Antithrombotic Therapy for Coronary Artery Disease

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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This chapter about antithrombotic therapy for coronary artery disease (CAD) is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST 2004; 126:179S–187S*). Among the key recommendations in this chapter are the following: For patients presenting with non–ST-segment elevation (NSTE) acute coronary syndrome (ACS), we recommend immediate and then daily oral aspirin (Grade 1A). For patients with an aspirin allergy, we recommend immediate treatment with clopidogrel, 300-mg bolus po, followed by 75 mg/d indefinitely (Grade 1A). In all NSTE ACS patients in whom diagnostic catheterization will be delayed or when coronary bypass surgery will not occur until > 5 days, we recommend clopidogrel as bolus therapy (300 mg), followed by 75 mg/d for 9 to 12 months in addition to aspirin (Grade 1A). In NSTE ACS patients in whom angiography will take place within 24 h, we suggest beginning clopidogrel after the coronary anatomy has been determined (Grade 2A). For patients who have received clopidogrel and are scheduled for coronary bypass surgery, we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (Grade 2A). In moderate- to high-risk patients presenting with NSTE ACS, we recommend either eptifibatide or tirofiban for initial (early) treatment in addition to treatment with aspirin and heparin (Grade 1A). For the acute treatment of NSTE ACS, we recommend low molecular weight heparins over unfractionated heparin (UFH) [Grade 1B] and UFH over no heparin therapy use with antiplatelet therapies (Grade 1A). We recommend against the direct thrombin inhibitors as routine initial antithrombin therapy (Grade 1B). For patients after myocardial infarction, after ACS, and with stable CAD, we recommend aspirin in doses from 75 to 325 mg as initial therapy and in doses of 75 to 162 mg as indefinite therapy (Grade 1A). For patients with contraindications to aspirin, we recommend long-term clopidogrel (Grade 1A). For primary prevention in patients with at least moderate risk for a coronary event, we recommend aspirin, 75 to 162 mg/d, over either no antithrombotic therapy or vitamin K antagonist (VKA) [Grade 2A]; for patients at particularly high risk of events in whom the international normalized ratio (INR) can be monitored without difficulty, we suggest low-dose VKA (target INR, 1.5) [Grade 2A].

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Key words: acute coronary syndrome; antithrombotic; aspirin; clopidogrel; coronary artery disease; prophylaxis

Abbreviations: ACC = American College of Cardiology; ACS = acute coronary syndrome; ACEI = angiotensin-converting enzyme inhibitors; ACT = activated clotting time; ADP = adenosine diphosphate; AHA = American Heart Association; AMI = acute myocardial infarction; APRICOT = Antithrombo tics in the Prevention of Reocclusion in Coronary Thrombolysis; aPTT = activated partial thromboplastin time; ASPECT = Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CAPRIE = Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events; CARS = Coumadin Aspirin Reinfarction Study; CHF = congestive heart failure; CI = confidence interval; CrCl = creatinine clearance; CRP = C-reactive protein; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; DTI = direct thrombin inhibitor; ESSENCE = Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events; ESTEEM = Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Recent Myocardial Damage; FRIC = Fragmin in Unstable Coronary Artery Disease; FRISC = Fragmin During Instability in Coronary Artery Disease; GP = glycoprotein; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; HIT = heparin-induced thrombocytopenia; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; INR = international normalized ratio; ISIS = International Studies of Infarct Survival; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NS = not significant; NSTE = non–ST-segment elevation; OASIS = Organization to Assess Strategies for Ischemic Syndromes; OR = odds ratio; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network; PCI = percutaneous coronary intervention; PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SC = subcutaneous; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction; TPT = Thrombosis Prevention Trial; UA = unstable angina; UFH = unfractionated heparin; VKA = vitamin K antagonist; WARCEF = Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction; WARIS = Warfarin-Aspirin Reinfarction Study; WASH = Warfarin/Aspirin Study in Heart Failure; WATCH = Warfarin Antiplatelet Trial and Chronic Heart Failure

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Antithrombotic therapies, both antiplatelet as well as anticoagulant, have become the mainstays of treatment for coronary artery diseases (CADs). Based on the important role of thrombosis in the pathogenesis and complications of the atherosclerotic process, antithrombotic therapy has become essential treatment for both

acute and chronic CAD. This section will cover the broad topic of CAD with the exception of reperfusion therapies for ST-segment elevation acute myocardial infarction (AMI) and antithrombotic therapy for patients undergoing percutaneous coronary intervention (PCI).

Interpretation of the results of the trials of antithrombotic therapies in CAD requires familiarity with the changing nomenclature for categorizing patients with acute coronary disease. Following the observation by DeWood et al[1] in the late 1970s that intracoronary thrombosis was a key mechanism in the pathophysiology of AMI, the focus in acute cardiovascular research throughout the 1980s and into the early 1990s centered on reperfusion therapy. Data from the large trials demonstrated the importance of rapid and accurate diagnosis coupled with rapid administration of fibrinolytic therapy. Such an approach reduced premature deaths and therefore became incorporated into the quality assessment of the care given to these patients.

During this period of intense investigation of AMI, investigators became increasingly aware of a much larger group of patients presenting to hospitals for evaluation of acute chest pain who did not have the dramatic findings of ST-segment elevation on the initial ECG. Overview analyses[2] from the Fibrinolytic Trialists' Collaboration showed that among patients with suspected AMI, virtually all ECG subgroups benefited from treatment with fibrinolysis with the notable exception of patients presenting initially with ST-segment depression.

The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb trial[3] was one of the first large-scale attempts to study the spectrum of patients presenting with acute chest pain, stratifying the randomization on the basis of their initial ECG findings (ST-segment elevation or not). GUSTO IIb results showed that patients without ST-segment elevation represent a different population from those with ST-segment elevation. They were older, more likely to be female, and have more comorbidity than the group with ST-segment elevation. For descriptive purposes, these patients were being categorized not on the basis of their admitting diagnosis, but rather on the diagnosis that became clear 12 to 24 h later, namely unstable angina (UA) or myocardial infarction (MI), typically non–Q-wave infarction.

Investigators were performing fewer studies in the UA and non–Q-wave MI patients, due in part to the heterogeneity of the presenting symptoms and signs and in part to a lack of knowledge of the seriousness of the condition. Unlike patients presenting with ST-segment elevation, these patients had much more diverse and much less dramatic initial clinical presentations. Consequently, their initial medical evaluation was less urgent and less focused, and they were typically admitted to the hospital for observation (ie, to rule out MI) rather than treated aggressively. Recognition of the size and clinical importance of this neglected group of patients shifted the focus of acute cardiovascular clinical research from fibrinolytic therapy in ST-segment elevation infarction patients to those with non–ST-segment elevation (NSTE).

The diagnoses of UA and non–Q-wave infarction are made retrospectively, after a period of observation and a review of serial ECGs and cardiac enzymes. The results of these trials showed that these patients have a moderate-to-high risk of early adverse outcomes, and therefore may benefit from more rapid assessment, triage, and treatment.[4]

A change in the terminology describing these patients reflects this evolution in thinking. Patients presenting with symptoms consistent with acute ischemic chest pain can be quickly differentiated by their ECG as having an acute coronary syndrome (ACS) with or without persistent ST-segment elevation. Those with ST-segment elevation can be rapidly evaluated for treatment with reperfusion therapy, and those without ST-segment elevation can be further risk stratified (including with troponin testing) and treated with appropriate antiplatelet and antithrombin therapies.

The recently revised American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with UA and NSTE MI reflect this changing nomenclature.[5] The initial focus of the guidelines is to consider the patients with acute ischemic symptoms as having an ACS, and then to further differentiate them into ACS with or without ST-segment elevation. The immediate treatment decisions then flow from this differentiation and categorization.

This chapter is organized around the various disease states, with a focus on the antithrombotic recommendations for each patient group: (1) those presenting with NSTE ACSs; (2) ACS patients post-MI; (3) patients with chronic, stable CAD; (4) patients with congestive heart failure (CHF); and (5) patients without a clinical diagnosis of CAD. Table 1 describes the question definition and eligibility criteria for the studies considered in each section of the recommendations that follow.

1.0 Acute Management of NSTE ACSs

1.1 Antiplatelet therapies

1.1.1 Aspirin

The chapter by Patrono et al in this Supplement describes aspirin and other antiplatelet agents. Aspirin causes irreversible inhibition of platelet cyclooxygenase, thereby preventing the formation of thromboxane A_2, a platelet aggregant and potent vasoconstrictor.[6] Aspirin has no effect on platelet aggregation induced by other agonists, and is therefore a weak platelet inhibitor. The adverse effects of aspirin are primarily related to bleeding, particularly GI, which is less common at the low dosage of 75 to 162 mg/d needed to inhibit platelet aggregation than at higher doses.

An estimated 5.2 to 40% of aspirin-treated patients have some level of GI intolerance.[6] An analysis[7] from the Duke Databank for Cardiovascular Diseases reported that among a sample of 2,694 patients with CAD, > 13% did not report aspirin use at the 1-year follow-up; more detailed surveying revealed that 1.9% had symptoms or signs consistent with a true allergic reaction.

Various drugs inhibiting thromboxane A_2 synthase or blocking the thromboxane A_2 receptor, or both, have been

Section	Population	Intervention(s) or Exposure	Outcome	Methodology
1.1.1	NSTE ACS	Aspirin	Mortality MI Stroke Bleeding	RCTs
1.1.2	NSTE ACS	Thienopyridines	Composite: death, MI, stroke; ischemia Bleeding	RCTs
1.1.2	NSTE ACS	Dipyridamole	Composite: death, MI, stroke Ischemia Bleeding	RCTs
1.1.4	NSTE ACS	GP IIb/IIIa inhibitors	Composite: death, MI Ischemia Bleeding	RCTs
1.2.1	NSTE ACS	UFH	Composite: death, MI Ischemia Bleeding	RCTs
1.2.1	NSTE ACS	Level of anticoagulation	Composite: death, MI Ischemia Bleeding	Observational studies
1.2.2	NSTE ACS	LMWHs	Composite: death, MI Ischemia Bleeding	RCTs
1.2.3–1.2.4	NSTE ACS	Antithrombin therapy, indirect and direct, selective factor Xa inhibitors	Composite: death, MI Ischemia Bleeding	RCTs and observational studies
1.2.5	NSTE ACS	DTIs	Composite: death, MI Ischemia Bleeding	RCTs and observational studies
2.1	Post MI and post ACS (secondary prevention)	Oral antiplatelet therapies (aspirin and thienopyridines)	Mortality MI Stroke Bleeding	RCTs
2.2	Post MI and post ACS (secondary prevention)	Oral VKAs	Composite: death, MI, stroke Bleeding	RCTs
2.3	Post MI and post ACS (secondary prevention)	Aspirin combined with oral VKAs	Composite: death, MI, stroke Angiographic outcomes Bleeding	RCTs
2.4	Post MI and post ACS (secondary prevention)	Oral DTIs	Composite: death, MI, stroke Angiographic outcomes Bleeding	RCTs
3.1	Chronic, stable CAD	Oral antiplatelet therapies (aspirin and thienopyridines)	Mortality MI Stroke Bleeding	RCTs
3.2	Chronic, stable CAD	Oral VKAs	Composite: death, MI, stroke Bleeding	Observational studies
4.1	CHF	Oral antiplatelet therapies with and without ACEIs and oral VKAs	Composite: death, MI, stroke Bleeding	RCTs and observational studies
5.1	Primary prevention	Oral antiplatelet and anticoagulant therapy	Mortality MI Stroke Bleeding	RCTs

investigated in clinical trials. Although they do not decrease prostacyclin production, they have shown no advantage over aspirin.

Evidence from clinical trials. Oral antiplatelet therapy, mainly aspirin, has been the cornerstone of short-term treatment for > 10 years.[6] Despite its biochemical limitations, aspirin profoundly reduces adverse clinical events among a broad group of patients treated for acute and chronic vascular diseases.[8–12]

In the systematic review by the Antithrombotic Trialists' Collaboration,[8] there were 5,031 patients with UA in 12 trials comparing aspirin to either placebo or no treatment. Treatment with aspirin was associated with an odds reduction in vascular events of 46%.

Most of the excess bleeding related to aspirin is GI. In the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study[13] comparing clopidogrel vs aspirin among patients with chronic vascular disease, the risk of GI bleeding that led to aspirin discontinuation was 0.93%.

While the risk of side effects, particularly GI bleeding, appears to increase with increasing dose, the relationship between efficacy and aspirin dose is less certain. Analyses[8] from the Antithrombotic Trialists' Collaboration suggested that the benefits of aspirin were consistent on a relative basis across a wide range of doses (< 160 mg/d to approximately 1,500 mg/d), while other analyses by Kong et al[14] suggested that the effect of aspirin is weaker at higher doses. Although a head-to-head comparison is necessary to completely resolve the issue, given that the bulk of the available evidence suggests equivalent or even superior effectiveness at lower doses, clinicians can be confident in administering relatively low aspirin doses.

Recommendations

1.1.1. For all patients presenting with NSTE ACS, without a clear allergy to aspirin, we recommend immediate aspirin, 75 to 325 mg po, and then daily, 75 to 162 mg po (**Grade 1A**).

1.1.2 Thienopyridines

Ticlopidine and clopidogrel are adenosine diphosphate (ADP) receptor antagonists that inhibit ADP-induced platelet aggregation and prolong bleeding time (see chapter by Patrono et al).[15] Combining platelet antagonists that have different mechanisms of actions is attractive. Aspirin inhibits the thromboxane A_2-mediated activation and clopidogrel inhibits ADP-mediated activation.

Evidence from clinical trials. The safety profile of ticlopidine is unfavorable, with frequent GI side effects, rash, neutropenia (rarely fatal), thrombocytopenia, and liver function abnormalities (rare). Clopidogrel has a much more favorable safety profile and is well tolerated, as demonstrated in the CAPRIE study[13] of > 19,000 patients. The benefit derived from antiplatelet therapy in patients with coronary heart disease, UA, AMI, and previous MI is well established; however, the question of added benefit from multitargeted antiplatelet regimens, particularly among high-risk patients with NSTE ACS, until recently remained unanswered.

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial,[16] 12,562 patients with NSTE ACS were randomly assigned to receive clopidogrel (300 mg immediately followed by 75 mg qd) or placebo in addition to aspirin, 75 to 325 mg/d, for 3 to 12 months. The first primary outcome—a composite of death from cardiovascular causes, nonfatal MI, or stroke—occurred in 9.3% and 11.4% of patients receiving clopidogrel and placebo, respectively (relative risk [RR], 0.80; 95% confidence interval [CI], 0.72 to 0.90; p < 0.001). Considered individually, CURE[16] showed significant reductions in nonfatal MI (5.2% vs 6.7%; RR, 0.77; 95% CI, 0.67 to 0.89) and trends toward reduction in death (5.1% vs 5.5%;

RR, 0.93; 95% CI, 0.79 to 1.08), and stroke (1.2% vs 1.4%; RR, 0.86; 95% CI, 0.63 to 1.18) with clopidogrel. The rate of the second primary outcome—death from cardiovascular causes, nonfatal MI, stroke, or refractory ischemia—was also lower in the clopidogrel group (16.5% vs 18.8%; RR, 0.86; 95% CI, 0.79 to 0.94; p = 0.001). Significantly fewer patients in the clopidogrel group had severe ischemia (2.8% vs 3.8%; RR, 0.74; 95% CI, 0.61 to 0.90; p = 0.003) or recurrent angina (20.9% vs 22.9%; RR, 0.91; 95% CI, 0.85 to 0.98; p = 0.01). The benefits of clopidogrel were consistent across a broad range of patient subsets, including those with MI, ST-segment deviation, elevated cardiac biomarkers, diabetes mellitus, age > 65 years, and high-risk features. Although the absolute use of concomitant glycoprotein (GP) IIb/IIIa inhibitors was low in CURE,[16] the treatment effect of clopidogrel was consistent among those receiving and not receiving the IV platelet inhibitors.

There was a 34% RR reduction (RRR) [95% CI, 0.51 to 0.86] in the occurrence of cardiovascular death, MI, stroke, or severe ischemia at 24 h among patients receiving clopidogrel (p < 0.01). A significant benefit was reported at 7 days (RR, 0.77; 95% CI, 0.67 to 0.89), and an appreciable trend at 30 days (RR, 0.86; 95% CI, 0.73 to 1.01).

Major bleeding (defined as disabling hemorrhage, intraocular hemorrhage leading to visual loss, or bleeding requiring transfusion of at least 2 U of blood) was significantly more common in clopidogrel-treated patients (3.7% vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; p = 0.001). Life-threatening bleeding (fatal hemorrhage or causing a reduction in hemoglobin of 5 g/dL or to substantial hypotension requiring inotropic support, or surgical intervention; symptomatic intracranial hemorrhage or transfusing of ≥ 4 U of blood) was also more common, although the difference did not reach conventional levels of statistical significance (2.2% vs 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56). There was not an excess rate of fatal bleeding, bleeding that required surgical intervention, or hemorrhagic stroke. The number of patients requiring transfusion of ≥ 2 U of blood was higher in the clopidogrel group (2.8% vs 2.2%, p = 0.02).

The rate of major bleeding with clopidogrel was higher early (within 30 days of randomization (2.0% vs 1.5%; RR, 1.31; 95% CI, 1.01 to 1.70) and also late (> 30 days after randomization: 1.7% vs 1.1%; RR, 1.48; 95% CI, 1.10 to 1.99). Bleeding associated with coronary artery bypass grafting (CABG) was particularly high among patients receiving clopidogrel within 5 days of surgery (9.6% vs 6.3%; RR, 1.53; p = 0.06). Overall, the risk of minor bleeding was significantly higher in clopidogrel-treated patients (5.1% vs 2.4%; p = 0.001).

Recommendations

1.1.2.1. For all NSTE ACS patients with an aspirin allergy, we recommend immediate treatment with clopidogrel, 300-mg bolus po, followed by 75 mg/d indefinitely (**Grade 1A**).

1.1.2.2. In all NSTE ACS patients in whom diagnostic catheterization will be delayed or when coronary bypass

surgery will not occur until > 5 days following coronary angiography, we recommend clopidogrel be administered immediately as bolus therapy (300 mg), followed by 75 mg/d for 9 to 12 months in addition to aspirin (**Grade 1A**).

Underlying values and preferences: This recommendation places a relatively high value on avoiding MI and a relatively low value on avoiding major bleeding.

1.1.2.3. In NSTE ACS patients in whom angiography will take place rapidly (≤ 24 h), we suggest beginning clopidogrel after the coronary anatomy has been determined (**Grade 2A**).

Underlying values and preferences: This recommendation places a relatively high value on avoiding serious bleeding balanced against a low absolute benefit of clopidogrel in the first 24 h of treatment.

1.1.2.4. For patients who have received clopidogrel and are scheduled for coronary bypass surgery, we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (**Grade 2A**).

1.1.3 Dipyridamole

The effects of dipyridamole appear to be related to an increase in platelet cyclic adenosine monophosphate. Its antithrombotic effects are more evident on prosthetic surfaces. In contrast to aspirin, it does not increase the risk of GI bleeding even when combined with warfarin. Currently, there is no evidence to support use of dipyridamole either instead of, or in addition to, aspirin and the thienopyridines in the acute treatment of patients presenting with NSTE ACS.

1.1.4 GP IIb/IIIa inhibitors

GP IIb/IIIa receptor inhibitors have been tested as arterial antithrombotics, and three have gained market approval for clinical use: abciximab, a monoclonal antibody fragment; eptifibatide, a peptide inhibitor; and tirofiban, a peptidomimetic inhibitor. Abciximab and eptifibatide are indicated as adjunctive antithrombotics in patients undergoing PCI, while eptifibatide and tirofiban are approved among patients presenting with NSTE ACSs.

The chapter by Popma et al in this Supplement covers the use of the GP IIb/IIIa inhibitors during PCI, and the chapter by Ohman et al contains information regarding their role in NSTE MI. This chapter will review use of these drugs in patients with NSTE ACS.

