Hemorrhagic Complications of Anticoagulant and Thrombolytic Treatment *

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Hemorrhagic Complications of Anticoagulant and Thrombolytic Treatment*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This article about hemorrhagic complications of anticoagulant and thrombolytic treatment is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Bleeding is the major complication of anticoagulant and fibrinolytic therapy. The criteria for defining the severity of bleeding vary considerably between studies, accounting in part for the variation in the rates of bleeding reported. The major determinants of vitamin K antagonist (VKA)-induced bleeding are the intensity of the anticoagulant effect, underlying patient characteristics, and the length of therapy. There is good evidence that VKA therapy, targeted international normalized ratio (INR) of 2.5 (range, 2.0-3.0), is associated with a lower risk of bleeding than therapy targeted at an INR > 3.0.

The risk of bleeding associated with IV unfractionated heparin (UFH) in patients with acute venous thromboembolism is < 3% in recent trials. This bleeding risk may increase with increasing heparin dosages and age (> 70 years). Low-molecular-weight heparin (LMWH) is associated with less major bleeding compared with UFH in acute venous thromboembolism. Higher doses of UFH and LMWH are associated with important increases in major bleeding in ischemic stroke. In ST-segment elevation myocardial infarction, addition of LMWH, hirudin, or its derivatives to thrombolytic therapy is associated with a small increase in the risk of major bleeding, whereas treatment with fondaparinux or UFH is associated with a lower risk of bleeding.

Thrombolytic therapy increases the risk of major bleeding 1.5-fold to threefold in patients with acute venous thromboembolism, ischemic stroke, or ST-elevation myocardial infarction.

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Key words: anticoagulant; bleeding; complications; thrombolysis

Abbreviations: APTT = activated partial thromboplastin time; ASSENT = Assessment of the Safety and Efficary of a New Thrombolytic Agent; CI = confidence interval; COX = cyclooxygenase; DTI = direct thrombin inhibitor; DVT = deep vein thrombosis; FRIC = Fragmin in Unstable Coronary Artery Disease; FRISC = Fragmin during Instability in Coronary Artery Disease; GISSI = Gruppo Italiano per lo Studio della Sopravivenza nell Infarto Miocardico; GUSTO = Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries; HIT = Hirudin for Improvement of Thrombolysis; ICH = intracranial hemorrhage; INR = international normalized ratio; ISIS = International Study on Infarct Survival; LMWH = low-molecular-weight heparin; NSAIDs = nonsteroidal antiinflammatory drugs; OASIS = Organization to Assess Strategies for Ischemic Syndromes; OR = odds ratio; PCI = percutaneous coronary intervention; PE = pulmonary embolism; RCT = ramdomized controlled trial; RR = relative risk; rt-PA = recombinant tissue plasminogen activator; SPAF = Stroke Prevention in Atrial Fibrillation; TEE = transesophageal echocardiography; TIMI = Thrombolysis in Myocardial Infarction; tPA = tissue plasminogen activator; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

The major complication of anticoagulant and thrombolytic therapy is bleeding. This review addresses the incidence of hemorrhage in patients receiving oral anticoagulants, heparin, or thrombolytic agents and the clinical and laboratory risk factors that predispose to bleeding. The focus is on

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major bleeding, intracranial bleeding, and fatal bleeding. Readers can find details of the method used to select relevant articles in the seven previous symposia of the American College of Chest Physicians.[1–7]

Studies varied in their definition of bleeding complications. Bleeding was generally classified as major if it was intracranial or retroperitoneal, if it led directly to death, or if it resulted in hospitalization or transfusion.[3,4] In some studies major bleeding only included "fatal or life-threatening bleeding." The component "bleeding requiring blood transfusions" was in some studies based on a minimum requirement of a certain number of units, in other studies defined as a certain reduction of the hemoglobin level. Studies of postoperative prophylaxis against thrombosis sometimes also used "bleeding index" of ≥ 2 as a criterion for major bleeding. The index is calculated as the number of units of packed blood cells or whole blood transfused + (prebleeding − postbleeding hemoglobin values in grams per deciliter). Section 1.3 discusses the classifications used for bleeding after thrombolytic therapy. The International Society on Thrombosis and Hemostasis issued in 2005 a recommendation for definition of major bleeding in studies on antihemostatic products (anticoagulant, antiplatelet or thrombolytic drugs) in nonsurgical studies.[8]

This chapter focuses on bleeding related to vitamin K antagonists (VKAs), heparins, thrombin inhibitors, and thrombolytic agents. The first section considers risk factors for bleeding in patients receiving any of these agents and the second reviews bleeding rates for specific clinical conditions. Weitz et al briefly discusses bleeding related to emerging antithrombotic agents in another article in this supplement. Table 1 describes the search and eligibility criteria used for our review.

