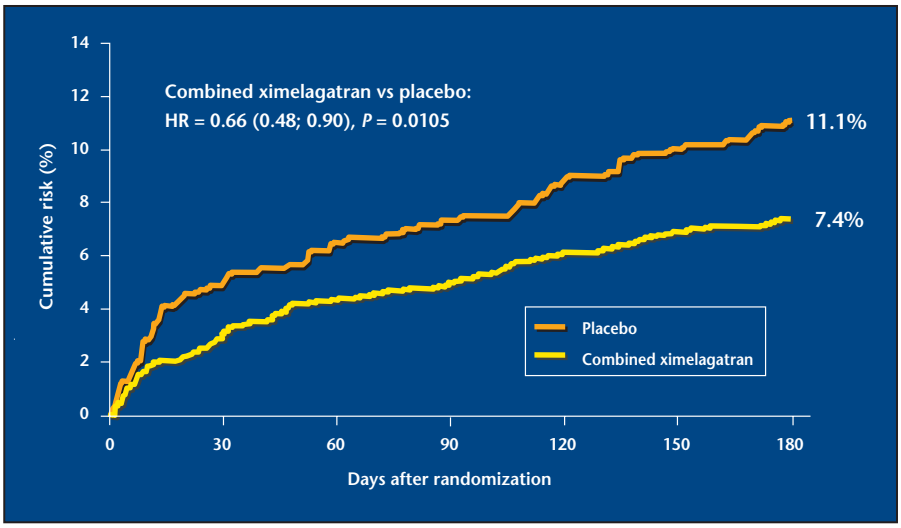
Patients were randomized to 1 of 4 doses of ximelagatran (24 mg, 36 mg, 48 mg, or 60 mg) twice daily or placebo for 6 months (Figure 1). The definition of severe recurrent ischemia was a strict one, requiring severe angina at rest in spite of optimal therapy, plus new ischemic ECG changes, elevation in cardiac markers (not meeting MI definition), or admission for unplanned coronary angiography.

The baseline characteristics of the study population were typical for ACS trials, with the exception of slightly older mean age of 69 years (by design), 22% with prior MI, and 22% with diabetes. About two-thirds had ST elevation MI, and the rest had non-ST elevation MI. Patients were enrolled an average of 6 days after the index MI. Aspirin was used at entry in 99% and heparin in 90% of the population.

ESTEEM Efficacy Results

Ximelagatran was significantly more effective than placebo at reducing the primary end point of death, MI, and severe recurrent ischemia ($P = 0.036$). There was no evidence of a dose-dependent effect, with each dose of ximelagatran having a lower rate of the primary end point than placebo. At 6 months, the rate of the primary

Figure 3. *Rates of combined end points (death/myocardial infarction/stroke) over a 6-month period in the placebo versus combined ximelagatran groups in the ESTEEM Trial. Reproduced with permission from Wallentin et al.*[21]