Clinical trials. A systematic overview by Boersma and colleagues[20] included all 31,402 patients presenting with NSTE ACS enrolled in trials of GP IIb/IIIa inhibitors randomizing ≥ 1,000 patients. Overall, there was a significant 1.2% absolute decrease in the 30-day incidence of death or MI (5.7% vs 6.9%). The data were consistent across multiple subgroups with the exception of women, in whom the estimate of the treatment effect favored placebo (interaction p < 0.0001 for the difference in effect between men and women; Fig 1). In the overview by Boersma and colleagues,[17] men and women who are troponin positive have a similar beneficial treatment ef-

fect, while men and women who are troponin negative do not appear to gain a benefit from the platelet inhibitors. Men were twice as likely in this analysis to be troponin positive as women. This suggests that the observed gender difference is less likely to be a treatment issue and more likely to be an issue with diagnosis. This hypothesis warrants further consideration and evaluation but is consistent with the general observation that these therapies are most beneficial among the groups at highest risk, such as those with diabetes[18,19] or dynamic ST-segment changes.[20] Boersma, in an overview analysis of three trials (Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms [PRISM-PLUS], and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy [PURSUIT])[21,22] also demonstrated a convincing effect of the GP IIb/IIIa inhibitors before, after, and independent of coronary procedures.

Abciximab. The GUSTO IV ACS trial[22,23] enrolled 7,825 patients presenting with ischemic symptoms and either biomarker or ECG evidence of MI/ischemia. Patients were randomized to one of three treatment groups, in addition to receiving heparin or aspirin: placebo, abciximab bolus plus 24-h infusion, or abciximab bolus plus 48-h infusion.[23] Patients were treated conservatively without early cardiac catheterization. The primary end point was the 30-day composite of death and MI. At 30 days, there were no significant differences among the treatment groups with regard to the primary efficacy composite, but abciximab was associated with a fivefold increased risk in major bleeding (1.0% vs 0.2%) and an increased risk of thrombocytopenia.

Eptifibatide. The large, international PURSUIT study[24] enrolled 10,948 patients presenting with a NSTE ACS and randomized to one of three drug regimens on a background of aspirin and unfractionated heparin (UFH): eptifibatide, 180 μg/kg bolus, followed by an infusion of either 2.0μg/kg/min or 1.3 μg/kg/min or placebo bolus plus infusion. The primary end point of the PURSUIT study[24] was the composite of death or MI at 30 days. Since neither dose of eptifibatide had yet been studied in randomized clinical trials, the study was designed to drop the lower dose if the high dose appeared to have an acceptable bleeding profile after approximately 1,000 patients had been enrolled per treatment group. In the primary analysis of high dose vs placebo, eptifibatide reduced the 30-day composite from 15.7 to 14.2% (p = 0.042). The benefit was maintained at 6 months. Bleeding was increased overall among the treated patients, with GUSTO moderate or severe bleeding occurring at a rate of 12.8% among eptifibatide patients compared with 9.9% among placebo patients. This bleeding difference was confined to patients not undergoing CABG. There was a significant increase in thrombocytopenia among the patients treated with the platelet inhibitor.[25] There was no increase in the risk of intracranial hemorrhage among those treated with eptifibatide.

Characteristic	Category	Prevalence/ event rate	Odds ratio	p for interaction
Age (years)	<60	(35%/7·3%)	0·86	0·10
	60-69	(30%/11·1%)	0·91	
	≥70	(35%/15·5%)	0·96	
Sex	Female	(35%/11·1%)	1·15	<0·0001
	Male	(65%/11·3%)	0·81	
Region	Western Europe	(29%/10·6%)	0·92	0·46
	Southern Europe	(11%/12·2%)	0·92	
	Eastern Europe	(16%/12·4%)	0·97	
	North America	(32%/11·3%)	0·85	
	South America	(4%/12·3%	0·86	
Diabetes	No	(78%/10·6%)	0·93	0·48
	Yes	(22%/13·7%)	0·88	
Smoking	Never	(38%/11·1%)	0·93	0·43
	Former	(33%/12·1%)	0·87	
	Current	(29%/10·4%)	0·96	
Previous MI	No	(66%/10·1%)	0·92	0·74
	Yes	(34%/13·4%)	0·92	
Heart failure	No	(90%/10·6%)	0·92	0·69
	Yes	(10%/16·6%)	0·86	
Previous CABG	No	(88%/11·1%)	0·90	0·20
	Yes	(12%/12·2%)	1·03	
Previous PTCA	No	(88%/11·4%)	0·92	0·48
	Yes	(12%/10·3%)	0·85	
ST depression	No	(44%/8·9%)	0·83	0·057
	Yes	(56%/13·1%)	0·98	
SBP*	<120	(23%/12·2%)	0·85	0·19
	120-139	(33%/12·3%)	0·80	
	≥140	(44%/12·1%)	0·97	
Heart rate*	<80	(66%/11·8%)	0·86	0·50
	≥80	(34%/13·0%)	0·92	
CK-MB†	<1 ULN	(54%/9·6%)	0·94	0·55
	≥1 ULN	(46%/14·1%)	0·98	
All				

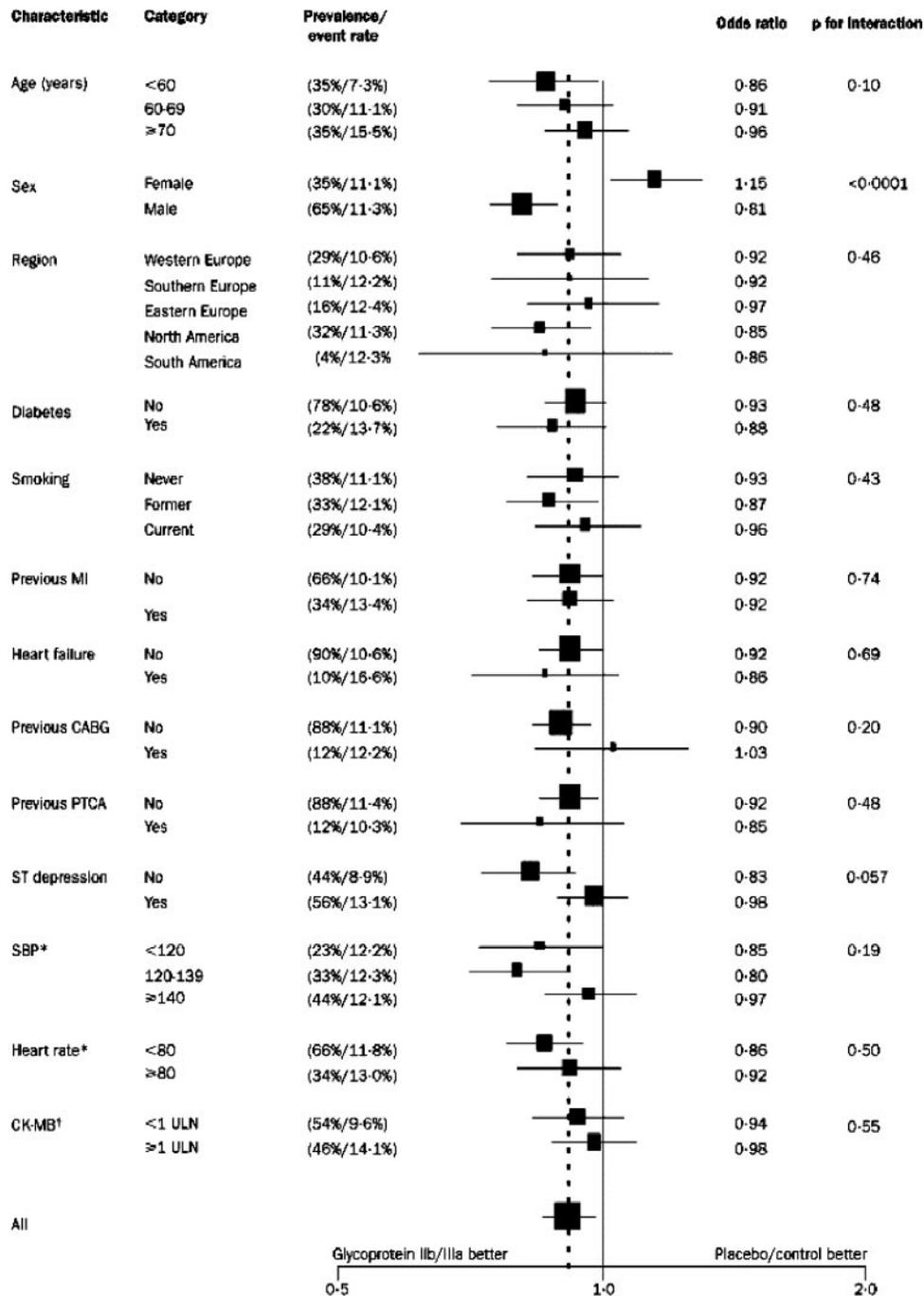Glycoprotein IIb/IIIa better — Placebo/control better

0·5   1·0   2·0

FIGURE 1. Systematic overview of GP IIb/IIIa inhibitor trials among patients presenting with NSTE ACS. This shows the major subgroups at baseline. PTCA = percutaneous translminal coronary angioplasty; SBP = systolic BP; CK = creatine kinase; ULN = upper limit of normal. Reprinted with permission from Elsevier (The Lancet 2002; 359:189–198).

Lamifiban. Lamifiban, while not approved for clinical use, has been studied in two moderate-to-large-scale randomized clinical trials: Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) A and PARAGON B.[26] PARAGON A enrolled 2,282 patients in a modified 3 × 2 factorial design to either high- or low-dose lamifiban or placebo, and UFH or placebo.[26] No patients were enrolled into a group with double placebo. The primary end point of the trial was the 30-day composite of death or MI. The primary results showed no significant differences among the treatment groups with an increased risk of bleeding among lamifiban patients. *Post hoc* analyses demonstrated that a mid-range concentration of

lamifiban was associated with substantial reductions in the 30-day and 6-month composite end points.[27]

Based on these *post hoc* analyses, PARAGON B[27] was designed to test the adjusted dosing strategy of lamifiban; consequently, 5,225 patients were randomized to receive lamifiban (adjusted for weight and estimated creatinine clearance [CrCl]) or placebo on a background of aspirin and either UFH or low molecular weight heparin (LMWH).[28] The primary end point was the 30-day composite of death, MI, or severe recurrent ischemia. There was no significant benefit of lamifiban over placebo (11.8% vs 12.8%, p = 0.329) while lamifiban was associated with a greater incidence of intermediate bleeding (14.0% vs 11.5%, p = 0.002). Based on the nonsignificant findings of these two trials, product registration was not sought.

Tirofiban. Two moderate-size trials have been completed and reported with tirofiban in an NSTE ACS population: Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM)[29] and PRISM-PLUS.[30] The PRISM trial[29] randomized 3,231 patients presenting with an ACS to either tirofiban (loading dose of 0.6 µg/min for 30 min followed by 0.15 µg/kg/min for 47.5 h) or heparin. The drugs were to be administered for 48 h, and cardiac catheterization was to be deferred until the study drug was discontinued. The 48-h primary composite of death, MI, or refractory ischemia was reduced with tirofiban from 5.6 to 3.8% with heparin (p = 0.01). The absolute benefit of tirofiban was maintained through 30 days although the relative benefit was lessened, as expected when additional events accrued in both treatment arms after discontinuation of the therapy. Both groups had a 0.4% incidence of major bleeding.

In the PRISM-PLUS trial,[29] 1,915 patients were randomized to treatment with tirofiban alone, tirofiban with heparin, or heparin alone. The primary end point was the composite of death, MI, or refractory ischemia at 7 days. During an interim review by the Data Safety and Monitoring Board, the tirofiban-alone arm was dropped due to excess mortality at 7 days. The trial continued with the remaining two treatment arms. Tirofiban plus heparin was associated with a significant reduction in the primary composite compared with heparin alone (12.9% vs 17.9%, p = 0.004). This benefit was maintained at 30 days and 6 months. Thrombolysis in Myocardial Infarction (TIMI) trial major bleeding was not significantly increased among the non-CABG patients (1.4% vs 0.8%, p = 0.23).[30]

Broad drug class issues to consider with GP IIb/IIIa inhibitors. Three trials,[28,29,31] PRISM, CAPTURE (Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment), and PARAGON B, have reported a preferential treatment effect of the GP IIb/IIIa inhibitor among patients with elevated troponin levels. Newby et al[31a] have shown that there is a strong treatment interaction with this subgroup, suggesting that the quantitative difference in effect seen in this group is greater than in the troponin-negative population. The ACC-AHA Taskforce Guidelines are consistent with this in putting forth GP IIb/IIIa inhibitors as a class IA recommendation for moderate- to high-risk patients.[5]

Part of the reason for the recommendations that this class of drugs should be used in moderate- to high-risk patients is their value in an invasive strategy.[5,32] None of the six large randomized trials specifically addressed the issue of whether the GP IIb/IIIa inhibitors add incremental value to medical therapy without PCI or CABG by randomizing an appropriate group of patients. Inappropriate analysis of postrandomization subgroups (ie, PCI subgroups that accrue after randomization and thus are subject to bias) suggested that the GP IIb/IIIa inhibitors preferentially benefit patients undergoing percutaneous procedures more than those not undergoing such procedures.[33] Two important issues help to understand this controversy. First, at the time of presentation, it is challenging to predict which specific patients will undergo PCI or CABG based on clinical characteristics alone. It is knowledge of the coronary anatomy gained from a diagnostic cardiac catheterization that dictates revascularization strategy. Second, although the evidence suggests that an early invasive strategy (early cardiac catheterization followed by anatomy-driven revascularization) is superior to a conservative management strategy, the optimal timing of the early catheterization strategy is unknown. In US-based practices, where the median time to catheterization is approximately 24 h, there is a substantial period prior to the procedure that corresponds with the period of highest risk.

The use of multiple antithrombotic agents is complicated for this group of patients. It is clear from the trial data that GP IIb/IIIa inhibitors add clinical value on background therapy of aspirin and heparin. But, the major trials of the GP IIb/IIIa inhibitors were performed prior to the completion of the CURE trial, which itself was predominantly conducted in countries where there was a low usage of the IV platelet inhibitors. Thus, while the effect of clopidogrel, administered in addition to aspirin and heparin, was consistent among the groups receiving and not receiving concomitant GP IIb/IIIa inhibitors, the incremental value of adding GP IIb/IIIa inhibitors to aspirin, heparin, and clopidogrel remains all uncertain.

Recommendations

1.1.4.1. In moderate- to high-risk patients presenting with NSTE ACS, we recommend either eptifibatide or tirofiban for initial (early) treatment in addition to treatment with aspirin and heparin (**Grade 1A**). In these moderate- to high-risk patients who are also receiving clopidogrel, we recommend eptifibatide or tirofiban as additional initial treatment (**Grade 2A**).

1.1.4.2. For patients presenting with NSTE ACS, we recommend **against** abciximab as initial treatment except when coronary anatomy is known and PCI is planned within 24 h (**Grade 1A**).

1.2 Antithrombin Therapies

Pharmacologic therapies designed to attenuate thrombin generation and activity are clinically attractive because of the critical role of thrombosis in ACSs.

1.2.1. UFH

UFH is a heterogeneous mixture of polysaccharide molecules (average molecular weight, 15,000 to 18,000 d) [see chapter by Hirsh et al in this Supplement]. In addition to a high degree of size/length heterogeneity, there is also a substantial amount of compositional heterogenicity. Typically, one third of the molecules found within a standard pharmaceutical heparin preparation contain the pentasaccharide sequence required for antithrombin binding and anticoagulant activity.

A pooled analysis of the Antithrombotic Therapy in Acute Coronary Syndromes study,[34,35] Research on Instability in Coronary Artery Disease,[36] and Théroux et al[11] studies yields an RR of 0.44 (95% CI, 0.21 to 0.93) for death/MI with combination aspirin and UFH therapy compared with aspirin alone.[35–38]

The first trial, conducted by Théroux and colleagues,[11] compared aspirin (325 mg bid), UFH (5,000-U bolus, 1,000 U/h IV), their combination, and placebo in 479 patients. It is the only study that compared UFH (alone) and aspirin (alone) as well as combination therapy. Refractory angina occurred in 8.5%, 16.5%, and 10.7% of patients, respectively (0.47 RR for UFH compared with aspirin; 95% CI, 0.21 to 1.05; p = 0.06). MI occurred in 0.9%, 3.3%, and 1.6% of patients, respectively (RR, 0.25; 95% CI, 0.03 to 2.27; p = 0.18) while any event was observed in 9.3%, 16.5%, and 11.5% of patients, respectively (RR, 0.52; 95% CI, 0.24 to 1.14; p = 0.10). Serious bleeding, defined as a fall in hemoglobin of ≥ 2 g or the need for a transfusion, occurred in 1.7%, 1.7%, and 3.3% of patients, respectively. A majority of events were associated with cardiac catheterization.

The remaining trials investigated potential advantages of combination therapy (UFH plus aspirin) over aspirin monotherapy. Although not statistically different, consistent trends across each study favored combined pharmacotherapy and its ability to reduce death or MI (combined end point).

Therapeutic levels of anticoagulation. The optimal level of anticoagulation in ACS is not well defined. The reason likely relates to inherent complexities in the pharmacokinetics and pharmacodynamics of UFH, the dynamic nature of coronary arterial thrombosis, and the use of coagulation tests designed primarily to assess hemostatic potential. In essence, current laboratory-based tests are oriented more toward the potential of the drug than to treat the thrombus.

The activated partial thromboplastin time (aPTT), used widely to monitor UFH, provides a general assessment of coagulation potential; however, it is most sensitive to factor IIa activity. The "therapeutic" level of anticoagulation with UFH may vary with disease state. In venous thromboembolism, heparin levels > 0.2 U/mL (protamine titration method) accompanied by aPTT values > 1.5 times the upper limit of control appear to reduce the recurrence of thromboembolism.[39,40] A similar aPTT range may be sufficient in the context of left ventricular mural thrombus prophylaxis,[41] and the maintenance of

coronary arterial patency following tissue-type plasminogen activator administration.[42]

The TIMI IIIB investigators[43] evaluated the relationship between levels of systemic anticoagulation and clinical events among 1,473 patients with NSTE ACS. Although heparin levels (chromogenic anti-IIa activity) and aPTT values (measured serially over a 72- to 96-h UFH infusion period) did not differ significantly between patients experiencing vs those free of clinical events (spontaneous ischemia, MI, death), a trend favored heparin levels > 0.2 U/mL and aPTTs in the 45- to 60-s range as being protective. In addition, high levels of anticoagulation (aPTT > 80 s) were not beneficial.

The GUSTO-IIB study[44] included 5,861 patients with NSTE ACS who received UFH for 72 h. A dose of 60 U/kg bolus and 12 U/kg/h infusion resulted in the highest proportion of aPTT values within the prespecified target range of 50 to 70 s. After adjustment for baseline variables, a higher 12-h aPTT was associated with death or reinfarction at 30 days. A prolonged aPTT at 6 h increased the risk of moderate or severe bleeding. An aPTT of 50 to 60 s at 12 h was associated with the lowest risk of hemorrhagic complications.

The available evidence supports a weight-adjusted dosing regimen with UFH as a means to provide a more predictable and constant level of systemic anticoagulation.[45–47] An initial bolus of 60 to 70 U/kg (maximum, 5,000 U) and initial infusion of 12 to 15 U/kg/h (maximum, 1,000 U/h) titrated to a target aPTT of 50 to 75 s is recommended.[5] A "weaning" schedule at the time of treatment completion may reduce rebound thrombin generation and ischemic/thrombotic events,[46] although the proven clinical benefit of this approach requires an adequately powered randomized clinical trial.

Recommendation

1.2.1. For patients presenting with NSTE ACS, we recommend UFH over no heparin therapy for short-term use with antiplatelet therapies (**Grade 1A**). We recommend weight-based dosing of UFH and maintenance of the aPTT between 50 s and 75 s (**Grade 1C+**).

1.2.2 LMWH

LMWH preparations represent a class of heparin-derived compounds with varying molecular weights (2,000 to 10,000 d). LMWH has pharmacokinetic and pharmacodynamic biophysical advantages over UFH (see chapter by Hirsh et al for details).