1.0 Treatment and Risk of Bleeding

1.1 VKAs

The increase in risk of major bleeding in patients treated with VKA compared to controls is low in well-controlled patients. In the pooled analysis of the first five trials with warfarin in atrial fibrillation the annual rate of major bleeding was 1.0% in control patients vs 1.3% in patients treated with warfarin.[9] The annual rate of intracranial hemorrhage (ICH) was 0.1% in controls and 0.3% in patients treated with warfarin.[9] In a metaanalysis of trials with different durations of VKA therapy after venous thromboembolism (VTE), analyzing the period from the discontinuation of treatment in the short-duration arm until discontinuation of treatment in the long-duration arm, Ost et al[10] reported an annual rate of major bleeding of 0.6% among those who had stopped anticoagulation vs 1.1% among those continuing with anticoagulation. Go et al[11] followed a cohort of 11,526 patients with atrial fibrillation from the integrated health system in Northern California and found that the risk of major bleeding was similarly low in routine clinical care without a statistically significant difference in nonintracranial major hemorrhage between those treated and not treated with VKA. The annual rate of ICH was 0.23% without VKA and 0.46% with VKA ($p = 0.003$). In a prospective inception cohort of 2,745 patients with mixed indications for warfarin, Palareti et al[12] described a rate of fatal or major bleeding (including fatal events) of 1.35 per 100 patient years, and the rate of ICH was 0.4 per 100 patient-years. Higher annual rates of major hemorrhage in patients treated with warfarin in clinical routine practice have been reported, for example, 1.7% in a prospective cohort of 402 patients[13] and 3.4% in a retrospective study of 505 patients.[14]

In conclusion, in clinical studies characterized by careful monitoring of anticoagulant intensity, treatment with VKA increases the risk of major bleeding by 0.3–0.5%/yr and the risk of ICH by approximately 0.2%/yr compared to controls. In clinical routine practice the rates are less consistent.

Determinants of Bleeding: The major determinants of oral VKA-induced bleeding are the intensity of the anticoagulant effect, patient characteristics, the concomitant use of drugs that interfere with hemostasis, and the length of therapy.

1.1.1 Intensity of Anticoagulant Effect

Randomized controlled trials (RCTs) enrolling patients with deep vein thrombosis (DVT),[15] artificial heart valves,[16–21] ischemic stroke,[22] atrial fibrillation,[23–25] or antiphospholipid antibody syndrome with previous thromboembolism[26,27] have all reported a strong relationship between the targeted intensity of anticoagulant therapy and the risk of bleeding. The frequency of major bleeding in patients assigned to warfarin therapy at a targeted international normalized ratio (INR) of approximately 2.0–3.0 was less than half the frequency in patients assigned to warfarin therapy at a targeted INR > 3.0.[15,17,19,21] In a case-control study, the risk of ICH doubled for each increase of approximately 1 in the INR.[28]

The actual intensity of the treatment with VKA is strongly associated with the risk of bleeding. In multivariable analysis of risk factors for bleeding in an inception cohort, actual INR of at least 4.5 vs

Table 1—*Risk Factors for Anticoagulant- or Thrombolytic-Related Bleeding: Question Definition and Eligibility Criteria*