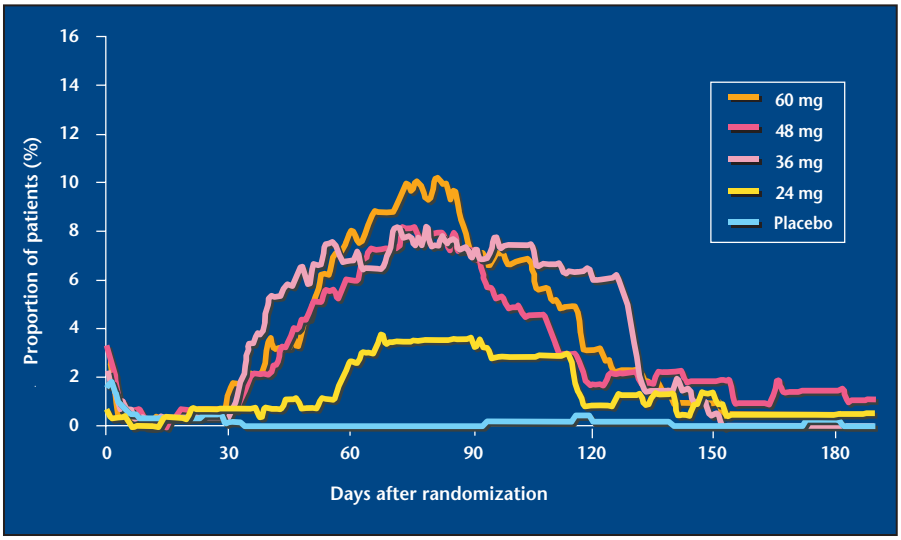


Figure 4. *Rates of alanine amino-transaminase levels measured greater than 3 times the upper limit of normal in all five arms of the ESTEEM Trial. Eight patients in the ximelagatran groups and 1 patient in the placebo group also had elevated bilirubin greater than 2 times the upper limit of normal. Data from Wallentin et al.*[21]

end point was 12.7% in the ximelagatran groups and 16.3% in the placebo group, or a 24% relative risk reduction. The Kaplan-Meier curves (Figure 2) show an early separation and a sustained effect for the primary end point. Death and nonfatal MI was reduced from 8.9% in placebo to 6.8% in the combined arms. An important post-hoc analysis was the impact on a composite thrombotic clinical end point (death, MI, and stroke), which was reduced by 34% ($P = 0.01$), from 11.1% to 7.4% (Figure 3).

ESTEEM Safety Results

Major bleeding, defined as fatal or associated with a 2 g/dL drop in hemoglobin or at least a 2 unit transfusion, was not significantly higher with ximelagatran (1.8%) than with placebo (0.9%). Whereas major bleeding did not appear to be dose-dependent and the number of events was small, total bleeding (major plus minor) was higher for ximelagatran (21.9% vs 13.2%) and increased as the dose increased.

There was no evidence of a dose-dependent effect, with each dose of ximelagatran having a lower rate of the primary end point than placebo.

Similar to what has been seen in other trials, a small proportion of patients developed liver function abnormalities during treatment with ximelagatran. The reason for this is currently not clear, but liver enzyme elevations appear to occur early, resolving spontaneously in some patients and after drug withdrawal in others. Alanine amino-transaminase elevations greater than 3 times the upper limit of normal were observed in about 11% of patients (6.5% at the lower, 24 mg-twice-daily dose) treated with ximelagatran (Figure 4). Nine patients in the ximelagatran and 3 in the placebo group had bilirubin elevation greater than 2 times normal. Elevation of transaminase generally was detected after 2-6 months of treatment, and peaked after 60-120 days. The protocol called for weekly testing of alanine amino-transaminase for a value greater than 2 times normal, study drug withdrawal for greater than 3 times normal with no improvement in 4 weeks, and study drug discontinuation for greater than 5 times normal. Otherwise, the occurrence of all reported adverse events and serious adverse events were similar between ximelagatran and placebo.

ESTEEM in the Context of Other Trials

In the high-risk population of medically-treated, post-MI patients in ESTEEM, there was an impressive 3.6% absolute (24% relative) risk reduction in the primary end point and 3.7% absolute (34% relative) risk reduction in the combined end point

Table 2
Reduction in Vascular Events Post-Acute Coronary Syndrome

Agent	RRR	Absolute Reduction	Reference
Aspirin	25 %	3.5 %	22
Warfarin	29 %	5.0 %	20
Clopidogrel	20 %	2.1 %	16
Ximelagatran	34 %	3.7 %	21

RRR, relative risk reduction.

of death, MI, and stroke. This was accompanied by an increase in minor bleeding and a transient increase in alanine aminotransaminase levels in a small proportion of patients. The reduction of vascular events compares favorably to other effective and commonly used antithrombotic therapies[19-22] in this population (Table 2). Thus, in these patients, ximelagatran has promise as a treatment of important clinical value. A phase III trial is warranted.