Clinical trials with LMWHs. Clinical trials comparing the benefits of UFH and aspirin among patients with UA and NSTE MI are summarized in Tables 2–4. The original experience with LMWH[48] included 205 patients with UA who were randomized to either aspirin (200 mg/d), aspirin (200 mg/d) plus UFH (5,000-U bolus, 400 U/kg/d infusion), or aspirin (200 mg/d) plus high-dose nadroparin (214 IU/kg bid by subcutaneous [SQ] injection). Patients underwent continuous ST-segment monitoring during the first 48 h of treatment. Overall, 73% of patients receiving LMWH were free from ischemic events, compared with

Table 2—*Acute vs Chronic Phase of FRIC**

Trial	Population	LMWH	Follow-up, d	End Point	UFH, No. (%)	LMWH, No. (%)	RR	p Value
FRIC,[50] acute phase (1–6 d)	n = 1,482	Dalteparin	6	Death/MI/recurrent angina	55 (7.6)	69 (9.3)	1.18	0.33
	UA or NQMI	120 anti-Xa U/kg SC bid		Death	3 (0.4)	11 (1.5)	3.37	0.55
				Death/MI	26 (3.6)	29 (3.9)	1.07	0.80
				MI	23 (3.2)	19 (2.6)	0.81	0.50
				Recurrent angina	39 (5.4)	45 (6.0)	0.92	0.69
				Revascularization	39 (5.3)	36 (4.8)	0.88	0.55
FRIC,[50] chronic phase (6–45 d)	n = 1,133	Dalteparin	6–45	Death/MI/recurrent angina	69 (12.3)	69 (12.3)	1.01	0.96
	UA or NQMI	7,500 anti-Xa SC qd		Death/MI	26 (4.7)	24 (4.3)	0.92	0.76
				Death	11 (2.0)	11 (2.0)	0.89	0.79
				MI	20 (3.6)	17 (3.1)	0.92	0.80
				Recurrent angina	57 (10.3)	60 (10.8)	1.09	0.64
				Revascularization	76 (14.2)	76 (14.3)	1.01	0.97

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39% of those receiving UFH and 40% of patients receiving aspirin alone. There were fewer silent ischemic events in the LMWH group (18%), compared with those receiving UFH (29%) or aspirin alone (34%). Recurrent angina occurred in 9%, 26%, and 19% of patients, respectively, and MIs were not observed in LMWH-treated patients (compared with 1% in the UFH group and 6% in the aspirin-alone group). Major bleeding occurred infrequently in all treatment groups.

A larger study, Fragmin During Instability in Coronary Artery Disease (FRISC)-1,[49] included 1,506 patients with UA and NSTE MI who were randomized to LMWH (dalteparin, 120 IU/kg SC [maximum 10,000 IU] bid for 6 days, then 7,500 IU qd for 35 to 45 days) or placebo; all patients received aspirin (300 mg first dose, 75 mg/d thereafter). The risk of death or MI was reduced by 63% with LMWH at day 6. The probability of death, MI, and need for revascularization remained lower in the LMWH-treated patients at 40 days; however, little difference between groups was observed beyond the treatment period. Survival analysis revealed a risk of reactivation (recurrent myocardial ischemia) and reinfarction when the dose was reduced (at day 7). At 4 to 5 months after the completion of treatment, there were no significant differences in the rates of death, new MI, or revascularization.

In the Fragmin in Unstable Coronary Artery Disease (FRIC) study,[50] 1,482 patients with UA and NSTE MI were assigned either twice-daily weight-adjusted SC injections of LMWH (dalteparin, 120 IU/kg) or dose-adjusted (target aPTT 1.5 times the control) IV UFH for 6 days (acute treatment phase) [Table 2]. Patients randomized to UFH received a continuous infusion for at least 48 h, and were given the option of either continuing the infusion or changing to an SC regimen (12,500 U q12h). In the blinded comparison that took place from days 6 to 45 (prolonged treatment phase), patients received either LMWH (dalteparin, 7,500 IU SC qd) or placebo. Aspirin, 75 to 165 mg/d, was started in all patients as early as possible after hospital admission and continued through-

out the study. During the first 6 days, the rate of death, recurrent angina, and MI was 7.6% in the UFH-treated patients and 9.3% in the LMWH-treated patients (RR, 1.18; 95% CI, 0.84 to 1.66). Revascularization was required in 5.3% and 4.8%, respectively (CI, 0.57 to 1.35). Between day 6 and day 45, the composite end point was reached in 12.3% of patients in both the LMWH and placebo groups. Revascularization procedures were undertaken in 14.2% and 14.3% of patients, respectively.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events (ESSENCE) trial[51] randomly assigned 3,171 patients with angina at rest or NSTE MI to either LMWH (enoxaparin, 1 mg/kg SC bid) or IV UFH (target aPTT, 55 to 85 s). Therapy was continued for a minimum of 48 h (maximum 8 days). All patients received aspirin (100 to 325 mg/d). The median duration of therapy for both groups was 2.6 days. At 14 days, the risk of death, recurrent angina, or MI was 16.6% among patients receiving LMWH and 19.8% for patients receiving UFH (16% risk reduction). A similar risk reduction (15%) for the composite outcome was observed at 30 days. The need for revascularization procedures within the first 30 days was also lower in LMWH-treated patients (27% vs 32.2%). The benefit of LMWH treatment was maintained at 1 year.[52]

The TIMI 11B study[53] compared enoxaparin and UFH in 3,910 patients with UA and NSTE MI. The trial design had several unique features. First, enoxaparin therapy was initiated with a 30-mg IV bolus, followed by 1 mg/kg SC bid. Second, UFH treatment was administered according to a weight-adjusted dosing strategy (70 U/kg bolus, followed by 15 U/kg/h infusion to a target aPTT of 1.5 to 2.5 times control). Lastly, there was an out-of-hospital treatment phase comparing enoxaparin and placebo for approximately 6 weeks (patients ≥ 65 kg received < 60 mg SC bid; those < 65 kg received 40 mg SC bid for a total of 43 days). Treatment with enoxaparin was associated with a significant reduction in the composite outcome of death, MI, or urgent revascularization compared with

Table 3—Double-Blind and Invasive vs Noninvasive Phase of FRISC-II Study*

Trial	Population	LMWH	Follow-up, d	End Point	Placebo (n = 1,056), % (No. of Events)	LMWH (n = 1,049), % (No. of Events)	Invasive (n = 1,207), % (No. of Events)	Noninvasive (n = 1,226), % (No. of Events)	RR	P Value
FRISC-II[56] Placebo vs LMWH double-blind phase (5–90 d)	n = 2,105 UA or NQMI	Dalteparin, 120 IU/kg SC bid for 1–5 day (open-treatment phase) plus	90	Death plus MI	8.0 (85)	6.7 (70)			0.81	0.17
				Death	1.6 (17)	1.4 (15)			0.88	NS
				Death/MI/Revasc	33.4 (374)	29.1 (328)			0.87	.0031
				Major bleed	1.5 (16)	3.3 (34)			2.2	
				ICH	0	0.8 (8)				
			45	Death plus MI	6.5 68	3.7 (39)			0.57	0.003
			30	Death plus MI	5.9 (61)	(3.1) (32)			0.53	0.031
FRISC-II[56] Invasive vs noninvasive phase (1–180 d)	n = 2,457 UA or NQMI	Dalteparin, 120 IU/kg SC bid for 1–5 d (open-treatment phase) plus	180	Death/MI (total)			9.4 (113)	12.1 (148)	0.78	0.031
				Death (total)			1.9 (36)	2.9 (36)	0.65	0.10
				MI (total)	7.8 (94)	10.1 (124)	0.77	0.045		
		Dalteparin vs placebo 7,500 IU SC bid for 5–90 d	180	Death/MI (placebo)			9.7 (58/601)	12.8 (78/609)	0.75	NS
				Death/MI (LMWH)			9.1 (55/606)	11.3 (70/617)	0.80	NS
				Major bleed (placebo)			1.3 (7/601)	1.9 (11/609)	0.68	NS
				Major bleed (LMWH)			2.3 (13/606)	3.6 (21/617)	0.64	NS
				ICH (placebo)	0.3 (2/606)		0	0		
				ICH (LMWH)		0.8 (5/617)	0.37			

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Trial	Population	LMWH	Follow-up, d	End Point	UFH, No. (%)	LMWH, No. (%)	RR	p Value
ESSENCE[51]	n = 3,171 UA or NQMI	Enoxaparin, 100 anti-Xa mg/kg, SC bid for 2–8 days	14	Death/MI/Recurrent angina	309 (19.8)	266 (16.6)	0.84	0.019
				Death	36 (2.3)	36 (2.2)	0.98	0.92
				Death/MI	96 (6.1)	79 (4.9)	0.80	0.131
				MI	70 (4.5)	51 (3.2)	0.71	0.06
				Recurrent angina	243 (15.5)	207 (12.9)	0.83	0.03
			30	Death/MI/recurrent angina	364 (23.3)	318 (19.8)	0.85	0.02
				Death	57 (3.6)	47 (2.9)	0.80	0.25
				Death/MI	120 (7.7)	100 (6.2)	0.81	0.08
				MI	81 (5.2)	62 (3.9)	0.75	0.08
				Recurrent angina	281 (18.0)	252 (15.7)	0.87	0.08
				Revascularization	504 (32.2)	434 (27.0)	0.84	0.001
				CABG	214 (13.7)	198 (12.3)	0.89	0.25
				PTCA	293 (18.7)	236 (14.7)	0.79	0.002
TIMI-11B,[53] acute phase (3–8 d)	n = 3,910 UA or NQMI	Enoxaparin, 30 mg bolus followed by 1 mg/kg SC bid	14	Death/MI/UR	326 (16.7)	277 (14.2)	0.82	0.029
				Death	55 (2.8)	43 (2.2)	0.78	0.22
				Death/MI	135 (6.9)	111 (5.7)	0.81	0.11
				MI	105 (5.4)	83 (4.2)	0.78	0.10
				Recurrent angina → UR	217 (11.1)	187 (9.6)	0.85	0.11
TIMI-11B,[53] chronic (8–43 d)	n = 2,346 UA or NQMI	Enoxaparin, 40 mg (<65 kg), 60 mg (≥65 kg) SC q12h	43	Death/MI/UR	385 (19.7)	337 (17.3)	0.85	0.048
				Death	78 (4.0)	75 (3.8)	0.96	0.81
				Death/MI	174 (8.9)	155 (7.9)	0.89	0.27
				MI	129 (6.6)	107 (5.5)	0.82	0.14
				Recurrent angina → UR	247 (12.6)	208 (10.7)	0.85	0.05

*Reprinted with permission from J Am Coll Cardiol 2000; 35:1699–1712. Copyright © 2000 American College of Cardiology Foundation. CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; UR = urgent revascularization; see Table 2 for expansion of abbreviation.

UFH at day 14 (14.2% vs 16.7%; RRR, 15%; p = 0.03). Continued treatment beyond the initial hospital phase did not provide added benefit (17.3% vs 19.7%; RRR, 12%; p = 0.05).

The Fraxiparine in Ischemic Syndromes study[54] compared the efficacy of nadroparin vs UFH in 3,468 patients with NSTE ACS. Patients were randomized to either UFH, 6-day treatment with nadroparin (86 IU/kg IV bolus, 86 IU/kg SC bid), or 14-day treatment with nadroparin. The combined outcome of cardiovascular death, MI, and recurrent/refractory angina at 14 days occurred in 18.1%, 17.8%, and 20% of patients, respectively (no significant difference). Hemorrhagic events were more common in patients receiving nadroparin for 14 days.

A pooled analysis of the ESSENCE and TIMI 11B trials, totaling 7,081 patients with NSTE ACS, revealed a 20% reduction in the risk of any ischemic event[55] favoring enoxaparin over UFH. The differences were statistically significant at 48 h and 43 days. The combined end point of death or MI was reduced by 20% at 48 h (p = 0.02) and 18% at 43 days (p = 0.02). A significant treatment benefit for enoxaparin on the rate of death, nonfatal MI, or urgent revascularization was observed at 1 year (hazard ratio, 0.88; p = 0.008; absolute difference, 2.5%). A progressively greater treatment benefit was observed as the level of patient risk at baseline increased.[55]

The FRISC II[56] included 2,267 patients with unstable

coronary disease who received 5 days of dalteparin (120 IU/kg SC q12h) and were then randomized to either an invasive or conservative treatment strategy. In separate randomization, patients received either dalteparin (5,000 to 7,500 IU SC q12h) or placebo injections for 3 months (Table 3). By 30 days, there was a significant reduction in death or MI favoring dalteparin-treated patients (3.1% vs 5.9%; p = 0.002). The benefit diminished over the next 2 months. An invasive strategy (coronary angiography and revascularization) was associated with a significant reduction in death or MI at 6 months compared with ischemia-driven revascularization (9.4% vs 12.1%, p = 0.03). The mortality rates were 1.9% and 2.9%, respectively.[57] At 24-month follow-up, there were reductions in mortality (3.7% vs 12.7%; risk ratio, 0.72; p = 0.005) and the composite end point of death or MI (12.1% vs 16.3%; risk ratio, 0.74; p = 0.003) in the invasive group compared with the noninvasive group. The need for repeat hospitalizations and late revascularization procedures was lower with an early invasive strategy as well.[58]

The Randomized Intervention Trial of Unstable Angina[59] randomized 1,810 patients with NSTE ACS who received enoxaparin (1 mg/kg SC bid for 2 to 8 days) and aspirin to either an early intervention or conservative strategy.[59] At 4 months, 9.6% of patients randomized to early intervention had died or experienced an MI or refractory angina compared with 14.5% in the conserva-

tive group (risk ratio, 0.66; 95% CI, 0.51 to 0.85; p = 0.001). Death or MI was similar in both treatment groups at 1 year (7.6% vs 8.3%, respectively; risk ratio, 0.91; 95% CI, 0.67 to 1.25; p = 0.58). Fewer patients undergoing early intervention experienced symptoms of angina or required antianginal medications.

In a prospective, comparative study[60] of LMWH preparations, 438 patients with NSTE ACS were randomized to receive either SC injections of 100 mg of enoxaparin bid or 175 IU/kg of tinzaparin qd for 7 days. There were no differences in the primary outcome (death, MI, refractory angina, or recurrence of UA); however, there was a lower incidence of recurrent UA and need for revascularization at 30 days among enoxaparin-treatment patients (p = 0.02). Hemorrhagic events were similar in the two groups.[60]

Duration of treatment with LMWH. The potential benefit of extended therapy with LMWH has been evaluated in several clinical trials. In the FRIC study[50] dalteparin was continued at a dose of 7,500 IU IV qd for 39 days. A minority of patients experienced NSTE MI; no additional benefit from extended therapy was observed. Similar findings were reported with enoxaparin (40 mg or 60 mg bid for 43 days) in the TIMI 11 trial (Table 4).[53]

The FRISC I trial[49] suggested that extended LMWH treatment (dalteparin, 7,500 IU qd) might benefit selected patients. The combined end point of death or MI was reduced by 40% (p = 0.003) at day 40 in nonsmokers, as well as in patients with NSTE MI, diabetes mellitus, prior MI, age > 70 years, and those treated for heart failure. During extended therapy, patients with an initial troponin level > 0.1 μg/L derived the greatest overall benefit (RRR, 0.48 at day 40; p = 0.01).[49]

The FRISC II trial[56,57] extended several important observations made in FRISC I. Patients experiencing chest pain associated with either ECG changes or elevated cardiac biomarkers received dalteparin, 120 IU/kg SC q12h, plus aspirin. Those assigned to a noninvasive strategy received dalteparin for 5 to 7 days (until an exercise tolerance test was performed). Patients in the invasive strategy arm of the trial received dalteparin for at least 5 days (until an invasive procedure was performed). Thereafter, either dalteparin (5,000 IU SC bid [women < 80 kg, men < 70 kg]; or 7,500 IU SC bid in heavier patients) or placebo was administered by self-injection for 90 days.

A total of 2,267 patients were included in the noninvasive arm of FRISC II. At 90 days, there was a 1.3% absolute (19% relative) RR in death or MI associated with prolonged dalteparin administration (p = 0.17). The combined end point was 3.1% in dalteparin-treated patients compared with 5.9% in those receiving placebo at 30 days (RR, 0.5; p = 0.002). The triple composite of death, MI, or revascularization was 13% lower (p = 0.031) at 90 days with prolonged LMWH administration. The rates of hemorrhage were 2.2% and 1.2%, respectively.

The available evidence favors an early invasive strategy for patients with NSTE ACS. Although prolonged LMWH administration provides an element of protection for high-risk patients, those individuals should be treated aggressively (and early) whenever possible. If coronary angiography and intervention are planned but delayed, continued therapy as a "bridge" to revascularization should be considered.

Platelet GP IIb/IIIa inhibitors and LMWH, combination therapy. The contribution of platelets and coagulation proteins to coronary arterial thrombosis supports combination pharmacotherapy in NSTE ACS. In the Anti Thrombotic Therapy Combination Using Tirofiban and Enoxaparin II study,[61] 525 patients with NSTE ACS were treated with tirofiban plus aspirin and randomized to received either UFH (5,000-U bolus, 1,000 U/h adjusted to an aPTT of 1.5 to 2.5 times control) or enoxaparin (1.0 mg/kg SC q12h). Therapy was administered for 24 to 96 h. In-hospital death or MI occurred in 9.0% and 9.2% of patients, respectively; however, refractory ischemia requiring urgent revascularization and rehospitalization because of UA occurred more frequently in the UFH group (4.3% vs 0.6%; risk ratio, 0.72 [p = 0.01]; and 7.1% vs 1.6%; risk ratio, 0.44 [p = 0.002], respectively). TIMI major bleeding occurred in 1.0% and 0.3% of patients, respectively.

National Investigators Collaborating on Enoxaparin 3 trial[62] was an open-label observational study of enoxaparin conducted at 56 sites in North America. All patients (n = 628) had chest pain at rest lasting at least 20 min within the prior 24 h and CAD documented by ECG changes, elevated cardiac biomarkers, or history (MI, PCI, coronary angiogram with ≥ 50% luminal narrowing, or abnormal exercise tolerance test result). Patients received aspirin (162.5 to 325 mg) and enoxaparin (1.0 mg/kg SC) q12h. For the primary end point of non-CABG major bleeding, the cumulative incidence was 1.9%. At 30 days, the incidence of death or MI (double end point) and death, MI, or urgent revascularization (triple end point) was 6.2% and 11.6%, respectively.

In a GUSTO IV substudy,[63] 646 patients received dalteparin (120 IU/kg SC every 12 h), aspirin, and either 24 h or 48 h of abciximab administered as an initial bolus followed by a continuous infusion. Death or MI at 30 days occurred in 9.6% of dalteparin-treated patients and 8.5% of UFH-treated patients. The rates of major non-CABG bleeding were 1.2% and 0.7%, respectively.

The Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment study[64] randomized 746 patients with NSTE ACS to open-label enoxaparin (1 mg/kg SC bid) or UFH (70 U/kg bolus, 15 U/kg/h to a target aPTT of 1.5 to 2.0 times control) for 48 h. All patients received aspirin and eptifibatide (180 μg/kg bolus, 2 μg/kg/min infusion). Major non-CABG bleeding at 96 h (primary safety outcome) was significantly lower among enoxaparin-treated patients than those receiving UFH (1.8% vs 4.6%, p = 0.03). Minor bleeding occurred more often in the enoxaparin group (30.3% vs 20.8%, p = 0.003). Patients receiving enoxaparin were less likely to experience ischemia (determined by continuous ECG monitoring) [primary outcome] during the initial (14.3% vs 25.4%, p = 0.002) and subsequent (12.7% vs 25.9%, p < 0.0001) 48-h monitoring periods. Combined death or MI at 30 days was also lower in enoxaparin-treated patients (5% vs 9%, p = 0.03).

In PARAGON B,[65] 5,225 patients with NSTE MI received either lamifiban or placebo in combination with aspirin and heparin, 805 patients received a LMWH preparation, while the remainder received UFH. The incidence of death, MI, or severe recurrent ischemia was 12.2% for the overall cohort and lowest in the lamifiban-plus-LMWH group (10.2%). The incidence of death or MI was 11.0% and 9.0%, respectively. The benefit for those receiving lamifiban plus LMWH was sustained at 6 months with lower revascularization rates (42.8% vs 51.5%) and a lower composite of death or MI (11.9% vs 13.8%). After correcting for baseline differences, there was a significantly lower revascularization rate at 30 days with use of LMWH (p = 0.001). Major bleeding was 1.6% for patients receiving UFH and lamifiban, and 1.5% in those receiving LMWH and lamifiban.