Section	Population	Intervention or Exposure/Comparison	Outcome(s)	Methodology	Exclusion Criteria
1.1.1	Patients on oral anticoagulants (VKAs)	Intensity of anticoagulant effect (high vs low)	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCTs Cohort studies Case control	None
1.1.2	Patients on oral anticoagulants (VKAs)	Patient characteristics (age, sex, comorbid conditions: coronary artery disease, congestive heart failure, renal insufficiency, liver disease, malignancy, diabetes, genetic defects) including multivariable models	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCTs Cohort studies	None
1.1.3	Patients on oral anticoagulants (VKAs)	Concomitant drugs; antiplatelet drugs; acetaminophen; NSAIDs	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCTs Cohort studies Case control	None
1.1.4	Patients on oral anticoagulants (VKAs)	Length (duration) of therapy/time	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCTs Cohort studies	None
1.1.5	Patients on oral anticoagulants (VKAs)	Bleeding risk models	Any bleeding; major bleeding; intracranial bleeding and fatal bleeding	Cohort studies	None
1.2.1	Patients on heparins	Heparin/dose response	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
1.2.2	Patients on heparins	Method of administering heparin	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
1.2.3	Patients on heparins	Patient risk factor	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
1.5.1	Patients on thrombolytic therapy	Patient characteristics (age, sex, ethnicity, BP, weight, preexisting diseases)	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
1.5.2	Patients on thrombolytic therapy	Thrombolytic regimen (comparison of agents, regimens with additional antihemostatic agents)	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.1.1	Patients with acute DVT or PE	Initial thrombolytic therapy vs UFH or LMWH	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.1.2	Patients with acute DVT or PE	Initial therapy (5 to 7 d) with UFH or LMWH	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.1.3	Patients with acute DVT or PE	Comparison of different LMWH regimens (doses, once or twice per d)	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.1.4	Patients with acute DVT or PE	Fondaparinux vs LMWH or UFH	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.1.5	Patients with acute DVT or PE	Oral thrombin inhibitor vs LMWH plus VKA	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.2.1	Patients on long-term (> 4 wk) treatment for DVT or PE	VKAs vs UFH or LMWH	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None

< 4.5 was the strongest independent risk factor (relative risk [RR], 5.96; 95% confidence interval [CI], 3.68–9.67; $p < 0.0001$).[12] Mean INR ± SD at the time of a bleeding event, as well as the last INR ± SD before a bleeding event were elevated compared to matched patients without bleeding (5.9 ± 5.9 vs 2.3 ± 0.7; $p < 0.001$, and 3.0 ± 1.2 vs 2.1 ± 0.8; $p < 0.001$, respectively), though there

Table 1—*Continued*

Section	Population	Intervention or Exposure/Comparison	Outcome(s)	Methodology	Exclusion Criteria
2.1.2.2	Patients on long-term treatment for DVT or PE	UFH vs LMWH	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.2.3	Patients on long-term treatment for DVT or PE	VKA, comparison of different durations (shorter vs longer)	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.2.4	Patients on long-term treatment for DVT or PE	VKA, different intensities for extended treatment (high vs lower dose)	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.1.2.5	Patients on long-term treatment for DVT or PE	Oral thrombin inhibitor vs placebo	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding		
2.2.1	Patients with atrial fibrillation	VKAs, aspirin or aspirin plus clopidogrel	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.2.2	Patients with atrial fibrillation	Oral direct thrombin inhibitor vs VKA	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None
2.3.1	Patients with prosthetic heart valves	VKAs (high vs low dose, alone vs combination with aspirin)	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	
2.4.1.1	Patients with acute stroke	UFH, LMWH, VKAs, aspirin (direct comparison of any of the four)	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.4.1.2	Patients with acute stroke	UFH or LMWH vs antiplatelet agent	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.4.1.3	Patients with acute stroke	Thrombolytic therapy vs placebo	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.4.2	Patients on long-term treatment for ischemic cerebral vascular disease	VKAs vs conventional therapy	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.5.1	ST-segment elevation myocardial infarction	Thrombolytic therapy vs placebo	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.5.2	ST-segment elevation myocardial infarction	UFH, LMWH or fondaparinux (comparisons)	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.5.3	ST-segment elevation myocardial infarction	Direct thrombin inhibitor vs heparin	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.5.4	ST-segment elevation myocardial infarction	Secondary prophylaxis with anticoagulant agents	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.6.1	Unstable angina, non-ST elevation myocardial infarction	UFH, LMWH or fondaparinux (comparisons)	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.6.2	Unstable angina, non-ST elevation myocardial infarction	DTI vs heparin	Any bleeding, major bleeding, intracranial and fatal bleeding	RCT	None
2.7	Percutaneous coronary intervention	DTI vs heparin	Any bleeding, major bleeding, intracranial bleeding and fatal bleeding	RCT	None

appears to be only a brief warning period before an imminent bleed, since the second-last INR was similar in the two groups.[29] The intensity of anticoagulant effect is probably the most important risk factor for ICH, independent of the indication for therapy, with the risk increasing dramatically with INR > 4.0– 5.0.[28,30–33]

Studies conducted in a number of different clinical settings have addressed prophylaxis against thromboembolism with low-intensity VKA (targeted INR < 2.0) with variable results. A low-intensity regimen did not increase the risk of major bleeding compared with placebo in patients with malignancy,[34,35] in patients undergoing rehabilitation after stroke,[36] or as extended secondary prevention of VTE.[37] Conversely, low-intensity warfarin was associated with an excess of major bleeding compared to placebo (10.7% vs 0%, p = 0.03) in patients with end-stage renal disease for the prevention of graft failure,[38] and did not reduce the risk of clinically important bleeding compared to treatment targeted at INR 2.0–3.0 (hazard ratio, 1.2; 95% CI, 0.4–3.0) in the extended secondary prevention of VTE.[39]

Increased variation in the anticoagulant effect manifested by variation in the INR is associated with an increased frequency of bleeding independent of the mean INR.[23,40,41] This most likely is due to an increased frequency and degree of marked elevations in the INR.