Conclusions

ACS as the acute manifestation of CHD has become the most common worldwide cause of death. Antithrombotic therapies provide a cornerstone of contemporary treatment, yet there is an unmet need for more effective antithrombotic strategies, including during the high-risk, post-discharge months. More effective, safe, and convenient oral anticoagulants such as ximelagatran provide an important opportunity to build on current treatments to improve patient outcomes. ■

References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*. 1997;349(9061):1269-1276.
2. American Heart Association. *Heart Disease and Stroke Statistics – 2004 Update*. Dallas, Tex.:American Heart Association;2002.
3. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). 2002. Available at: http://www.acc.org/clinical/guidelines/unstable/angina.pdf.
4. Furman MI, Dauerman HL, Goldberg RJ, et al. Twenty-two year (1975 to 1997) trends in the incidence, in-hospital and long-term case fatality rates from initial Q-wave and non-Q-wave myocardial infarction: a multi-hospital, community-wide perspective. *J Am Coll Cardiol*. 2001;37:1571-1580.
5. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA*. 1999;281(8):707-713.
6. Bahit CM, Granger CB, Wallentin L. Persistence of the prothrombotic state after acute coronary syndromes: implications for treatment. *Am Heart J*. 2002;143:205-216.
7. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003;108:1664-1672.
8. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation*. 2000;101:570-580.
9. Buffon A, Biasucci LM, Liuzzo G, et al. Widespread coronary inflammation in unstable angina. *N Engl J Med*. 2002;347:5-12.
10. Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. *Circulation*. 2001;103:604-616.
11. Van Belle E, Lablanche JM, Bauters C, et al. Coronary angioscopic findings in the infarct-related vessel within 1 month of acute myocardial infarction: natural history and the effect of thrombolysis. *Circulation*. 1998;97:61-68.
12. Merlini PA, Bauer KA, Oltana L, et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. *Circulation*. 1994;90:61-68.
13. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet*. 1999;354:701-707.
14. Ferguson JJ, Califf RM, Antman EM, et al; SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA*. 2004;292:45-54.
15. Bahit MC, Topol EJ, Califf RM, et al.

Main Points

- Over the past decade, there has been a shift in the pattern of acute coronary syndromes (ACS), such that a smaller proportion of acute myocardial infarction (MI) is characterized by ST elevation and a larger proportion is non-ST elevated, creating a greater likelihood for reinfarction in the long term.
- The administration of anticoagulant therapy is complicated by the phenomenon of "heparin rebound," an increased risk of reactivation in the hours after discontinuation of antithrombin therapy. Thus, more effective acute and post-discharge antithrombotic therapies are needed to improve the outcome of patients with ACS.
- The longer-term benefits of anticoagulation therapy following acute MI have been demonstrated with the vitamin K antagonist warfarin but it has not become a mainstay in treatment, partly because of the inconvenience and difficulty of adequately monitoring treatment and the concern over major bleeding.
- Ximelagatran, the first in a new class of oral direct thrombin inhibitors, is characterized by rapid onset of action, a predictable pharmacokinetic profile, and a 4 to 5 hour half-life, allowing twice-daily dosing with dependable anticoagulant effect.
- The Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent and Myocardial Damage (ESTEEM) phase II trial studied 4 dosing regimens of ximelagatran in the post-ACS setting and noted a 24% relative risk reduction versus placebo for death, reinfarction, and severe recurrent ischemia, in the first 6 months following the initial event.
- The reduction of vascular events seen in ESTEEM compares favorably to other effective and commonly used antithrombotic therapies in this population, thus holding promise as a treatment of important clinical value in ACS and warranting a phase III trial.

Reactivation of ischemic events in acute coronary syndromes: results from GUSTO-IIb. *J Am Coll Cardiol*. 2001;37(4):1001-1007.
16. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001; 345:494-502.
17. Petersen JL, Mahaffey KW, Hasselblad V, et al. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA*. 2004; 292:89-96.
18. Kottke-Marchant K, Bahit MC, Granger CB, et al. Effect of hirudin vs heparin on haemostatic activity in patients with acute coronary syndromes; the GUSTO IIb haemostatis substudy. *Eur Heart J*. 2002;23:1202-1212.
19. The Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet*. 2002;359(9313):294-302.
20. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med*. 2002;347;969-974.
21. Wallentin L, Wilcox RG, Weaver WD, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. *Lancet*. 2003;362:789-797.
22. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71-86.