Anticoagulation monitoring with LMWHs. LMWH preparations catalyze thrombin inhibition to a lesser extent than UFH and, as a result, they induce less prolongation of the aPTT. Because prolongation of the aPTT correlates inversely with the anti-Xa:anti-IIa ratio, tinzaparin (ratio 1.5:1) produces a higher aPTT (for an equivalent dose) than enoxaparin (ratio 3.0:1). The more rapid dissipation of anti-IIa activity following LMWH administration also contributes to a weaker effect of LMWH preparations on the aPTT.

Anti-Xa activity can be measured by chromogenic and chronometric assays. As with other coagulation tests, variability does exist. A majority of clinical trials, whether based on deep vein thrombosis prophylaxis, venous thromboembolism treatment, or ACS, have not required drug titration according to anti-Xa monitoring; however, an ability to define safe and effective levels of anticoagulation is important for clinical reasons. Defining a target level of factor Xa inhibition is also important in patients with altered drug clearance such as renal insufficiency (particularly with LMWH preparations characterized by a high anti-Xa:anti-IIa ratio). Lastly, monitoring capabilities may be useful when drug reversal is required because of the possibility of hemorrhagic complications during invasive procedures with inherent bleeding risks.

In the TIMI 11A study,[66] there was a relationship between enoxaparin dose and hemorrhagic complications, particularly in those undergoing coronary angiography, PCI, or CABG. Patients receiving enoxaparin at a dose of 1.25 mg/kg q12h had a peak anti-Xa activity (chromogenic assay) of 1.5 IU/mL, while those receiving 1.0 mg/kg q12h averaged 1.0 IU/mL. Anti-Xa activity among patients with major hemorrhage was 1.8 to 2.0 IU/mL. An analysis of anti-Xa inhibition pharmacokinetics revealed that high trough and peak activity (upper quintiles) was associated with major hemorrhagic events.[66]

The optimal level of factor Xa inhibition has not been determined for patients with ACS receiving LMWH. The available information derived from nonrandomized clinical studies of PCI suggests that anti-Xa activity > 0.5 IU/mL is associated with a low incidence of ischemic/thrombotic and hemorrhagic events.[67,68] Global coagulation tests, including traditional aPTT and activated clotting time (ACT) assays, may provide some insight for LMWH preparations characterized by low anti-Xa:anti-IIa activity.[69]

Antithrombin therapies and renal function. The mechanism of LMWH clearance is predominantly renal (nonsaturable), which explains the linear characteristics of reported elimination curves.[70,71] Renal performance may not influence pharmacokinetics following single-dose IV administration of enoxaparin.[72,73]

The anti-Xa pharmacokinetics of several other LMWH preparations have been investigated in small-scale, multiple-dose trials. The findings suggest that severe renal insufficiency (CrCl < 30 mL/min) is associated with reduced drug clearance, particularly with lower molecular weight (or proportion of short-chain molecules) preparations. Studies evaluating appropriate dose titration to established target levels of anti-Xa activity in patients with end-stage renal disease should be undertaken to provide guidance in achieving optimal patient care.

Recommendations

1.2.2.1. For the acute treatment of patients with NSTE ACS, we recommend LMWHs over UFH (**Grade 1B**).

1.2.2.2. We recommend against routine monitoring of the anticoagulant effect of the LMWHs (**Grade 1C**).

1.2.2.3. We suggest continuing LMWHs during PCI treatment of the NSTE ACS patient when it has been started as the "upstream" anticoagulant (**Grade 2C**).

1.2.2.4. For patients receiving GP IIb/IIIa inhibitors as upstream treatment of NSTE ACS, we suggest LMWH over UFH as the anticoagulant of choice (**Grade 2B**).

1.2.3 Indirect, selective factor Xa inhibitors: synthetic pentasaccharide

The pentasaccharide sequence contained within heparin molecules is a prerequisite for antithrombin binding and subsequent coagulation protease neutralization. Fondaparinux (molecular weight, 1,728 d) is a synthetic pentasaccharide that facilitates antithrombin (indirect)-mediated factor Xa (selective) inhibition. It does not inactivate thrombin. The anti-Xa activity of the drug increases with increasing plasma concentrations, peaking within 3 h of SC administration. Elimination occurs solely through renal mechanisms, and the plasma half-life is 17 to 21 h.

Fondaparinux is currently US Food and Drug Administration approved for prophylaxis of deep vein thrombosis in patients undergoing hip fracture, hip replacement, or knee replacement surgery. Its use in patients with NSTE ACS is limited to a single phase II study. In the Pentasaccharide in Unstable Angina study,[74] 1,147 patients were randomized to receive either enoxaparin (1 mg/kg SC bid) or fondaparinux (2.5 mg, 4 mg, 8 mg, or 12 mg/d SC) for 3 to 7 days. The primary efficacy end point was a composite of death, MI, or recurrent ischemia at 9 days and 30 days. The composite end point was reached in 40.2%, 30.0%, 43.5%, 41.0%, and 34.8%, respectively, and major and minor bleeding at day 30 occurred in 3.9%, 5.4%, 5.4%, 4.6%, and 4.8% of patients, respectively.

In a pilot trial,[75] 61 patients undergoing balloon angioplasty received a single, 5-min IV infusion of 12 mg of pentasaccharide. Two patients (3.28%; 95% CI, 0.4 to 11.4%) experienced abrupt vessel closure. ACT and aPTT measurements remained within the normal range; however, thrombin-antithrombin complex, prothrombin fragment 1.2 and factor VIIa levels decreased by 50 to 60% within 2 h of injection of the test drug. There were no major hemorrhagic events.

Fondaparinux elimination is prolonged in patients with renal impairment. Total clearance is reduced by 25% in patients with mild renal impairment (CrCl, 50 to 80 mL/min), approximately 40% lower among patients with moderate renal impairment (CrCl, 30 to 50 mL/min) and 55% lower in the setting of severe renal impairment (CrCl < 30 mL/min). Fondaparinux elimination is also reduced (by 25%) in patients > 75 years old (compared with patients < 65 years old). There are insufficient data to recommend fondaparinux in patients presenting with NSTE ACS. Large, randomized trials are underway evaluating the safety and efficacy of fondaparinux among patients presenting with both ST-segment elevation and NSTE ACS.

1.2.4 Direct, selective factor Xa inhibitors: DX-9065a

DX-9065a is the first in a class of small molecule, direct, specific, and reversible factor Xa inhibitors. It is a synthetic, nonpeptide amidinoaryl derivative (571 d) with rapid binding kinetics for factor Xa but not thrombin.[76,77] The cumulative experience with it among patients with CAD is limited to a single phase 1B study and a phase II study in the setting of PCI. The Xa Neutralization for Atherosclerotic Disease Understanding 1B trial[78] included 73 patients aged 55 to 75 years with clinically stable CAD. They were randomized to receive either placebo or a 72-h IV infusion of DX-9065a in doses required to achieve plasma concentrations of 15, 50, 100, or 200 ng/mL. All patients received aspirin. Based on a three-compartment model, plasma half-life (α) was 0.14 to 0.3 h, while half-life (β) and half-life (γ) were 1.93 to 3.2 h and 76.6 to 98.9 h, respectively. Independent predictors of pharmacokinetic response were dose, age, body weight, female sex, and baseline CrCl. The major route of elimination (75 to 80%) for DX-9065a is through renal clearance mechanisms with a biphasic urinary profile that supports tubular secretion as a contributing factor.

All plasma-based pharmacodynamic (coagulation) measurements paralleled DX-9065a drug concentrations. At the highest concentration (200 ng/mL), the maximum prothrombin time/international normalized ratio (INR), aPTT, and anti-Xa levels were prolonged by 40%, 25% and 80%, respectively. There were no major hemorrhagic events. A trend toward more minor hemorrhage events was observed in the highest DX-9065a group.

The Xa Neutralization for Atherosclerotic Disease Understanding 1B PCI pilot study[79] included 175 patients who were randomized to receive either DX-9065a, to achieve escalating concentrations (75, 100, or 150 ng/mL), or UFH. All patients received aspirin, clopidogrel and, in most instances, a GP IIb/IIIa receptor antagonist. The 75 mg/mL concentration phase was discontinued after a coronary arterial thrombotic event. The subsequent phases were carried out without observing an excess of either ischemic/thrombotic or hemorrhagic events. A phase II NSTE ACS study has recently been completed. Data are unavailable.[80] There are insufficient data to recommend DX 9065a as anticoagulant treatment for patients presenting with NSTE ACS.

1.2.5 Direct thrombin inhibitors

Hirudins. Direct thrombin inhibitors (DTIs) were developed to overcome several limitations of heparin compounds, which include platelet-activating properties, complex pharmacokinetics (with UFH), and an inability of the heparin-antithrombin complex to inactivate fibrin-bound thrombin. Hirudin is a potent, direct, bivalent thrombin inhibitor. The terminal half-life is 60 min with clearance by renal mechanisms (see chapter by Weitz et al in this Supplement). Hirudin doses used in clinical practice prolong aPTT and ACT coagulation tests, and correlate fairly well with plasma concentrations. In contrast, the thrombin time is too sensitive for application in dose titration and assessment of anticoagulant effects, while the prothrombin time is not sensitive enough.

Clinical trial results. A systematic overview of randomized clinical trials was performed to obtain precise estimates of DTIs in the management of ACS.[81] A total of 11 randomized trials including 35,970 patients were identified and included in the analysis. Compared with UFH, DTIs were associated with a lower risk of death or MI at the end of treatment (up to 7 days; 4.3% vs 5.1%; odds ratio [OR], 0.85; 95% CI, 0.77 to 0.94; p = 0.001) and at 30 days (7.4% vs 8.2%; OR, 0.91; 95% CI, 0.84 to 0.99; p = 0.02). Seven trials included 30,154 patients either with an ACS (UA or NSTE MI) or undergoing PCI (Fig 2). In those with ACS, treatment with a DTI was associated with a reduction in death or MI compared with UFH (3.7% vs 4.6%; OR, 0.80; 95%, CI, 0.70 to 0.92). Similar reductions were observed in PCI trials (3.0% vs 3.8%; OR, 0.79; 95% CI, 0.59 to 1.06). There was a statistically insignificant increased rate of major bleeding with DTIs in trials of ACS (1.6% vs 1.4%; OR, 1.11; 95% CI, 0.93 to 1.34), but there was a significant decrease in PCI trials (3.7% vs 7.6%; OR, 0.46; 95% CI, 0.36 to 0.59). There were no differences in the rates of intracranial hemorrhage.

The risk reduction in death or MI at the end of treatment was similar in trials comparing hirudin or bivalirudin with UFH, but there was a slight excess with univalent inhibitors (4.7% vs 3.5%; OR, 1.35; 95% CI, 0.89 to 2.05). When major bleeding outcomes were analyzed by agent, hirudin was associated with an excess of major bleeding compared with UFH (1.7% vs 1.3%; OR, 1.28; 95% CI, 1.06 to 1.55), whereas both bivalirudin (4.2% vs 9.0%; OR, 0.55; CI, 0.34 to 0.56) and univalent inhibitors (0.7% vs 1.3%; OR, 0.55; 95% CI, 0.25 to 1.20) were associated with lower rates of major bleeding.

Individual trials. An early dose-escalating trial[82] of recombinant hirudin included 116 patients who had ischemic chest pain, an abnormal ECG result, and a coronary
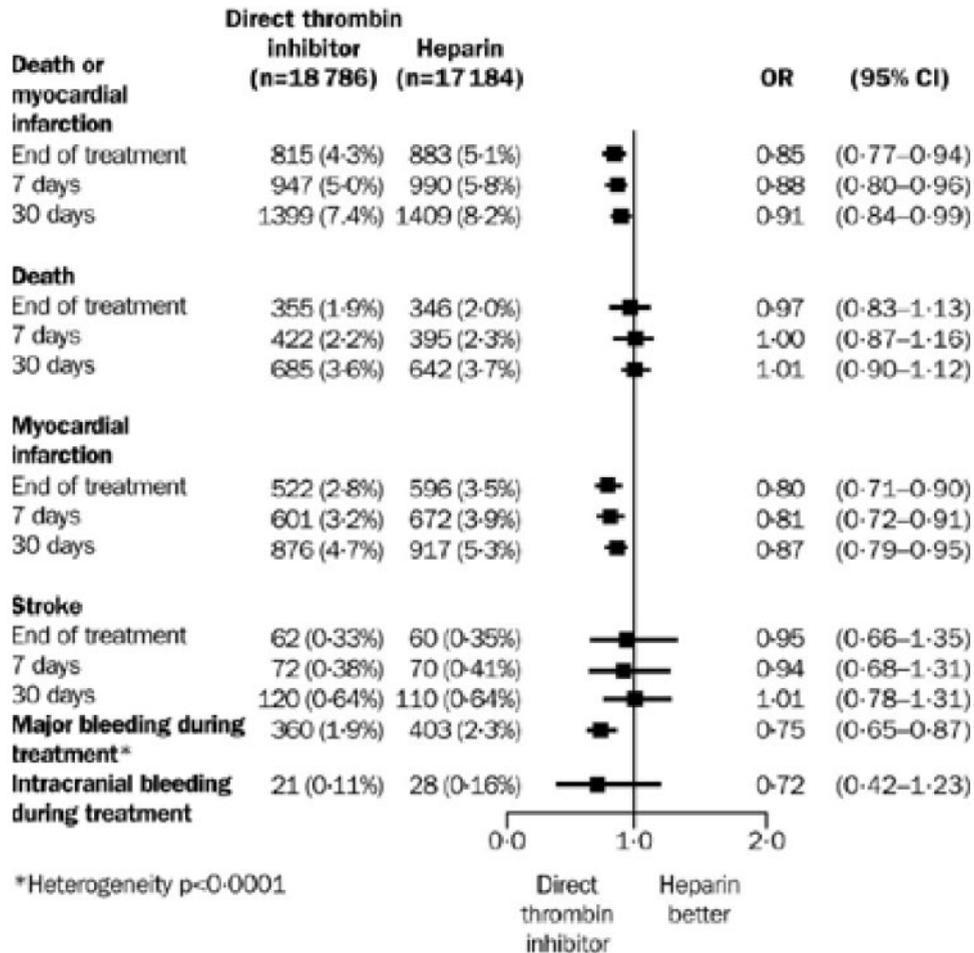
Death or myocardial infarction	Direct thrombin inhibitor (n=18 786)	Heparin (n=17 184)		OR	(95% CI)
End of treatment	815 (4·3%)	883 (5·1%)		0·85	(0·77–0·94)
7 days	947 (5·0%)	990 (5·8%)		0·88	(0·80–0·96)
30 days	1399 (7·4%)	1409 (8·2%)		0·91	(0·84–0·99)
Death					
End of treatment	355 (1·9%)	346 (2·0%)		0·97	(0·83–1·13)
7 days	422 (2·2%)	395 (2·3%)		1·00	(0·87–1·16)
30 days	685 (3·6%)	642 (3·7%)		1·01	(0·90–1·12)
Myocardial infarction					
End of treatment	522 (2·8%)	596 (3·5%)		0·80	(0·71–0·90)
7 days	601 (3·2%)	672 (3·9%)		0·81	(0·72–0·91)
30 days	876 (4·7%)	917 (5·3%)		0·87	(0·79–0·95)
Stroke					
End of treatment	62 (0·33%)	60 (0·35%)		0·95	(0·66–1·35)
7 days	72 (0·38%)	70 (0·41%)		0·94	(0·68–1·31)
30 days	120 (0·64%)	110 (0·64%)		1·01	(0·78–1·31)
Major bleeding during treatment*	360 (1·9%)	403 (2·3%)		0·75	(0·65–0·87)
Intracranial bleeding during treatment	21 (0·11%)	28 (0·16%)		0·72	(0·42–1·23)

0·0   1·0   2·0

Direct thrombin inhibitor better   Heparin better

*Heterogeneity p<0·0001

FIGURE 2. Systematic overview of DTI trials among patients with ACS and who are undergoing PCI. This shows a comparison of DTIs with heparin on both the ischemic and safety end points. Reprinted with permission from Elsevier (The Lancet 2002; 359:294–302).

angiogram confirming > 60% stenosis of a culprit artery or saphenous vein graft with apparent thrombus. The results revealed a measurable and dose-dependent anticoagulant effect and improvement (compared with UFH) in average cross-sectional area, minimal cross-sectional area, minimal luminal diameter, and percentage diameter stenosis.

In the GUSTO-IIb trial[3] patients with NSTE ACS were randomized to receive either UFH or hirudin (0.1 mg/kg IV bolus, 0.1 mg/kg/h infusion). At 24 h, the risk of death or nonfatal MI was reduced in hirudin-treated patients (1.3% vs 2.1%; p = 0.001). The primary end point of death or nonfatal MI at 30 days was reached in 8.9% and 9.8% of patients, respectively (OR, 0.89; p = 0.006). The risk of moderate bleeding was increased with hirudin treatment (8.8% vs 7.7%; p = 0.03).

The Organization to Assess Strategies for Ischemic Syndromes (OASIS)-1 study[83] randomized 909 patients with UA or suspected MI without ST-segment elevation to receive UFH (5,000-U bolus, 1,000 to 1,200 U/h infusion), low-dose hirudin (0.2 mg/kg bolus, 0.1 mg/kg/h infusion), or moderate-dose hirudin (0.4 mg/kg bolus, 0.15 mg/kg/h infusion). Doses of UFH and hirudin were titrated to a target aPTT of 60 to 100 s. Compared with UFH, hirudin reduced the composite incidence of cardiovascular death, MI, or refractory angina at 7 days (OR, 0.57; 95% CI, 0.32 to 1.02) and a composite of death, MI, or refractory/severe angina requiring revascularization at 7 days (OR, 0.49; 95% CI, 0.27 to 0.86). Overall event rates were lowest in the moderate-dose hirudin group. Major hemorrhage occurred in approximately 1% of patients and did not differ significantly among the groups. The incidence of minor bleeding was higher in hirudin-treated patients (21.3%, 16.2%, and 1.5% for moderate-dose hirudin, low-dose hirudin, and UFH, respectively).

The favorable results in OASIS-1 prompted a large phase III trial, OASIS-2,[83] which randomized 10,141 patients with NSTE ACS to a 72-h infusion of either moderate-dose hirudin (as defined in OASIS-1) or UFH. The primary outcome (composite of death or MI at 7 days and 35 days) was reported in 3.6% and 4.2% of patients (OR, 0.87; 95% CI, 0.75 to 1.01), respectively. Although the differences between groups in the individual trials were not statistically significant, the combined OASIS-1 and OASIS-2 experience revealed a significant reduction

in the likelihood of death or MI at 35 days among hirudin-treated patients (OR, 0.86; 95% CI, 0.74 to 0.99).

Hirudin is almost exclusively excreted through the kidneys and, as a result, renal function must be considered carefully prior to administration. The majority of clinical trials excluded patients with a creatine level of ≥ 2.0 mg/dL. Even in the setting of mild renal impairment (CrCl, 50 to 80 mL/min), excessive levels of systemic anticoagulation (and accompanying risk for hemorrhage) can occur with nonmodified dosing. When hirudins are administered to patients with renal insufficiency, frequent aPTT monitoring is highly recommended.

Bivalirudin. Bivalirudin is a 20 amino-acid polypeptide that interacts with both the active and anion binding sites of thrombin; however, once bound there is a slow but progressive recovery of the active site function of thrombin, which may play a role in preserving hemostatic potential. Bivalirudin is US Food and Drug Administration approved for use in high-risk patients undergoing PCI, including those with a recent NSTE ACS. Approval was based on data from several randomized clinical trials,[84] the largest performed by Bittl et al.[85] Among 4,312 patients with new-onset, severe, accelerating, or rest angina undergoing PCI, a 22% reduction in death, MI, or urgent revascularization at 7 days was observed in those receiving bivalirudin compared with UFH (6.2% vs 7.9%; p = 0.03). The absolute and relative differences were maintained at 90 days. There was a marked RRR (62%) in bleeding complications among bivalirudin-treated patients compared with those treated with UFH.

In patients with normal renal function, the pharmacokinetics of bivalirudin administered IV are dose proportional (linear) and characterized by rapid clearance. There is a direct relationship between bivalirudin dose, plasma concentration, and prolongation of coagulation tests (aPTT, ACT).