Approaches to improve the anticoagulant control, such as anticoagulant management services or clinics and point-of-care INR testing, thus minimizing INR fluctuations could improve the safety and effectiveness of VKAs. Ansell et al describe this in another article in this supplement.

1.1.2 Patient Characteristics

The risk of major bleeding during warfarin therapy is related to specific comorbid conditions or patient characteristics. An increasing body of evidence supports age as an independent risk factor for major bleeding.[12,31,42–52] In a systematic review of studies with a specification of the risk of bleeding in different age categories, Hutten et al[45] identified 8 eligible articles, which showed a clear tendency toward a twofold increase in bleeding among the elderly. In a multivariable analysis by Pengo et al[47] age > 75 years was the only variable independently related to primary bleeding, *ie*, bleeding unrelated to organic lesions (RR, 6.6; 95% CI, 1.2–37; p = 0.032). The risk for ICH is also increased among older patients, especially those ≥ 75 years old when the INR is supratherapeutic.[9,28,31,50,53] The adjusted odds ratio (OR) for ICH at age ≥ 85 years compared to those 70–74 years old is 2.5 (95% CI, 2.3–9.4) at an INR range of 3.5−3.9 vs an adjusted OR of 1.3 (95% CI, 0.8–2.2) at an INR range of 2.0–3.0.[31] Among patients 80 years and older discharged on oral anticoagulant therapy, insufficient education on oral anticoagulant therapy as perceived by the patient or caregiver (OR, 8.83) and polypharmacy (OR, 6.14) were much stronger independent predictors of major bleeding than INR above therapeutic range (OR, 1.08).[54] Female sex was not found to be an independent risk factor for major bleeding,[47,51] but women appear to have more minor bleeding than men.[51]

Studies have reported a history of bleeding as a risk factor for subsequent bleeding,[55–57] but this observation has been inconsistent.[23,50,58] A history of nonbleeding peptic ulcer disease has, however, not been associated with subsequent GI bleeding.[12,41,58]

Investigators have reported associations between other comorbid diseases and bleeding during warfarin therapy; these include treated hypertension,[42,59–65] cerebrovascular disease,[50] ischemic stroke,[44,66] serious heart disease,[50,67] diabetes,[42,59] renal insufficiency,[41,50,55,56,68] alcoholism, or liver disease.[57] Several studies identified the presence of malignancy as a significant predictor of major bleeding.[12,45,57,58,69,70] In two studies,[12,71] excessive anticoagulation was not the explanation for an increased risk of bleeding; one study[71] identified the dissemination of the cancer as a risk factor.

Pharmacogenetic factors also influence the risk of bleeding during anticoagulant therapy; in particular, the polymorphism of the cytochrome P450 CYP2C9 enzyme. The risk appears to be related to excessive dosing in patients who are slow metabolizers of VKA with the CYP2C9*2 and CYP2C9*3 variants. Accordingly, CYP2C9 variant alleles have been investigated to determine if they can serve as risk markers in patients on oral anticoagulant therapy. In patients with a low warfarin requirement (≤ 1.5 mg/d) the OR for having one or two CYP2C9 variants was 6.21 (95% CI, 2.48–15.6) and they also had more major bleeding than randomly selected control patients (rate ratio, 3.68; 95% CI, 1.43–9.50).[72] Among patients treated with phenprocoumon, bleeding was increased among those with the *3 allele compared to the other alleles (OR, 3.1; 95% CI, 1.02–9.40) in one study.[73] Patients receiving acenocoumarol and with the *2 and/or *3 alleles had more frequent minor but not major bleeding events than those with the wild type allele (OR, 1.99; 95% CI, 1.2–3.3) and more often INR values > 6.0.[74]

Genetic polymorphism of platelet glycoprotein IIb/IIIa was evaluated in a cohort of consecutive patients who had ventricular assist devices implanted and who were treated with phenprocoumon and aspirin.[75] Patients with the A1A1 genotype developed more bleeding complications than those with the A2A2 genotype (39% vs 0%, p = 0.021) despite

no differences in the INR, platelet activation tests, and anticoagulant dosing. In a case control study, the plasma level of soluble thrombomodulin was a risk factor for bleeding with a crude OR of 3.25 (95% CI, 1.4–7.51) when the highest quartile of thrombomodulin levels was compared to the lowest quartile.[76]

1.1.3 Concomitant Treatment With Antiplatelet Drugs, Acetaminophen, Nonsteroidal Antiinflammatory Drugs, or Cyclooxygenase Type 2 Inhibitors

In many studies of VKA alone vs the combination of VKA and aspirin the intensity of VKA therapy was lower in the combination group, which underestimates the additional risk contributed by aspirin. Hart et al[77] published a metaanalysis of 6 RCTs with a total of 3,874 patients. The risk of ICH more than doubled when aspirin was added to warfarin (RR, 2.4; 95% CI, 1.2–4.8; p = 0.02). Table 2 summarizes two studies with the same intensity of VKA in both groups of patients with prosthetic heart valves.[78,79] In both trials, there was a trend to more major bleeding when aspirin was added, with a statistically significant difference in one of them,[78] but the event rate was very high here since the immediate postoperative period was included. The point estimate for ICH was also higher in the combination group in one study.[79] Additionally, in a third study the effect of adding either 100 mg or 600 mg of aspirin to warfarin was compared (Table 2). The higher dose of aspirin was associated with a trend to higher rate of major bleeding.[80] The effect of combination therapy on bleeding was assessed in a retrospective cohort analysis of 10,093 patients with atrial fibrillation who were treated with warfarin for stroke prophylaxis. Antiplatelet therapy, which was added in 19.4% of the cases, was associated with an increase of major bleeding from 1.3% to 1.9% within 90 days of discharge from the hospital.[81]

A metaanalysis of 10 trials with 5,938 patients treated after myocardial infarction or acute coronary syndrome addressed the risk of adding warfarin to patients receiving aspirin.[82] There was a statistically significant increase of major bleeding with the combination compared to aspirin alone (rate ratio, 2.5; 95% CI, 1.7–3.7). A population-based study[83] of > 20,000 elderly survivors of acute myocardial infarction between 1996 and 2000 recorded the rate of hospitalization for bleeding. Compared to aspirin alone, the adjusted ORs for bleeding were 1.65 (95% CI, 1.02–2.73) for patients receiving aspirin plus thienopyridine derivative, and 1.92 (95% CI, 1.28–2.87) for patients receiving aspirin plus warfarin. Thus, antiplatelet and anticoagulant combinations result in modest increases in the risk of bleeding.[82]

A number of medications can influence the pharmacokinetics and pharmacodynamics of VKAs[84,85] but a detailed discussion of such drug interactions is beyond the scope of this chapter. We will, however, briefly consider the influence of acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), and cyclooxygenase type 2 (COX-2) inhibitors on the risk of bleeding with VKAs.

In a nested case-control study, concomitant intake of acetaminophen and a VKA has been associated with an increased risk of excessive anticoagulation (INR > 6).[86] This observation was supported by the results of two randomized studies. In the first, a modest increase of mean INR of 0.46 was observed in healthy volunteers after 1 week with 1.5 or 3 g of

Table 2—*Rate of Bleeding With VKA Alone or in Combination With Aspirin: Clinical Description and Results (Section 1.1.3)*

Study/yr	Intervention	Indication	No. of Patients (Patient-Years)	Bleeding*		
				Major	Fatal	Intracranial
Turpie et al[79]/1993	Warfarin (INR 3.0–4.5) plus placebo	Prosthetic heart valves	184 (~ 462)†	4.1	0.7	0.7
	Warfarin (INR 3.0–4.5) plus aspirin 100 mg		186 (~ 462)†	5.2	0.6	1.5
Laffort et al[78]/2000	VKA (INR 2.5–3.5)	Prosthetic heart valves	120 (120)	8.3‡	3	0
	VKA (INR 2.5–3.5) plus aspirin 200 mg		109 (109)	19.2	3	0
Altman et al[80]/1996	Acenocoumarol (INR 2.0–3.0) plus aspirin 100 mg	Prosthetic heart valves	207 (416)	3.6	0.5	0.2
	Acenocoumarol (INR 2.0–3.0) plus aspirin 600 mg		202 (366)	5.2	0.3	0.3