Patients with moderate and severe renal impairment have reductions in bivalirudin clearance of 45% and 68%, respectively. An analysis of data derived from 4,312 patients with UA[85] showed increased bleeding risk for both bivalirudin- and UFH-treated patients with progressive degrees of renal insufficiency. The incidence of major bleeding was, however, consistently less for bivalirudin than UFH at all levels of renal impairment.[85]

Argatroban. Argatroban is a small-molecule, peptidomimetic arginine derivative that interacts solely with the active site of thrombin (competitive, univalent inhibitor). It is metabolized in the liver, a process that generates several active intermediates. Although the half-life of argatroban is not altered by renal function, clearance is markedly influenced by hepatic performance.

Argatroban, like the other IV univalent direct thrombin antagonists, inogatran and efegatran, has not undergone definitive phase III testing for use among patients with NSTE ACS. Its use in the management of heparin-induced thrombocytopenia (HIT) will be discussed in the next section.

HIT. HIT is discussed in a separate chapter (see chapter by Warkentin and Greinemacher in this Supple-ment), and recommendations about prevention and management of HIT are given.

PCI. The safety of bivalirudin among patients with HIT has been reported in 39 individuals[86]; of these, 44% had a diagnosis of acute HIT, while the remainder had a history of prior HIT. The indication for anticoagulation was a PCI for 17 patients (44%); the procedure was deemed successful in 94% of patients.

The Anticoagulation Therapy With Bivalirudin To Assist in the Performance of PCI in Patients With Heparin-Induced Thrombocytopenia study[86] was an open-label registry of 50 patients with HIT (new or previous). Preliminary results reported that all patients had successful procedures (TIMI 3 flow or < 50% residual stenosis), and that there were no major bleeding events.[86]

Lewis and colleagues[87] conducted a prospective historical control study evaluating the efficacy and safety of argatroban as anticoagulant therapy in patients with clinically suspected HIT (with or without thrombosis). The results are discussed in detail in the chapter on HIT.

Recommendation

1.2.5. In patients presenting with NSTE ACS, we recommend **against** using DTIs as routine initial antithrombin therapy (**Grade 1B**).

Underlying values and preferences: This recommendation acknowledges the limitations of the individual trials of DTIs in NSTE ACS as well as the complexities of using the DTIs compared with either UFH or LMWH.

2.0 Post MI and Post ACS

2.1 Antiplatelet therapies

Short-term antiplatelet therapy trials. Elwood and Williams[88] reported a randomized trial of a single dose of 300 mg of aspirin administered by general practitioners on first contact to 2,350 patients thought to have experienced AMIs. It did not show a significant difference in mortality in the 1,750 patients with confirmed MIs.[89] The results of the International Studies of Infarct Survival (ISIS)-2 pilot study[90] showed decreased mortality with randomization to aspirin or placebo in 619 patients treated with streptokinase for AMIs. Verheught et al[91] showed a reduction in left anterior descending coronary artery occlusion in 49 patients randomly assigned to aspirin after streptokinase therapy for anterior MI. They also showed aspirin to be more effective than heparin in the prevention of revascularization, recurrent MI, and death after thrombolytic therapy for AMI in the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis trial.[92] ISIS-2[93] was a randomized, placebo-controlled, blinded trial of short-term therapy with IV streptokinase, oral aspirin (160 mg/d for 1 month), both, or neither among 17,187 patients with suspected AMIs. In addition to a 23% risk reduction in 5-week vascular mortality among patients receiving streptokinase, there was a 21% reduction among those receiving aspirin and a 40% reduction among those receiving a combination of streptokinase and aspirin, which are all highly significant reductions. The early reduction in

mortality with aspirin persisted when the patients were observed for a mean of 15 months. Aspirin reduced the risk of nonfatal reinfarction by 49% and nonfatal stroke by 46%. The increased rate of early nonfatal reinfarction noted when streptokinase therapy was used alone is consistent with marked platelet activation after fibrinolytic therapy, and was completely resolved when aspirin was added (3.8% vs 1.3%). Aspirin added to the benefit of streptokinase therapy in all groups examined. In particular, among patients > 70 years old, the combination markedly reduced the mortality rate from 23.8 to 15.8% (p < 0.001) without increasing the risk of hemorrhage or stroke. Because of poor prognosis in older patients who have experienced AMIs, the absolute number of lives saved with aspirin and thrombolytic therapy increases dramatically with age (ie, 2.5 per 100 treated patients < 60 years of age and 7 to 8 per 100 treated patients ≥ 60 years of age).

ISIS-2[93] showed conclusively that short-term aspirin therapy for AMI decreases mortality and reinfarction, has benefits in addition to those of fibrinolysis, and prevents the increase in reinfarction that occurs after fibrinolytic therapy. Consequently, aspirin therapy for patients who have experienced AMIs is not only desirable but necessary when fibrinolytic therapy is used. These benefits were achieved with an aspirin dose of 160 mg/d. Although associated with an increased rate of minor bleeding from 1.9 to 2.5%, aspirin therapy was not associated with any significantly increased risk of major bleeding, including hemorrhagic stroke. The benefit of aspirin, in contrast to that of streptokinase, was independent of the time of onset of treatment. However, early administration seems prudent.

Long-term antiplatelet therapy trials. The Antiplatelet Trialists' Collaboration update[94] included 287 studies involving 135,640 high-risk (acute or previous vascular disease or another predisposing condition) patients in comparisons of antiplatelet therapy vs control and 77,000 similar patients in comparisons of different antiplatelet regimens. The analysis extended the direct evidence of benefit from antiplatelet therapy to a much wider range of patients at high risk of occlusive vascular disease.[94]

Overall, 7,705 serious vascular events (10.7%) were recorded among 71,912 high-risk patients allocated antiplatelet vs an adjusted total of 9,502 such events (13.2%) among 72,139 allocated control patients (22% odds reduction; p = 0.0001). Antiplatelet therapy was associated with a highly significant 15% proportional reduction in vascular deaths (p = 0.0001) [without heterogeneity between the high-risk groups], all-cause mortality (p < 0.0001), nonfatal MI (34% odds reduction; p < 0.001), nonfatal MI or death from coronary heart disease (26% odds reduction; p < 0.001), and stroke (25% odds reduction; p < 0.001). Overall, the proportional risk of experiencing a major intracranial hemorrhage was increased 50% with antiplatelet therapy (OR, 1.6). The proportional increase in fatal hemorrhage was not significantly different from that for nonfatal hemorrhage, although only the excess of nonfatal hemorrhagic events achieved statistical significance.

Among 18,788 patients with a history of MI, allocation to antiplatelet therapy for a mean duration of 27 months resulted in 36 fewer serious vascular events per 1,000 patients (25% odds reduction; p < 0.001). This benefit reflects large and highly significant reductions in nonfatal MI (18 fewer per 1,000; p < 0.0006), as well as a smaller but still significant reduction in nonfatal stroke (5 fewer per 1,000; p < 0.002). The overall benefits were larger than the excess risk of major extracerebral hemorrhage (3 per 1,000 or patients or 1 per 1,000 patients per year).

Data were available on 19,288 patients with suspected AMI. Allocation to antiplatelet therapy for a mean of 1 month led to a 30% odds reduction in vascular events (38 fewer serious vascular events per 1,000 patients treated; p < 0.001). This reflects large and highly significant reductions in nonfatal reinfarction (13 fewer per 1,000; p < 0.0001) and vascular death (23 fewer per 1,000; p < 0.0001), together with a smaller but still significant reduction in nonfatal stroke (2 fewer per 1,000; p = 0.02; Fig 3). The risk of major extracranial bleeding was approximately 1 to 2 per 1,000 patients treated.

The updated meta-analysis[94] provides some additional information on the effects of different doses of aspirin. Overall, among 3,570 patients in three trials directly comparing aspirin doses (≥ 75 mg/d vs < 75 mg/d), there were significant differences in vascular events (two trials compared aspirin, 75 to 325 mg/d, vs < 75 mg/d; one trial compared aspirin, 500 to 1,500 mg/d, vs < 75 mg/d). Considering both direct and indirect comparisons of aspirin dose, vascular events were reduced 19% with 500 to 1,500 mg/d, 26% with 160 to 325 mg/d, and 32% with 75 to 150 mg/d. Whether the greater reductions observed with decreasing doses are clinically meaningful will require a large, randomized comparison of aspirin doses in patients with coronary heart disease. Similarly, the relative benefits for patients with NSTE ACS compared with other subsets must be more clearly defined through large-scale studies.

The effect of antiplatelet drugs other than aspirin (vs control) was assessed in 166 trials that included 81,731 patients. Indirect comparisons provided no clear evidence of differences in reducing serious vascular events (χ^2 for heterogenicity between any aspirin regimen and other antiplatelet drugs = 10.8; not significant [NS]). Most direct comparisons assessed the effects of replacing aspirin with another antiplatelet agent. In the CAPRIE trial,[13] which included 19,185 patients with a history of MI, stroke, or peripheral vascular disease, patients receiving clopidogrel had 10% fewer serious vascular events than patients receiving aspirin (p = 0.03).

The effect of adding another antiplatelet drug to aspirin (vs aspirin alone) has been assessed in 43 trials including 39,205 patients. Overall, a 15% reduction in serious vascular events was observed (p = 0.0001). The benefits of adding an IV GP IIb/IIIa receptor antagonist to aspirin were particularly evident among patients undergoing PCI.

Antiplatelet therapy is effective in reducing the number of vascular events in patients with evidence of atherosclerotic disease (acute MI, prior MI, UA, stable angina, stroke, transient ischemic attack [TIA] or peripheral vascular disease). The benefits are consistent across all age
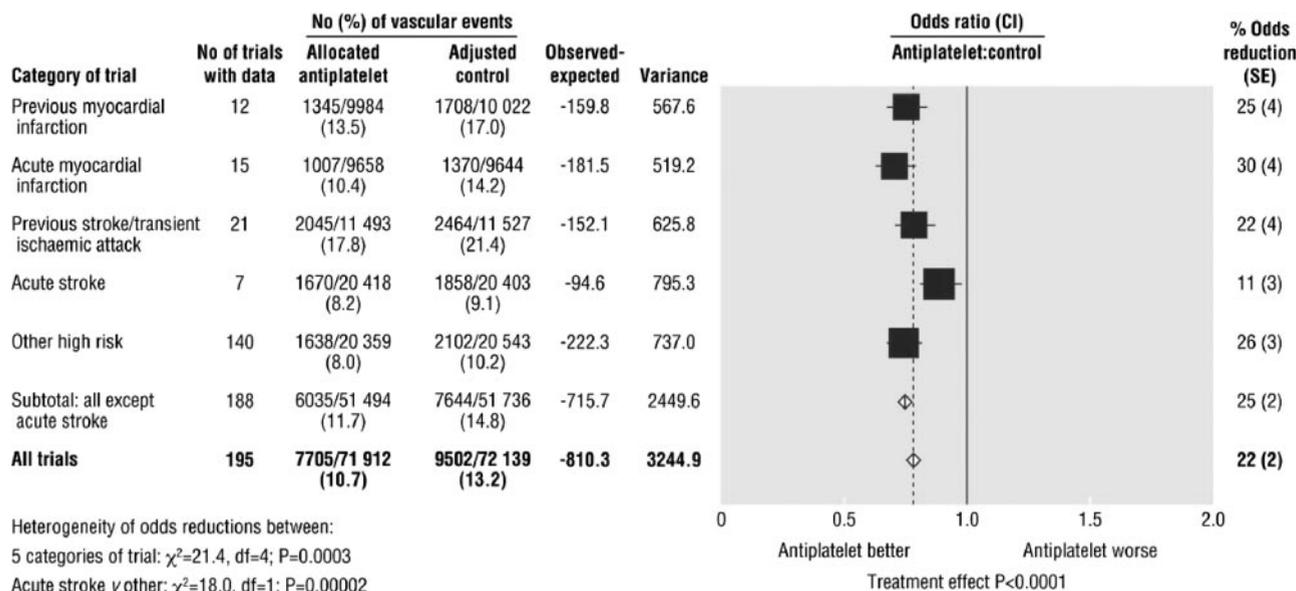
Category of trial	No of trials with data	No (%) of vascular events		Observed-expected	Variance	Odds ratio (CI) Antiplatelet:control	% Odds reduction (SE)
		Allocated antiplatelet	Adjusted control				
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6		25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2		30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8		22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3		11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0		26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6		25 (2)
All trials	**195**	**7705/71 912 (10.7)**	**9502/72 139 (13.2)**	**-810.3**	**3244.9**		**22 (2)**

Heterogeneity of odds reductions between:
5 categories of trial: χ^2=21.4, df=4; P=0.0003
Acute stroke v other: χ^2=18.0, df=1; P=0.00002

FIGURE 3. Systematic overview of antiplatelet therapy in vascular disease. Attention is directed to the subset of patients with AMI. *df* = degrees of freedom. Reprinted with permission from the BMJ Publishing Group. Antithrombotic Trialist's Collaboration. Collaborative meta-analyses of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71–86.

ranges and risk profiles, reducing vascular events by one fourth, nonfatal MI by one third, and vascular death by one fifth.

Recommendations

In patients with ACSs with and without ST-segment elevation:

2.1.1. We recommend aspirin in initial doses from 160 to 325 mg, and then indefinite therapy, 75 to 162 mg/d (**Grade 1A**).

2.1.2. For patients with a history of aspirin-induced bleeding or with risk factors for bleeding, we recommend lower doses (≤ 100 mg) of aspirin (**Grade 1C+**).

2.1.3. For patients in whom aspirin is contraindicated or not tolerated, we recommend clopidogrel, 75 mg/d, for long-term administration (**Grade 1A**).

2.2 Anticoagulant therapies

Short-term anticoagulant trials. Since 1948, there have been > 30 reports of the use of anticoagulants in patients who have experienced AMIs. However, only three of these trials were sufficiently large to detect a modest but clinically important reduction of mortality. One of these studies found a statistically significant reduction of mortality, while the other two found statistically significant reductions in stroke and pulmonary embolism.

Using rigorous overview approaches, Collins et al[95] summarized the data on early deaths, reinfarction, strokes, pulmonary embolism, and clinically important episodes of bleeding from the 26 unconfounded, properly randomized

trials of anticoagulant therapy administered to patients in the acute phase of suspected MI (Table 5). The trials were categorized as those comparing low-dose SC heparin vs no antithrombotic therapy, high-dose SC heparin vs no antithrombotic therapy, high-dose IV heparin vs no antithrombotic therapy, and high-dose heparin therapy followed by oral anticoagulant therapy vs no antithrombotic therapy. Using these categories, they separately evaluated those trials in which the comparisons were made among patients not receiving aspirin and those among patients receiving aspirin (93% of whom also received fibrinolytic therapy).

It is clear from this overview that in the absence of aspirin and fibrinolytic therapy, heparin reduces deaths by a statistically significant and clinically important amount (*ie*, approximately 35 fewer deaths per 1,000 patients; p = 0.002). The low-dose SC regimens are probably not effective in reducing death, but there is no clear difference in efficacy among the high-dose regimens. The beneficial effect on mortality is supplemented by reductions of reinfarction (15 per 1,000 patients; p = 0.08), stroke (10 per 1,000 patients; p = 0.01), and pulmonary embolus (19 per 1,000 patients; p = 0.001). The benefits must be balanced against an increase in the incidence of noncerebral major bleeding (13 per 1,000 patients; p = 0.01), which appeared to be confined to the high-dose heparin regimens. Following successful thrombolysis, there is a 5 to 30% risk of infarct-related artery reocclusion and a reinfarction rate of approximately 4% when aspirin is not used.[96] The thrombolytic agents may paradoxically lead to platelet activation and to the generation of increased amounts of thrombin.[97] Hence, there is a good theoretic rationale for the conjoint use of heparin.

Table 5—Randomized Clinical Trials of Anticoagulation With UFH Among Patients With AMI*

Trial or Stratum	No. Randomized With Follow-up Heparin	Control‡	Death Heparin	Control‡	Reinfarction Heparin	Control‡	Stroke Heparin	Control‡	Pulmonary Embolism Heparin	Control‡	Deep Vein Thrombosis¶ Heparin	Control‡	Major Bleed# Heparin	Control‡
Low-dose heparin (10,000–20,000 IU/d; mean, 12,000) no antithrombotic														
Handley[4]†	35	35	3	0	0	0	0	0	1	1	6	7	0	0
Gallus et al[5]†	14	13	NA	NA	NA	NA	NA	NA	0	1	1	2	0	0
Warlow et al[6]†	73	73	6	5	NA	NA	NA	NA	0	3	2	11	0	NA
Emerson and Marks[7]†	38	43	0	1	NA	NA	NA	NA	NA	NA	2	14	NA	NA
Cade et al[8]†	63	2 × 30	NA	NA	3	NA	0	0	2	NA	2	2 × 3	0	NA
Renvig et al[9]†	144	143	12	13	NA	8	NA	NA	0	2	3	8	0	0
Zawilska et al[10]†	50	53	5	6	NA	NA	NA	NA	NA	1	2	10	1	0
High-dose heparin (≥ 20,000 IU/d; mean, 25,000) vs no antithrombotic														
Carleton et al[11]†	60	65	13	18	4	4	NA	NA	2	3	NA	NA	9	5
Steffensen[12]†	103	109	33	45	4	4	NA	NA	2	6	NA	NA	0	0
Handley et al[13]†	30	30	2	3	NA	NA	NA	NA	0	2	0	7	1	0
Gueret et al[14]†	46	44	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1/2 ISIS-2 pilot[15]†														
Fibrinolytic	104	100	7	11	3	6	1	1	NA	NA	NA	NA	1	0
No fibrinolytic	50	52	9	5	1	2	3	1	NA	NA	NA	NA	0	0
Diaz and Torres[16]†	10	10	0	0	NA	NA	NA	NA	NA	NA	NA::2NA	NA	NA	NA
SCATI[17]†														
Fibrinolytic	218	215	10	19	18	21	0	2	1	0	NA	NA	4	2
No fibrinolytic	142	136	11	16	2	3	2	0	0	0	NA	NA	NA	NA
Bleich et al[18]†	46	49	6	5	NA	NA	2	0	NA	NA	NA	NA	1	1
High-dose heparin (≥ 20,000 IU/d; mean, 29,000) plus oral anticoagulant vs no antithrombotic														
Drapkin and Merskey[19]†	745	2 × 391	111	2 × 83	88	2 × 51	13	2 × 9	28	2 × 24	NA	NA	NA	NA
VA Coop[20]†	513	513	49	58	17	24	4	19	10	24	3	10	13	6
Wray et al[21]†	46	46	2	3	NA	NA	NA	NA	0	0	NA	NA	0	0
Pitt et al[22]†	35	37	0	0	NA	NA	NA	NA	0	0	4	11	NA	NA
Nordrehaug et al[23]†	26	27	4	2	1	1	0	1	0	0	NA	NA	0	0
Arvan and Boscha[24]†	16	18	1	2	1	1	0	2	0	0	NA	NA	2	0
High-dose heparin (24,000–25,000 IU/d) plus aspirin vs aspirin alone														
1/2 ISIS-2 pilot[15]†														
Fibrinolytic	106	103	8	6	1	5	0	0	NA	NA	NA	NA	0	1
No fibrinolytic	54	50	2	3	1	2	1	0	NA	NA	NA	NA	0	0
ECSG-6[25]†	324	320	9	11	10	10	4	1	NA	NA	NA	NA	3	4§
OSIRIS[26]†	64	64	1	3	2	1	3	2	0	0	NA	NA	6	4
DUCCS-1[27]†	128	122	12	8	9	4	4	1	NA	NA	NA	NA	14	7
GISSI-2[28,29]†	10,361	10,407	884	932	282	303	115	119	8||	16||	NA	NA	103	57
ISIS-3[30]†														
Fibrinolytic	20,656	20,643	1,875	1,954	645	707	261	240	70	88	NA	NA	209	156
No fibrinolytic	2,275	2,282	141	175	59	71	9	12	4	13	NA	NA	7	5

*Reprinted with permission from the BMJ Publishing Group. Collins R, MacMahon S, Flathe M, et al. Clinical effects of anticoagulant therapy in suspected myocardial infarction: systematic overview of randomized trials. BMJ 1996; 313:652–659. NA = not applicable.

†These references refer to the original source document.

‡2 × = control groups counted twice in adjusted totals (but not in statistical calculations) to balance larger treatment groups in studies with 2:1 allocation ratio.

§For ECSG-6, information was available on major bleeds only until coronary angiography, when study treatment was to stop.

||Pulmonary embolism available only for Italian part of GISSI-2 and not for international extension.

¶Includes only deep vein thrombosis detected by radiolabelled fibrinogen or venogram.

#Requiring transfusion, for example.

In the present era, most patients suspected of experiencing an AMI will receive aspirin, and a substantial portion will also receive fibrinolytic therapy. Accordingly, the most relevant trials are those comparing heparin vs no heparin among patients receiving aspirin and fibrinolytic therapy. In the overview by Collins et al,[95,98] within the trials of patients receiving aspirin/fibrinolytic therapy, the baseline rates of death, reinfarction, stroke, and pulmonary embolus were markedly lower than those in the preaspirin/fibrinolysis era. Although the addition of heparin led to a reduction of death (5 per 1,000 patients; p = 0.03), reinfarction (3 per 1,000 patients; p = 0.04) and pulmonary embolus (1 per 1,000 patients; p = 0.01), the benefits were small and the statistical significance was marginal. The small mortality benefits observed at 7 days in the ISIS-1[99] and Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico-2[106] trials (which contributed most of the patients) became fewer and were no longer statistically significant after 35 days and 6 months of follow-up. Interestingly, the baseline rate of major bleeding was lower than in the preaspirin/fibrinolysis era, and the excess with heparin therapy was less (3 per 1,000 patients; p = 0.001). Hence, physicians are faced with a modest early benefit of heparin therapy of approximately five fewer deaths, three fewer reinfarctions, and one less pulmonary embolus, balanced against three additional episodes of major bleeding. Recommendations for this can be found in this Supplement in the chapter on ST-segment elevation AMI by Ohman et al.

Long-term anticoagulant trials. Anand and Yusuf[101,101a] have published a systematic overview of anticoagulation therapy in patients with CAD. Since it had long been suggested that the therapeutic window for oral anticoagulation is narrow, the investigators divided their analysis of anticoagulation control into those patients who had received high-intensity anticoagulation therapy (INR between 2.8 and 4.8), moderate-intensity anticoagulation therapy (INR, 2 to 3), and low-intensity anticoagulation therapy (INR < 2.0). In comparisons of anticoagulation plus aspirin vs aspirin alone, patients were classified as moderate-to-high-intensity anticoagulation therapy (INR approximately 2) and low-intensity anticoagulation therapy (INR < 2.0).

The analysis of anticoagulation therapy by Anand and Yusuf[101,101a] involved patients with coronary disease and was not confined to those who had experienced AMIs. The majority of patients began therapy within 3 months of a hospitalization, presumably for an MI. The major finding of this overview analysis was that moderate-intensity and high-intensity anticoagulation therapy were effective in reducing the incidence of MI and stroke compared with control subjects, but carried a several-fold increased risk of bleeding. In three trials involving a small population of patients (n = 480), the composite of death, MI, or stroke was reduced by 50% with moderate-to-high-intensity anticoagulation plus aspirin compared with heparin therapy alone. Low-intensity anticoagulation therapy plus heparin was not superior to aspirin therapy alone.

A series of randomized trials conducted prior to 1980 suggested that long-term oral anticoagulation following an AMI might decrease the number of reinfarctions, embolisms, and deaths. Subsequently, the Sixty Plus Reinfarction Study[102] enrolled patients > 60 years of age who had been receiving oral anticoagulation therapy following transmural MIs that had occurred at least 6 months earlier (mean, 6 years). The patients were randomly allocated in a blinded manner to continue treatment with oral anticoagulation therapy (INR, 2.7 to 4.5) or matching placebo. Major and minor extracranial hemorrhages were considerably more frequent in the anticoagulant-treated patients, but transfusion was rare and there were no fatal hemorrhages.

The Warfarin-Aspirin Reinfarction Study (WARIS) enrolled patients who had sustained AMI a mean of 27 days previously. They were randomized in a blinded fashion to treatment with warfarin (INR, 2.8 to 4.8) or placebo, and were advised not to take aspirin. There were statistically significant reductions in all-cause mortality, reinfarction, and stroke, and an efficacy analysis revealed more marked benefits. Venous thromboembolism was rare with placebo and did not occur with warfarin. There were five intracranial hemorrhages with warfarin treatment, three of them fatal, and there were eight episodes of major extracranial hemorrhage with warfarin treatment, for a combined incidence of major bleeding of 0.6%/yr.

The Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) research group[103] enrolled patients who had sustained an AMI within 6 weeks of hospital discharge. They were randomized in a blinded manner to treatment with acenocoumarol (nicoumalone), phenprocoumon (INR, 2.8 to 4.8), or placebo. The ASPECT group found a favorable trend for the reduction of all-cause mortality with statistically significant reductions in reinfarction and stroke. The combined annual incidence of major bleeding was 1.4%/yr with oral anticoagulation and 0.4%/yr with placebo. Efficacy analyses showed greater risk reductions with anticoagulation. An overview[104] of these trials reinforces the observations of benefit.

Neri Serneri et al[105] evaluated heparin (12,500 U SC qd) among 6- to 18-month survivors of Q-wave MI. There was a significant reduction in the rate of reinfarction with favorable trends for the reduction of all-cause and cardiovascular mortality. Efficacy analysis provided stronger evidence for a benefit of heparin. There were no major hemorrhages and no evidence of osteoporosis on bone density measurements.

2.3 Comparisons of antiplatelet and anticoagulant therapy and/or combinations of aspirin and warfarin trials

Oral anticoagulation has been compared directly with aspirin in several trials. The German-Austrian trial[106] enrolled 942 patients within 30 to 42 days of their experiencing AMIs and assigned them to aspirin, placebo, or phenprocoumon therapy. Over a 2-year follow-up period, the aspirin-treated patients had statistically insignificant reductions of 26% for all-cause mortality and 46.3% for coronary mortality compared with phenprocoumon. Aspirin showed a favorable trend compared with placebo, but phenprocoumon did not.

In the Enquete de Prevention Secondaire de l'lnfarctus du Myocarde trial,[107] 1,303 patients were randomized a mean of 11.4 days following AMI to aspirin or one of several anticoagulants. Over a mean follow-up period of 29 months, the all-cause mortality rate was 10.3% with anticoagulation and 11.1% with aspirin. The study was stopped early when it appeared that a statistically significant lower mortality rate with aspirin would not be found.

The Aspirin/Anticoagulants Following Thrombolysis with Anistreplase (Eminase) and Recurrent Infarction study[108] enrolled 1,036 survivors of AMI who had received anistreplase. They were randomized to treatment with anticoagulation (IV heparin followed by warfarin or other oral anticoagulant) or aspirin (150 mg/d) and were followed up for the principal outcome of cardiac death or recurrent MI by 30 days. The rates of the principal outcome were 11.0% with anticoagulation and 11.2% with aspirin. The trial was stopped early because of a declining enrollment rate, and was underpowered to rule out a difference between the two therapies. However, the rate of severe bleeding or stroke was significantly higher with anticoagulation than with aspirin (3.9% vs 1:7%, respectively; OR, 0.44; 95% CI, 0.20 to 0.97; p = 0.04).

The Coumadin Aspirin Reinfarction Study (CARS)[109] was a blinded study of 8,803 patients enrolled 3 to 21 days after an acute MI. The patients were randomized into one of three arms: 160 mg of aspirin, 1 mg of warfarin plus 80 mg of aspirin, or 3 mg of warfarin plus 80 mg of aspirin. During a median follow-up of 14 months, the primary composite outcome of reinfarction, nonfatal ischemic stroke, or cardiovascular death occurred at a rate of 8.6% in the 160-mg aspirin group, 8.8% in the 1-mg warfarin plus 80-mg aspirin group, and 8.4% in the 3-mg warfarin plus 80-mg aspirin group. Major hemorrhage occurred in 0.74% of the aspirin group and 1.4% of the 3-mg warfarin/80-mg aspirin group. Among 3,382 patients assigned to 3-mg warfarin/80-mg aspirin, the INRs were 1.51 at week 1, 1.27 at week 4, and 1.19 at 6 months. The CARS investigators concluded that low fixed-dose warfarin therapy (1 mg or 3 mg) combined with low-dose aspirin therapy (80 mg) did not provide clinical benefit beyond that achievable with 160 mg of aspirin.

The CARS results are consistent with the body of literature suggesting that warfarin is most effective at INR ranges between 2 and 3.5, at least in the short term. The results of the Thrombosis Prevention Trial (TPT)[110] suggest that warfarin therapy at a lower INR (approximately 1.5) may be beneficial in primary prevention. The Combined Hemotherapy and Mortality Prevention study[111] was an open-label Veterans Administration cooperative trial that sought to demonstrate a 15% reduction in all-cause mortality in survivors of AMI treated with combined therapy (ie, warfarin; INR, 1.5 to 2.5; plus aspirin, 81 mg) compared with aspirin therapy (162 mg) alone. The trial was conducted in 78 Veterans Administration medical centers. Patients were recruited within 14 days of experiencing AMI. The study consisted of 5,059 subjects, mostly men, with a mean age of 62 years. Approximately half had hypertension, had experienced angina, and were current smokers, and approximately 35% had had an anterior MI. Twenty-seven percent were diabetics, 9%

had experienced a stroke, and 8% had a history of heart failure. There were 6,940 patient-years of follow-up in the aspirin group and 6,789 patient-years in the combination group, with a median follow-up period of 2.75 years in both groups. Therapy was initiated in 91% of patients in the aspirin group and 81% in the combination therapy group, and was discontinued in 13% of patients in the aspirin group and 26% in the combination therapy group. The mean INR was 1.9. Using an intention-to-treat analysis, there was no significant difference in the total mortality rate (17.3% vs 17.3%), cardiovascular mortality (4.7% vs 4.2%), nonfatal stroke (4.7% vs 4.2%), and nonfatal MI (13.1% vs 13.3%, respectively). Major bleeding, mostly GI, was more common in the combination therapy group than in the aspirin group (combination therapy group, 1.25 major episodes of bleeding per 100 patient-years; aspirin-alone group, 0.69 major episodes of bleeding per 100 patient-years). Intracranial hemorrhages occurred in 0.2% of each group, and episodes of fatal bleeding were no different between the two groups. The investigators concluded that there was no survival advantage to adding warfarin to aspirin in survivors of AMI.

Oral anticoagulant therapy in combination with aspirin has been investigated. In the OASIS pilot study,[112] moderate intensity warfarin (INR, 2.0 to 2.5; 3 mg/d) reduced coronary event rates compared with control patients with ACS without ST-segment elevation. Most patients in both groups received aspirin. At 3 months, the rates of cardiovascular death, new MI, and refractory angina after hospital discharge were 5.1% in the warfarin group and 12.1% in the standard group, reflecting a 58% RRR in these events with warfarin plus aspirin compared with aspirin alone (95% CI, 0.15 to 1.15; p = 0.08).

More recently, the randomized, open-label, multicenter Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT)-II trial[113] enrolled 308 patients with AMI who received UFH, aspirin, and fibrinolytic therapy. In APRICOT-II,[113] those who achieved TIMI-3 flow in the infarct-related artery were then randomized to warfarin (heparin continued until INR of 2.0 to 3.0) plus aspirin, 80 mg/d, or aspirin (80 mg/d) alone (heparin discontinued).

Follow-up angiography at 3 months revealed reduced reocclusion rates (defined as TIMI < 2) in the warfarin-plus-aspirin group compared with those receiving aspirin alone (18 vs 30%, respectively; RR, 0.60; 95% CI, 0.39 to 0.93; p = 0.02), reflecting a 40% RRR in events. Most of this benefit centered on a significant reduction in the incidence of TIMI 0–1 (ie, anatomic reocclusions; 9% vs 25%, respectively). The results from APRICOT II support combination therapy in the post-MI setting for patients with ST-segment elevation MI.

The ASPECT II trial[114] provides further support for combined anticoagulant and antiplatelet therapy following ACS. In this study, 999 patients were randomly assigned to high-intensity warfarin (INR, 3.0 to 4.0), moderate-intensity warfarin (INR, 2.0 to 2.5) plus aspirin (80 mg/d), or aspirin (80 mg/d) alone. At 12 months, the primary end point was reached by significantly fewer patients in the warfarin-only and warfarin-plus-aspirin groups than the aspirin-only group (5%, 5%, and 9%, respectively;

$p \leq 0.05$), and mortality was significantly lower in the two warfarin groups compared with the aspirin group (1.2%, 2.7%, and 4.5%, respectively; $p = 0.01$). The risk of major bleeding was higher with combination therapy than with warfarin alone.

The open-label, multicenter WARIS II was a long-term secondary prevention study[115] based in Norway, in which 3,630 post-AMI patients were randomized to three groups consisting of high-intensity warfarin (INR, 2.8 to 4.2), moderate-intensity warfarin (INR, 2.0 to 2.5) plus aspirin (75 mg/d), or low-dose aspirin (160 mg/d) alone. The primary end point was the rate of first occurrence of the composite end point of all-cause mortality, nonfatal reinfarction, and stroke. Patients in WARIS II[115] were relatively young (approximately 60 years), approximately three fourths were male, and roughly half were smokers.

Approximately 6 of 10 patients had experienced a recent Q-wave MI or ST-segment elevation MI, and slightly more than half had received thrombolytic therapy. Patients were followed up for a mean of 4 years, with anticoagulation intensity managed on an outpatient basis. This study lasted significantly longer than other trials of antithrombotic therapy in patients after ACS.

At the 4-year follow-up, the primary end point was lower in the warfarin-plus-aspirin group than either the warfarin or aspirin-alone groups (15.0%, 16.7%, and 20.0%, respectively). Using a person/year model, these data gave an OR of 0.71 for the warfarin-plus-aspirin combination vs aspirin alone (95% CI, 0.60 to 0.83; $p = 0.001$), or a 29% RRR with combination therapy. The OR for warfarin vs aspirin was 0.81 (95% CI, 0.69 to 0.95; $p = 0.03$), reflecting the superiority of both warfarin arms over aspirin alone. However, the benefit of the warfarin-plus-aspirin group over the warfarin-only group did not reach statistical significance, with an OR of 0.87 (95% CI, 0.71 to 1.08; $p = 0.20$), which might mean that much of the benefit is related to the anticoagulant effect.

Importantly, the cumulative hazard curves for the primary end point showed a significant divergence between the warfarin groups and the aspirin-only group at 4 years ($p = 0.003$), demonstrating the benefits of long-term anticoagulation. However, major nonfatal bleeding was threefold to fourfold more frequent among the warfarin-only and combination groups than in the aspirin-only group, although absolute percentages per year were relatively low (0.68%, 0.57%, and 0.17%, respectively).

The results from WARIS II[115] suggest that combining aspirin with oral anticoagulation treatment is superior to treatment with aspirin alone. While these findings have significant clinical implications, it is important to consider the following areas of uncertainty: (1) the level of intensity of anticoagulation was carefully controlled in WARIS II, and it is unclear whether this degree of success can be achieved in routine clinical practice; and (2) the benefit seen with anticoagulant therapy in the WARIS II cohort (*ie*, relatively young and low rates of revascularization) may not translate directly to other post-ACS populations, especially patients undergoing PCI and those of advanced age who are at increased risk for hemorrhage complications.

Recommendations

2.3.1. In most health-care settings, for moderate- and low-risk patients with an MI, we recommend aspirin alone over oral vitamin K antagonists (VKAs) plus aspirin (**Grade 2B**).

Underlying values and preferences: This recommendation places a relatively low value on prevention of thromboembolism, and a relatively high value on avoiding the inconvenience, expense, and bleeding associated with VKA therapy.

2.3.2. In health-care settings in which meticulous INR monitoring is standard and routinely accessible, for both high- and low-risk patients after MI, we recommend long-term (up to 4 years) high-intensity oral VKA (target INR, 3.5; range, 3.0 to 4.0) without concomitant aspirin, or moderate-intensity oral VKA (target INR, 2.5; range, 2.0 to 3.0) with aspirin (both **Grade 2B**).

2.3.3. For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on echocardiography, and those with a history of a thromboembolic event, we suggest the combined use of moderate-intensity (INR, 2.0 to 3.0) oral VKA plus low-dose aspirin, ≤ 100 mg/d, for 3 months after the MI (**Grade 2A**).

2.4 Oral DTIs

The phase II Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage (ESTEEM)[116] trial is currently evaluating ximelagatran in combination with aspirin as long-term therapy in a predominantly noninterventional post-MI setting. ESTEEM is a dose-finding study comparing four doses of ximelagatran (24 mg, 36 mg, 48 mg, and 60 mg bid) plus aspirin, compared with aspirin alone for 6 months. ESTEEM is the first trial of > 7 days of direct thrombin inhibition in patients after ACS.

This pilot study[116] showed a 24% reduction ($p = 0.036$) in the primary opposite of death, MI, and severe recurrent ischemia for the combined ximelagatran groups vs placebo. Major bleeding was infrequent in both groups and was not significantly increased with ximelagatran. The emergence of orally administered DTIs, such as ximelagatran, which are effective, well tolerated, and lack a requirement for monitoring, may also facilitate the adoption of oral anticoagulant treatment in a variety of common clinical applications, including ACS.

3.0 Chronic, Stable CAD

Much of the data regarding the role of antithrombotic therapy in chronic CAD has been studied within the context of trials commencing therapy after recent ACS/MI, and is summarized above. In this section, only trials examining antithrombotic therapy in patients with CAD without antecedent coronary events will be considered.

3.1 Antiplatelet therapy

The Antithrombotic Trialists Collaboration metaanalysis[8] included new data on 2,920 patients with stable CAD.

Antiplatelet treatment (predominantly aspirin) was associated with a 33% reduction in vascular events (14.1% vs 9.9%). In addition, in this meta-analysis, antiplatelet treatment for high-risk patients who had not previously sustained MIs was associated with a clear reduction of 31% in nonfatal MI.

The Physicians' Health Study[117] included 333 male physicians with baseline chronic stable angina but without prior MI, stroke, or TIA. Alternate-day aspirin, 325 mg, reduced the risk of first MI by 70% during 60.2 months of follow-up (p = 0.003). After controlling for other cardiovascular risk factors, the RRR was 87% (p = 0.006).

The new data in the Antithrombotic Trialists Collaboration analysis predominantly reflected inclusion of the data from the Swedish Angina Pectoris Aspirin Trial,[100] which studied 2,035 patients with chronic stable angina randomly assigned to aspirin, 75 mg/d, or placebo, for a median of 15 months. Treatment with aspirin (in addition to background sotalol, which was administered as an antianginal therapy) was associated with a 34% RRR (CI, 24 to 94%; p = 0.003) in the primary end point (MI and sudden death), and a 22 to 32% RRR in other vascular end points.

Of 19,185 patients enrolled in the CAPRIE trial,[118] a new AMI developed in 617 patients; during 1 to 3 years of follow-up, AMI occurred in 5.04% of aspirin-treated patients, vs 4.2% of clopidogrel-treated patients (RRR, 19.2%; p = 0.0008). Risk of AMI could be predicted based on baseline characteristics, including the presence of previous angina, and such patients at higher risk appeared to have greater relative benefit from treatment with clopidogrel vs aspirin.[118]

3.2 Anticoagulant therapy

The Anand and Yusuf meta-analysis[101] of 31 randomized studies published between from 1960 to 1999 examined the effect of long-term anticoagulant use in patients with CAD. However, only a minority of patients included in this analysis (0 to 16%, stratified by intensity of anticoagulation) began anticoagulant therapy at least 3 months after an acute coronary event. A more recent update[101a] of this meta-analysis incorporated data from six new trials. However, these trials examined patients with ACS, AMI, or after PCI (as opposed to chronic CAD). Thus, the data do not support clear recommendations for initiating anticoagulation for patients with chronic CAD, or for the combination of anticoagulant and antiplatelet therapy.

Recommendations

3.1.1. For all patients with chronic stable CAD, we recommend the administration of aspirin, 75 to 162 mg po (**Grade 1A**). We suggest that aspirin be continued indefinitely (**Grade 2C**).

3.1.2. For patients with stable chronic coronary disease with a risk profile indicating a high likelihood of developing AMI, we suggest long-term therapy with clopidogrel in addition to aspirin (**Grade 2C**).

3.2. For patients with chronic CAD without prior MI, we suggest clinicians **not** use long-term oral VKAs (**Grade 2C**).

4.0. Congestive Heart Failure With and Without CAD

Five million Americans currently live with heart failure, and there are approximately 400,000 new cases each year; approximately 250,000 patients die and 75,000 have strokes attributable to heart failure annually. Because heart failure is marked by low cardiac output, relative stasis of blood in the intracardiac chambers, poor contractility, regional wall motion abnormalities, and the high prevalence of atrial fibrillation and various degrees of a hypercoagulable state, patients with heart failure have high rates of systemic and pulmonary embolism.[119–122] Defects in endothelial function, hemostatic mediators, and platelet abnormalities increase the risk of thromboembolism in heart failure. Molecular models of hemostasis in patients with idiopathic nonischemic cardiomyopathy have demonstrated increased levels of fibrinopeptide A and thrombin-antithrombin 3 complex. In the stable, ambulatory heart failure patient, plasma levels of platelet factor 4, β-thromboglobulin, and plasmin-α II plasmin inhibitor complex do not differ significantly from control subjects; there is very little platelet activation in such a patient. Patients presenting with decompensated heart failure, however, have heightened platelet activity as demonstrated by increased levels of soluble P-selectin. Thus the hypercoagulable state and heightened platelet activity observed in the heart failure patient creates a reasonable pathophysiologic construct for using antithrombotic therapy in these patients.[123–129]

Early autopsy studies of patients with cardiomyopathy reported high rates of thromboembolism. In 1958, Spodick[130] reported a 50% incidence of thromboembolism in autopsy cases of CHF; nearly 30 years later, Roberts et al[131] found evidence of thromboembolism in 37% of 152 autopsied patients with dilated cardiomyopathy. Five modern series[132–136] of CHF patients and subsequent thromboembolism suggest a lower rate.

In a landmark longitudinal series of 104 patients with dilated cardiomyopathy, Fuster et al[119] reported systemic arterial embolism at a rate of 3.5/100 patient-years. Natterson et al[137] reported a 3.2/100 patient-year rate of thromboembolism in heart failure patients awaiting cardiac transplant. Sharma et al[138] reviewed 144 consecutive patients with severe left ventricular dysfunction and reported a 12.5% rate of thromboembolism over 27.6 months. Although the current rate of thromboembolism is lower than in early observations, it appears that thrombosis may play an important role in the mechanism of death in many of these patients. Recent studies[139] have suggested that coronary thrombosis is common in heart failure patients dying of sudden death and even progressive pump failure.

CHF. Interaction of Etiology and Outcomes: The underlying etiology of heart failure has important implications for prognosis and for treatment, including with antithrombotic therapies. Patients with an isch-

emic etiology constitute 70% of patients with systolic left ventricular dysfunction and heart failure, while nonischemic etiologies make up 30%, with the leading causes being hypertension and idiopathic. This high prevalence of CAD in patients with CHF represents a significant change in etiologies over the last 50 years; in the 1950s and 1960s, hypertension and valvular heart disease were the dominant causes of CHF, and this may be reflected in part in the higher rates of thromboembolism found at autopsy during those decades. With CAD underlying 70% of heart failure today, the role of coronary thrombosis with platelet activation cannot be underestimated.

4.1 VKA, aspirin

Meta-analysis: A pooled analysis of multiple randomized trials of oral anticoagulation in patients with heart failure revealed that patients receiving warfarin had less thromboembolism and lower mortality than those receiving no anticoagulation. Bleeding complications were more common in the warfarin group. Because 75% of the information in the analysis came from 50-year-old evidence, the potential benefit of warfarin remains unclear.

Clinical trials: Early studies investigating anticoagulation were predominantly conducted in patients with nonischemic cardiomyopathy with a high prevalence of rheumatic heart disease and atrial fibrillation. In the 1950s, four small prospective controlled trials[130,140–143] of warfarin vs placebo were conducted in hospitalized patients. Despite major methodologic limitations of these trials, warfarin was more beneficial than placebo.

The only modern randomized controlled trial (RCT) of anticoagulation in patients with heart failure who were in sinus rhythm was the Warfarin/Aspirin Study in Heart Failure (WASH) study.[144] This pilot study had as its primary end point the feasibility of conducting a definitive study that would require 1,200 patients in the treatment arm. The principal secondary end point was a combination of all-cause mortality, nonfatal MI, and nonfatal stroke. The WASH study[144] employed an open-label but blinded end point analysis design. Patients had to have clinical heart failure treated with diuretics and echocardiographic evidence of left ventricular dysfunction. Two hundred seventy-nine patients were randomized to oral anticoagulation with warfarin (target INR, 2.5) vs aspirin, 300 mg, vs no antithrombotic therapy. The follow-up lasted 2.5 years. There was no significant difference in the composite end point of death, MI, and stroke in patients treated with warfarin vs aspirin vs no antithrombotic therapy (32% vs 24% vs 27%, respectively). Patients in the warfarin group spent fewer days in the hospital than those treated with aspirin or no antithrombotic therapy. There was an excess of all-cause hospitalizations due to exacerbations of heart failure in the aspirin group (p = 0.05). There were five hemorrhages in the study, one with aspirin treatment and four with warfarin treatment. Serious adverse events among patients receiving aspirin were 198 compared with 173 receiving warfarin and 178 receiving no antithrombotic therapy. The WASH study suggested that there is no advantage or disadvantage of antithrombin therapy compared with antiplatelet therapy or placebo, emphasizing the need for large-scale investigations of antithrombin or antiplatelet therapy in patients with CHF.[144–146]

The Heart Failure Long-term Antithrombotic Study[147] was a randomized, blinded, placebo-controlled study that compared aspirin and warfarin in patients in whom the heart failure was secondary to MI, and compared placebo and warfarin if the cause was idiopathic. Patients with class II-IV CHF, aged 20 to 80 years, with an ejection fraction ≤ 35% were randomized according to the etiology of their CHF. Although the trial did not achieve its recruitment target, preliminary results in 223 patients showed no difference in outcome in the two groups. Two federally funded trials currently underway have the most promising opportunity to answer the question of whether antithrombotic therapy in heart failure is beneficial.[147]

Four large-scale, nonrandomized cohort analyses of patients with heart failure and systolic dysfunction have been conducted. In the Studies of Left Ventricular Dysfunction study[148] of enalapril vs placebo in patients with left ventricular dysfunction (70% with an ischemic etiology), warfarin was associated with significantly lower risk of all-cause death and sudden death. The reduction of sudden death was independent of etiology. In the Cooperative North Scandinavian Enalapril Survival Study[149] of enalapril vs placebo in class IV CHF, long-term anticoagulation with warfarin was associated with a 40% lower mortality, despite the fact that only 25% of the deaths were due to sudden death.

The vasodilator heart failure studies provide further observational evidence regarding the role of oral anticoagulation in preventing thromboembolism among patients with CHF. In Vasodilator-Heart Failure Trial (V-HeFT)-I,[150] there was no significant difference in the rates of thromboembolism between patients receiving long-term warfarin therapy and those who did not receive anticoagulation. In Vasodilator-Heart Failure Trial (V-HeFT)-II,[151] there was an incidence of 2.1 events/100 patient-years among patients without antithrombotic therapy compared with 4.9 events/100 patient-years among patients who received warfarin. The incidence of thromboembolic events was higher in patients receiving warfarin (p = 0.01).[151] This may reflect the difficulty in ascertaining whether the warfarin therapy was actually used in this higher-risk patient population. In addition, these analyses were not adequately adjusted for other risk factors such as degree of heart failure, atrial fibrillation, age, gender, previous cerebrovascular disease, or left ventricular thrombus.[152] In the (Survival and Ventricular Enlargement (SAVE) trial[153] of post-MI heart failure, all of ischemic etiology, warfarin was associated with an 81% reduction in stroke risk and aspirin was associated with a 56% reduction in stroke. No direct comparison of warfarin and aspirin was reported. In a retrospective analysis of the 324 patients in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial[153a] who were administered warfarin, there was a significant reduction in stroke only among those with an ejection fraction < 20% (0.6% vs 3.3%; p < 0.05). The limitations of such analyses are important; it is not possible to completely adjust for differences in

baseline characteristics nor for variations in compliance, adherence, and crossovers in an unspecified retrospective analysis.

The Veterans Administration is completing the Warfarin Antiplatelet Trial and Chronic Heart Failure (WATCH) trial. Although originally planned to enroll 4,500 patients, the WATCH trial ended enrollment at 1,587 patients with New York Heart Association class II-IV with ejection fraction $\leq$ 40% who were randomized to warfarin or blinded antiplatelet therapy with aspirin or clopidogrel. The primary outcome was mortality plus cardiovascular events. Another trial, the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) study, is a two-arm, blinded, randomized multicenter trial with a target enrollment of 2,860 patients. The WARCEF study is designed to test whether patients with low ejection fraction randomized to warfarin (target INR, 2.5 to 3) or aspirin (325 mg) have differences in the composite end point of death, recurrent stroke, or intracranial hemorrhage. Given the limited recruitment of the WATCH study and the difficulty in recruiting patients into the WARCEF study, a pooled analysis is planned to address whether mortality is reduced with warfarin compared with aspirin (Dr. B Massie; personal communication; American College of Cardiology Annual Scientific Session; March 2004).

Results of a retrospective analysis of the Studies of Left Ventricular Dysfunction study (SOLVD) study suggested that angiotensin-converting enzyme inhibitors (ACEIs) are less effective in patients receiving aspirin. Four subsequent studies suggested a benefit of ACEIs when combined with or without aspirin. The results of an analysis of four randomized trials of ACEI therapy with or without aspirin found no significant differences in the reduction of risk of major vascular events (p = 0.15) except MI (p = 0.01).[154]

Recommendations

4.1.1. In patients with CHF due to a nonischemic etiology, we recommend **against** routine use of aspirin or oral VKAs (**Grade 1B**).

4.1.2. We recommend that when otherwise indicated patients receive aspirin whether or not they are receiving ACEIs (**Grade 1C+**).

5.0. Primary Prevention

5.1 Aspirin, VKA, or both

Five large trials have examined aspirin in men free of a history of previous major vascular events (MI or stroke). A meta-analysis[155] using published results has included data from the trials in US and UK physicians,[156,157] the TPT[158] and the Hypertension Optimal Treatment (HOT) trial[159] (Tables 6, 7). The doses of aspirin in the four trials were 162.5 mg/d (*ie*, 325 mg on alternate days), 500 mg/d, 75 mg/d, and 75 mg/d, respectively. Major noncerebral bleeding complications included episodes that caused death, transfusion, or operation for which there were data from two of the trials and episodes from the other two trials not classified as minor. The analysis indicated that aspirin was associated with an RRR in all cardiovascular events of 15% (95% CI, 6 to 22%) and an RRR in MI of 30% (21 to 38%), and a nonsignificant RRR of 6% in all-cause mortality. Aspirin increased the RR of strokes by 6% (NS), but increased the RR of bleeding complications significantly by 69% (38 to 107%).

It is interesting and of some clinical relevance that while the effect of aspirin on coronary events is much the same as in secondary prevention, there is little or no effect—if anything a possibly adverse effect—on strokes. The likely explanation is that, in contrast to those with clinical atherosclerosis in whom stroke risk is appreciable, these patients are at very low risk of atheroembolic stroke. The risk of major bleeding balanced the reduction in cardiovascular events when the risk of the latter was 0.2% per annum. The upper 95% CI for this estimate suggested that harm from aspirin is unlikely to outweigh benefits provided the risk of a cardiovascular event is at least 0.8% per annum, equivalent to a risk of a major coronary event of 0.6% per annum. Considering the number needed to treat, the analysis concluded that aspirin for primary prevention is safe and worthwhile at a risk of a major

Table 6—Systematic Overview of Trials With Acetylsalicylic Acid for Primary Prevention*

Variables	US	UK	TPT	HOT
Patients, No.	22,071	5,139	2,540	18,790
Aspirin	11,037	3,429	1,268	9,399
Placebo	11,034	1,710	1,272	9,391
Aspirin dose, mg/d	162.5	500	75	75
Trial duration, yr	5.0	6.0	6.8	3.8
Male gender, %	100	100	100	53
Mean age, yr	NA	NA	57.5	61.5
Age < 60 yr, %	75	47	NA	NA
Smokers, %	11	13	41	16
Hypertension, %	9	10	26	100
Diabetes mellitus, %	2	2	NA	8

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NA = not available. US = United States; UK = United Kingdom.

Table 7—Analysis of Trials Using Acetysalicylic Acid for Primary Prevention*

Trials	Absolute Risk in Control Group, %/yr	Absolute Benefit From Aspirin, %/yr	OR	95% CI
Cardiovascular events				
US[4]†	0.67	0.11	0.82	0.71 to 0.96
UK[10]†	1.34	− 0.04	1.02	0.82 to 1.27
TPT[5]†	1.71	0.41	0.74	0.57 to 0.97
HOT[6]†	1.05	0.16	0.85	0.73 to 0.99
Weighted mean	0.92	0.13	0.85	0.78 to 0.94
MI				
US[4]†	0.44	0.18	0.56	0.48 to 0.71
UK[10]†	0.93	0.03	0.96	0.73 to 1.25
TPT[5]†	1.33	0.31	0.76	0.57 to 1.03
HOT[6]†	0.36	0.13	0.65	0.49 to 0.85
Weighted mean	0.52	0.15	0.70	0.62 to 0.79
Strokes				
US[4]†	0.18	− 0.04	1.22	0.93 to 1.59
UK[10]†	0.41	− 0.07	1.16	0.80 to 1.68
TPT[5]†	0.32	0.10	0.69	0.38 to 1.26
HOT[6]†	0.42	0.01	0.98	0.78 to 1.24
Weighted mean	0.29	− 0.02	1.06	0.91 to 1.24
All-cause mortality				
US[4]†	0.41	0.02	0.96	0.79 to 1.15
UK[10]†	1.59	0.16	0.88	0.71 to 1.09
TPT[5]†	1.31	− 0.05	1.03	0.78 to 1.36
HOT[6]†	0.86	0.06	0.93	0.79 to 1.09
Weighted mean	0.73	0.05	0.94	0.85 to 1.04

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†These references refer to the original source document.

coronary episode of 1.5% per annum, safe but of limited value at a coronary event risk of 1.0% per annum and unsafe at a risk of 0.5%. Only the men in the TPT were at greater risk than 1.5% per annum, their risk for all cardiovascular events being 1.71% per annum and for MI 1.33% per annum; consequently, the absolute benefit of aspirin was greater than in the other trials. Advice on aspirin for primary prevention requires accurate estimation of the absolute coronary event risk, although this is often omitted in clinical practice. When aspirin is used, there is little reason to take > 75 mg/d without evidence from direct comparisons among different doses.

The Physicians' Health Study[156] was a blinded, placebo-controlled, randomized trial of 22,071 participants designed to test two primary prevention hypotheses in a population free of MI, stroke, TIA, cancer, and current liver or renal disease, peptic ulcer, or gout. It was postulated that aspirin would decrease mortality from cardiovascular disease and that beta-carotene would decrease cancer incidence. The participants, aged 40 to 80 years, were randomly allocated to treatment with low-dose aspirin, 325 mg every other day, or placebo; and to beta-carotene, 50 mg every other day, or placebo according to a 2 × 2 factorial design. The aspirin component was terminated in 1998 at the recommendation of the Data and Safety Monitoring Board because of a clear reduction of MIs, a low likelihood of detecting a benefit of aspirin on cardiovascular mortality before the year 2000, and the

high prevalence of aspirin use among participants following the occurrence of a nonfatal vascular event.

The principal outcome of cardiovascular death occurred at a rate of only 15% of that expected for a general population of similar white men over a similar period, and was not different between aspirin (0.23%/yr) and placebo (0.24%/yr). The total death rate also was not different (aspirin, 0.4%/yr; placebo, 0.42%/yr). There was a striking reduction in the rates of MI with aspirin (0.26%/yr) vs placebo (0.44%/yr; RRR, 44%; p < 0.00001). The overall stroke rate was higher with aspirin (0.22%/yr) vs placebo (0.18%/yr; p = 0.15) as was the rate of hemorrhagic stroke (0.04%/yr) vs placebo (0.02%/yr; p = 0.06). The combined outcome of "important vascular events" (nonfatal MI, nonfatal stroke, and death from a cardiovascular cause) was significantly reduced in the aspirin group (0.56%/yr) vs the placebo group (0.68%/yr; RRR, 18%; p = 0.01).

The British Doctors' Study[157] was an open-label, randomly allocated trial of aspirin, 500 mg/d, vs aspirin avoidance (2:1 ratio of aspirin vs avoidance) among 5,139 participants with no history of stroke, definite MI, or peptic ulcer. Participants were observed for up to 6 years. Vascular death rates, including that of sudden death from unknown cause, and those of peptic ulcer and gastric hemorrhage were lower with aspirin (0.79%/yr) vs no aspirin (0.84%/yr; RRR, 6%; p = NS). Total mortality was not significantly less with aspirin (1.44%/yr vs 1.6%/yr; p = NS), and there were not fewer confirmed MIs (aspi-

rin, 0.9%/yr; no aspirin, 0.93%/yr; p = NS). Although there were significantly fewer confirmed TIAs in the aspirin group (0.16%/yr vs 0.28%/yr; p < 0.05), there were more confirmed strokes in the aspirin group (aspirin 0.32%/yr vs 0.29%/yr; p = NS), and considerably more disabling strokes in the aspirin group (aspirin 0.19%/yr vs 0.07%/yr; risk ratio, 2.58; p < 0.05).

The TPT[158] differed from the two previous trials not only in recruiting men who had not experienced major, clinically manifest episodes of ischemic heart disease (IHD) but who were also at increased risk. The TPT[158] recruited 5,499 men aged 45 to 69 years at entry through 108 general practices in the United Kingdom. Eligible participants fell in the top 20% of a risk score distribution based on smoking, family history, body mass index, BP, serum cholesterol level, plasma fibrinogen level, and factor VII activity, each weighted according to its association with IHD in the first Northwick Park Heart Study.[160] Of eligible patients, 52% entered the trial. The two regimens evaluated consisted of low-intensity oral anticoagulation to an INR of approximately 1.5 with warfarin and a controlled-release 75-mg formulation of aspirin. The design was factorial with the following four treatment groups: active warfarin/active aspirin, active warfarin/placebo aspirin, placebo warfarin/active aspirin, and placebo warfarin/placebo aspirin.

The mean warfarin dose required was 4.1 mg/d (range, 0.5 to 12.5 mg/d). There were 410 events of IHD (142 fatal and 268 nonfatal). The main effect of warfarin (comparing active warfarin/active aspirin and active warfarin/placebo aspirin vs the other two groups; p = 0.02) was a 21% reduction in all events, chiefly due to a 39% reduction in fatal events (p = 0.003), so that warfarin reduced the death rate from all causes by 17% (p = 0.04). The main effect of aspirin (active warfarin/active aspirin and placebo warfarin/active aspirin vs active warfarin/placebo aspirin and placebo warfarin/placebo aspirin) was a reduction in all IHD events of 20%, which was almost entirely due to a 32% reduction (p = 0.004) in nonfatal events. Recent analyses have suggested a strong interaction between recruitment systolic BP and the treatment effect of aspirin; patients with BP levels ≤ 130 mm Hg derived considerably more benefit than those with higher BPs, while patients with BPs ≥ 145 mm Hg had neither a beneficial nor a harmful effect. In addition, there may have been a significant excess of fatal coronary events in men aged ≥ 65 years at entry. This could account for the 12% higher overall mortality rate from coronary events. In the individual treatment groups, the absolute reductions in all IHD events compared with placebo were the following: warfarin, 2.6 events per 1,000 person-years; aspirin, 2.3 events per 1000 person-years; and warfarin/aspirin, 4 events per 1,000 person-years. Neither active warfarin/placebo aspirin nor placebo warfarin/active aspirin alone affected the incidence of all strokes, although active warfarin/active aspirin increased hemorrhagic strokes (p = 0.009). Of the 10 hemorrhagic strokes that occurred, 7 were in the active warfarin/active aspirin group, and the mean systolic BP of these men at trial entry was 158 mm Hg, compared with 146 mm Hg in those experiencing other strokes, and 135 mm Hg in those who did not have

strokes. Major noncerebral bleeding episodes were about twice as frequent in the active-treatment groups as in the placebo-warfarin-plus-placebo-aspirin group, but the differences were nonsignificant and there was no significant difference in frequency among the three active treatment groups (active warfarin/active aspirin, active warfarin/placebo aspirin, and placebo warfarin/active aspirin). Less serious bleeding occurred most frequently in the active warfarin/active aspirin group.

The HOT trial[159] was principally concerned with the management of hypertension, specifically to assess optimum target diastolic BP. It also randomized participants to treatment with aspirin or placebo. A total of 19,193 subjects from 26 countries between 50 years and 80 years of age (mean, 61.5 years) with diastolic BP between 100 mm Hg and 115 mm Hg (average, 105 mm Hg) were randomly assigned a target BP and randomly assigned to daily treatment with 75 mg of aspirin or placebo. The average follow-up time was 3.8 years (range, 3.3 to 4.9 years), giving a total of 71,051 patient-years.

The random assignment to diastolic BP target groups was among ≤ 90 mm Hg, ≤ 85 mm Hg, or ≤ 80 mm Hg. Antihypertensive therapy with felodipine, 5 mg qd, was administered to all participants. Additional therapy and dose increments were with ACEIs or beta-blockers with the possibility of adding a diuretic agent. Major cardiovascular events were defined as all MIs (fatal and nonfatal), all strokes (fatal and nonfatal), and all cardiovascular deaths. Silent MI was documented by ECGs at randomization and at the final visit.

In summary, the BP-lowering (and main) component of the trial showed reductions in diastolic BP of 20.3 mm Hg, 22.3 mm Hg, and 24.3 mm Hg, respectively, in the target groups of ≤ 90 mm Hg, ≤ 5 mm Hg, and ≤ 80 mm Hg. The lowest incidence of major cardiovascular events occurred at an achieved mean diastolic BP of 82.6 mm Hg, and the lowest risk of cardiovascular mortality occurred at 86.5 mm Hg. Further reduction below these BPs was safe.

There were 209 episodes of MI, 82 in those assigned to aspirin and 127 to placebo, representing a reduction of 36% (p = 0.002), and the prevention of 1.5 episodes per 1,000 person-years. There were 315 major cardiovascular events in patients receiving aspirin compared with 368 in the placebo group, a reduction that was borderline in significance. There were no clear differences in cardiovascular mortality or total mortality. The number of strokes, including cerebral hemorrhages, were almost identical in the two groups. Nonfatal major bleeding and minor bleeding occurred more frequently in those receiving aspirin. The results of the HOT trial[160] suggest that the main beneficial effect of aspirin is a reduction in the number of nonfatal MIs.

Participants in the HOT trial[160] were at intermediate risk because of their BP levels at entry, and all received BP-lowering regimens. The rate of all MIs was reduced by aspirin therapy from 3.6 to 2.1 events per 1,000 patient-years (relative reduction, 36%; absolute reduction, 1.5 events per 1000 patient-years). There was no difference between the aspirin-treated and placebo groups in terms of the number of fatal hemorrhagic events, but there were 129 nonfatal major bleeding events in the aspirin-treated

group compared with 70 in the placebo group, the excess mainly attributable to GI, nasal, and "other" episodes. There were 12 nonfatal cerebral bleeding events in each group. There were 156 minor bleeding episodes in the aspirin-treated group compared with 87 in the placebo group, the main contribution to this excess being nasal bleeding.

The Primary Prevention Project[161] was an open-label, factorial trial to evaluate long-term treatment with aspirin (and vitamin E) in the prevention of major fatal and nonfatal cardiovascular events. Participants were men and women aged ≥ 50 years with at least one major recognized cardiovascular risk factor (age ≥ 65 years, systolic BP ≥ 160 mm Hg, or diastolic BP ≥ 95 mm Hg on at least three occasions, total cholesterol ≥ 6.4 mmol/L on at least two occasions, diabetes mellitus, body mass index ≥ 30, and family history of MI under the age of 55 years in a parent or sibling). Criteria for exclusion were treatment with platelet active agents, long-term use of anti-inflammatory agents or anticoagulants, contraindications to aspirin, other diseases with a poor prognosis, and those not likely to be able to comply with the trial requirements.

Eligible patients were randomly allocated to 100 mg/d of enteric-coated aspirin or to no aspirin (and to vitamin E or no vitamin E). The principal end point was the cumulative rate of cardiovascular death, nonfatal MI, and nonfatal stroke. Assuming a rate of 1.5% per annum for this end point, an estimated 7,500 participants would need to be followed up for 5 years to detect a 25% reduction at the 5% level of significance and with 90% power. At the second planned interim analysis of results in July 1998, the external safety and efficacy monitoring committee advised discontinuing the trial because of evidence from other trials of the value of aspirin (and because it was unlikely that there would be any demonstrable effect of vitamin E). Accordingly, randomization ended in December 1998.

Between 1994 and 1998, 4,495 participants were recruited, some 95% by general practitioners and 5% by hospital hypertension units. Mean age was 64.4 years, and 2,583 of those recruited (57.7%) were women. In all, 4,150 of the participants (92.3%) were followed up clinically. For 314 participants (7.0%), information on vital status was obtained through census offices. Mean follow-up was 3.6 years, giving a total of 16,390 person-years. By the end of the trial, 19.3% of participants randomized to aspirin had stopped taking treatment, the most common reason (7.9%) being side effects. Some 7.2% not randomized to aspirin were receiving it at the end of the trial.

The RR for the main combined end point was 0.71 (95% CI, 0.48 to 1.04; NS); for total cardiovascular events, 0.77 (95% CI, 0.62 to 0.95; p < 0.05); cardiovascular deaths, 0.56 (95% CI, 0.31 to 0.99; p < 0.05); noncardiovascular deaths, 2% (NS); all deaths, 19% (NS); all MI, 0.69 (95% CI, 0.38 to 1.23; NS); nonfatal MI, 0.69 (95% CI, 0.36 to 1.33; NS); all strokes, 0.67 (95% CI, 0.36 to 1.27; NS); angina pectoris (18%), 0.82 (95% CI, 0.58 to 1.17; NS); TIAs, 0.71 (95% CI, 0.44 to 1.15; NS); lower-extremity arterial disease, 0.60 (95% CI, 0.33 to 1.08; NS); and revascularization procedures, 0.70 (95% CI, 0.40 to 1.24; NS). Of the 19 MIs in those receiving aspirin, 15 MIs were nonfatal; in those not receiving aspirin, the respec-

tive numbers were 28 and 22. For stroke, 15 of the 16 events in those receiving aspirin were nonfatal, as were 18 of 24 events in the no-aspirin group.

For any cardiovascular event including cardiovascular deaths, nonfatal MI and nonfatal stroke, TIAs, angina pectoris, lower-extremity arterial disease, and revascularization procedures, the RRR was 0.77 (p = 0.014; CI not given). The direction and size of effects closely overlapped in men and women.

Of 16 strokes in the aspirin group, 2 were hemorrhagic and 3 were considered disabling, while of the 24 cases in the no-aspirin group 3 were hemorrhagic and 4 were disabling. There were 24 other bleeding episodes in those receiving aspirin, 17 of which were GI, compared with 6 in those not receiving aspirin and of which 5 were GI. There were 36 and 21 "other events" in those receiving or not receiving aspirin, respectively. There were 225 new cases of cancer that were "similarly distributed" between the two groups.

Aspirin therapy reduced ischemic cardiac events in four of the five trials, the effect being most marked for nonfatal MI. Although there were trends to increased total stroke and hemorrhagic stroke with aspirin in the US Physicians Trial and the UK Doctors Trial,[162] there were trends toward a lower number of total strokes with aspirin in the TPT and virtually no difference in the fourth trial (HOT). A main distinguishing characteristic between the first two trials and the other three was the considerably lower dose of aspirin, 75 mg/d, in the TPT and HOT trials and 100 mg in the Primary Prevention Project[161]. There is a consistent failure in all five trials to show a reduction in all-cause mortality by aspirin, although this is not surprising, as none of the single trials were sufficiently large enough to demonstrate or exclude an effect on all-cause mortality. In the US Physicians' Trial, the risk of MI among men aged 40 to 49 years was only 0.1%/yr (one MI per year per 1,000 men), whereas among men aged 60 to 69 years, the rate of MI was 0.82%/yr (8.2 MIs per year per 1,000 men). Among the older men, the absolute risk reduction with aspirin was approximately 4.4 infarcts per year per 1,000 men treated. Similarly, the absolute benefits were greater among men with diabetes mellitus, with systolic or diastolic hypertension, who smoked cigarettes, and who had a lack of exercise. It is possible that aspirin increases the number of fatal events of coronary heart disease in older men, although this observation requires confirmation or refutation in other trials.

In other settings of vascular disease, there are trials that indicate that women benefit from aspirin therapy when the underlying problem is UA or AMI. However, the lower age-matched risk of cardiac events for women compared with men suggests that there are likely to be fewer absolute benefits among women at a given age, particularly if there is no difference between men and women in bleeding episodes.

The trials used different characteristics for defining those at risk of coronary events. The UK and US Physicians trials recruited doctors not ineligible on account of previous cardiovascular events or receiving aspirin for other reasons, but otherwise specified no risk factors for selection into the trial (although these were recorded at

entry for comparison between the active- and placebo-treated groups and, in the case of the US trial, for subgroup analyses according to various risk factors). UK and US physicians may have been at somewhat higher risk than participants in the other trials on account of inclusion of large proportions of older men. The higher risk of cardiovascular and coronary events in the TPT was due to the inclusion of a larger number of risk factors for defining eligibility than for the other trials. More recently identified risk factors, such as the level of C-reactive protein (CRP), might also be useful in defining those at particular risk in the context of primary prevention, although the generally strong correlation between CRP and fibrinogen levels may mean that if one is measured the other does not materially add to the estimate of risk. In the US trial, aspirin appeared to reduce the risk of MI most in those with the highest CRP levels, although the TPT did not observe this differential treatment effect in those with high fibrinogen levels. In the TPT, there was a highly significant interaction between systolic BP at entry and the effectiveness of aspirin, those with the lowest pressures experiencing greatest benefit, while aspirin treatment neither increased nor decreased risk significantly in those with higher BPs. A similar though nonsignificant trend was observed in the US Physicians trial. However, since both aspirin and raised BP contribute to a risk of cerebral hemorrhage, several groups have rightly advised that raised BP should be treated anyway before aspirin is used. Whether aspirin should be used in low-risk patients has so far not attracted a great deal of attention, probably because it is generally assumed that the risks associated with aspirin are low. However, this conclusion may not be justified.

Effects in women. Two trials, HOT and PPP, included women. In the HOT trial, it appeared that while men benefited from aspirin, women did not. In the PPP trial, both men and women appeared to benefit about equally. Further information on this important point must await the results of a large US trial in women currently in progress. To our knowledge, the only other available data are from a large prospective cohort study[163] of 28,678 US registered nurses, aged 34 to 65 years, who had not received diagnoses of CAD, stroke, or cancer at baseline. Among women receiving one to six aspirins per week, the age-adjusted RR of a first MI was 0.68 (p = 0.005). This benefit was confined to women $\geq$ 50 years old (RR, 0.61; p = 0.002). There were trends toward fewer deaths from cardiovascular events (RR, 0.89; p = 0.56) and fewer important vascular events (RR, 0.85; p = 0.12), but there was no difference for the incidence of stroke (RR, 0.99). No benefits were observed among women receiving more than six aspirins per week. As in any cohort study, there are concerns that unanticipated and undocumented confounders may bias the conclusions. Such factors might explain the failure to observe a benefit among the women receiving more than six aspirins per week, although a β error might also be possible. Overall, the findings support those of aspirin trials in men. New data should come from the Women's Health Study.

Effects on fatal vs nonfatal events. Warfarin appears to have similar efficacy to aspirin for the prevention of all IHD outcomes, but it is particularly effective in reducing fatal events, resulting in a statistically significant reduction in all-cause mortality (RRR, 17%; p = 0.04).[164] More recently and using a method that corrects for noncompliance while preserving the benefits of randomization, the TPT suggests that full compliance with warfarin (to a target INR of 1.5) may lower the risk of fatal coronary events by 50% rather than the 39% originally reported. This possible reduction in the most serious manifestation of coronary heart disease contrasts with the generally more modest effect of aspirin on fatal events. A combination of warfarin and aspirin was particularly effective in reducing ischemic cardiac events. Although hemorrhagic stroke was increased by the warfarin/aspirin combination, this risk can probably be minimized by careful BP monitoring and effective antihypertensive therapy. Compared with placebo, the risk of noncerebral major bleeding was increased to a similar degree by aspirin, warfarin, and a combination of the two.

Recommendations

5.1.1. For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of > 10%), we recommend aspirin, 75 to 162 mg/d, over either no antithrombotic therapy or VKA (**Grade 2A**).

5.1.2. For patients at particularly high risk of events in whom INR can be monitored without difficulty, we suggest low-dose VKA with a target INR of approximately 1.5 (**Grade 2A**).

Underlying values and preferences: The recommendation of aspirin over VKA places a relatively low value on a small absolute reduction in coronary events and deaths and a relatively high value on avoiding the inconvenience, cost, and bleeding risk associated with oral VKAs.

Patients, particularly those in the highest risk groups residing in jurisdictions in which meticulous monitoring of anticoagulant intensity is routinely available, who place a relatively high value on small absolute risk reductions in coronary events, and are relatively untroubled by the inconvenience and bleeding risk associated with VKAs, are likely to be best served by administration of VKAs rather than aspirin.

SUMMARY OF RECOMMENDATIONS

1.0 Acute Management of Non-ST-Elevation Acute Coronary Syndromes (NSTE ACS)

1.1 Antiplatelet therapies

1.1.1 Aspirin

1.1.1. For all patients presenting with an NSTE ACS, without a clear allergy to aspirin, we recommend immediate aspirin, 75 to 325 mg po, and then daily oral aspirin, 75 to 162 mg (**Grade 1A**).

1.1.2 Thienopyridines

1.1.2.1. For all NSTE ACS patients with an aspirin allergy, we recommend immediate treatment with clopidogrel, 300 mg oral bolus, followed by 75 mg/d indefinitely (**Grade 1A**).

1.1.2.2. In all NSTE ACS patients in whom diagnostic catheterization will be delayed or when coronary bypass surgery will not occur until > 5 days following coronary angiography, we recommend clopidogrel be administered immediately as bolus therapy (300 mg), followed by 75 mg/d for 9 to 12 months in addition to aspirin (**Grade 1A**).

Underlying values and preferences: This recommendation places a relatively high value on avoiding MI and a relatively low value on avoiding major bleeding.

1.1.2.3. In NSTE ACS patients in whom angiography will take place rapidly (≤ 24 h), we suggest beginning clopidogrel after the coronary anatomy has been determined (**Grade 2A**).

Underlying values and preferences: This recommendation places a relatively high value on avoiding serious bleeding balanced against a low absolute benefit of clopidogrel in the first 24 h of treatment.

1.1.2.4. For patients who have received clopidogrel and are scheduled for coronary bypass surgery, we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (**Grade 2A**).

1.1.4 Glycoprotein IIb/IIIa inhibitors

1.1.4.1. In moderate- to high-risk patients presenting with NSTE ACS, we recommend either eptifibatide or tirofiban for initial (early) treatment in addition to treatment with aspirin and heparin (**Grade 1A**). In these moderate- to high-risk patients who are also receiving clopidogrel, we recommend eptifibatide or tirofiban as additional initial treatment (**Grade 2A**).

1.1.4.2. For patients presenting with NSTE ACS, we recommend **against** abciximab as initial treatment except when the coronary anatomy is known and PCI planned within 24 h (**Grade 1A**).

1.2 Antithrombin therapies

1.2.1 Unfractionated heparin

1.2.1. For patients presenting with NSTE ACS, we recommend UFH over no heparin therapy for short-term use with antiplatelet therapies (**Grade 1A**). We recommend weight-based dosing of UFH and maintenance of the aPTT between 50 s and 75 s (**Grade 1C+**).

1.2.2 Low-molecular-weight heparin

1.2.2.1. For the acute treatment of patients with NSTE ACS, we recommend LMWHs over UFH (**Grade 1B**).

1.2.2.2. We recommend against routine monitoring of the anticoagulant effect of the LMWHs (**Grade 1C**).

1.2.2.3. We suggest continuing LMWHs during PCI treatment of the NSTE ACS patient when it has been started as the upstream anticoagulant (**Grade 2C**).

1.2.2.4. For patients receiving GP IIb/IIIa inhibitors as upstream treatment of NSTE ACS, we suggest LMWH over UFH as the anticoagulant of choice (**Grade 2B**).

1.2.5 Direct thrombin inhibitors

1.2.5. In patients presenting with NSTE ACS, we recommend **against** DTIs as routine initial antithrombin therapy (**Grade 1B**).

Underlying valves and preferences: This recommendation acknowledges the limitations of the individual trials of DTIs in NSTE ACS as well as the complexities of using the DTIs compared with either UFH or LMWH.

2.0 Post MI and Post ACS

2.1 Antiplatelet therapies

In patients with ACSs with and without ST-segment elevation:

2.1.1. We recommend aspirin at initial doses from 160 to 325 mg, and then indefinite therapy, 75 to 162 mg/d (**Grade 1A**).

2.1.2. For patients with a history of aspirin-induced bleeding or with risk factors for bleeding, we recommend lower doses (≤ 100 mg) of aspirin (**Grade 1C+**).

2.1.3. For patients in whom aspirin is contraindicated or not tolerated, we recommend clopidogrel for long-term administration, 75 mg/d (**Grade 1A**).

2.3 Comparisons of antiplatelet and anticoagulant therapy and/or combinations of aspirin and warfarin trials

2.3.1. In most health-care settings, for moderate- and low-risk patients with a myocardial infarction, we recommend aspirin alone over oral VKAs plus aspirin (**Grade 2B**).

Underlying values and preferences: This recommendation places a relatively low value on prevention of thromboembolism, and a relatively high value on avoiding the inconvenience, expense, and bleeding associated with VKA therapy.

2.3.2. In health-care settings in which meticulous INR monitoring is standard and routinely accessible, for both high- and low-risk patients after MI, we recommend long-term (up to 4 years) high-intensity oral VKAs (target INR, 3.5; range, 3.0 to 4.0) without concomitant aspirin or moderate-intensity oral VKAs (target INR, 2.5; range, 2.0 to 3.0) with aspirin (both **Grade 2B**).

2.3.3. For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on echocardiography, and those with a history of a thromboem-

bolic event, we suggest the combined use of moderate-intensity (INR, 2.0 to 3.0) oral VKAs plus low-dose aspirin ($\leq$ 100 mg/d) for 3 months after the MI (**Grade 2A**).

3.0 Chronic, Stable CAD

3.1 Antiplatelet agents

3.1.1. For all patients with chronic stable CAD, we recommend the administration of aspirin, 75 to 162 mg po (**Grade 1A**). We suggest that aspirin be continued indefinitely (**Grade 2C**).

3.1.2. For patients with stable chronic coronary disease with a risk profile indicating a high likelihood of development of AMI, we suggest long-term therapy with clopidogrel in addition to aspirin (**Grade 2C**).

3.2 Vitamin K antagonists

3.2. For patients with chronic CAD without prior MI, we suggest clinicians **not** use long-term oral VKAs (**Grade 2C**).

4.0 Congestive Heart Failure With and Without CAD

4.1 VKA, aspirin

4.1.1. In patients with CHF due to a nonischemic etiology, we recommend **against** routine use of aspirin or oral VKAs (**Grade 1B**).

4.1.2. We recommend that when otherwise indicated, patients receive aspirin whether or not they are receiving ACEIs (**Grade 1C+**).

5.0 Primary Prevention

5.1 Aspirin, VKA, or both

5.1.1. For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of > 10%), we recommend aspirin, 75 to 162 mg/d, over either no antithrombotic therapy or VKAs (**Grade 2A**).

5.1.2. For patients at particularly high risk of events in whom INR can be monitored without difficulty, we suggest low-dose VKAs with a target INR of approximately 1.5 (**Grade 2A**).

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