*Data are presented as %/yr.
†Approximate values estimated from mean follow-up.
‡p = 0.02.

paracetamol and VKA.[87] In the second, a placebo-controlled, randomized crossover study in 20 patients on stable treatment with VKA, paracetamol at a dose of 1 g four times daily for 1 week resulted in an increase of INR of 1.20 from baseline compared to an increase of 0.37 after placebo.[88] In a population-based study, the standardized incidence ratio for upper-GI bleeding requiring hospitalization was 2.8 for VKA alone, 4.4 for VKA in combination with acetaminophen, and 3.8 for VKA combined with aspirin or corticosteroids.[89] In this study no correction for confounders was possible. In the study by Hylek et al,[86] concomitant treatment with acetaminophen was independently associated with excessive INR values (p for trend < 0.001), after adjustment for age, indication for warfarin, length of therapy, warfarin dose, number of prescription medications, previous INR, or long-term INR variability. Thus, the weight of the evidence indicates that in patients receiving VKA, acetaminophen or paracetamol causes a rise in the INR. Although intercurrent illnesses necessitating the intake of acetaminophen may contribute to a rise in the INR, patients on VKA should be monitored more frequently when taking acetaminophen or paracetamol and should be alerted to the possibility of bleeding complications, particularly from the upper GI tract.

NSAIDs are associated with upper-GI bleeding.[90] The possible mechanisms are a direct harmful effect on the mucosa, impaired platelet function, or interaction with pharmacokinetics of VKAs. A retrospective study in patients taking acenocoumarol as the only medication showed that addition of diclophenac, naproxen, or ibuprofen caused an increase of the INR by 1 to 4 in 46% of the patients.[91] In contrast, RCTs with VKA vs placebo did not show excessive prolongation of the INR in patients receiving acenocoumarol and diclophenac,[92] or acenocoumarol and nabumetone,[93] or in healthy volunteers with warfarin and ketoprophen.[94]

Several studies have examined the relationship between NSAIDs and VKA-related bleeding with the relative risk ranging from 3 to 6. Shorr et al[95] performed a retrospective cohort study of Tennessee Medicaid enrollees aged > 65 years from 1984 through 1986. They found that the incidence of hospitalization for hemorrhagic peptic ulcer disease in patients receiving anticoagulants was threefold the incidence for nonusers. In patients receiving VKAs, the risk of hospitalization for hemorrhagic peptic ulcer disease was increased a further threefold by current use of NSAIDs. This study was limited by its lack of adjustment for such confounders as duration of anticoagulant, intensity of anticoagulant control, and concurrent medical illnesses.

Two registry studies from Denmark identified patients who had received prescriptions for VKA and/or NSAIDs and data were then linked to a hospital database on discharges after upper-GI bleed.[89,96] The number of bleeds on NSAIDs alone was 3.6 times higher than expected in the general population not exposed to NSAIDs. Concurrent anticoagulant use increased the risk of bleeding to 8 to 11 times of the expected. Limitations of these studies include the inability to identify important confounders that could have contributed to the bleeding.

Because selective inhibitors of COX-2 are associated with less gastric mucosal injury and platelet dysfunction than nonselective NSAIDs, studies have attempted to discern if bleeding rates for these classes of analgesic agents differ when used simultaneously with VKAs. For example, a nested case-control[97] study, using multiple linked healthcare databases of 98,821 patients ≥ 66 years, who were continuously prescribed warfarin, reported that 361 patients ($< 0.3\%$) were hospitalized for upper GI bleeding during a 1-year study period. Risks for GI bleeding were similar for warfarin combined with NSAIDs (OR, 1.9; 95% CI, 1.4–3.7), celecoxib (OR, 1.7; 95% CI, 1.2–3.6), or rofecoxib (OR, 2.4; 95% CI, 1.7–3.6) compared to controls. This is in contrast to other studies that have noted less bleeding with concomitant use of warfarin and COX-2 inhibitors than with warfarin and NSAIDs. In a smaller retrospective analysis[98] of patients seen in an anticoagulation pharmacy clinic, the RR for major bleeding was only slightly higher (RR, 1.04; 95% CI, 0.13–7.85) for patients receiving warfarin plus COX-2 inhibitors vs warfarin alone. Similarly, a nested case-control study[99] that identified patients, who bled while receiving VKA, from records of an outpatient anticoagulant clinic and hospital records examined whether COX-2 inhibitors are associated with less bleeding complications in VKA users compared with NSAIDs. They reported that COX-2 inhibitors were associated with less bleeding complications than NSAIDs. However, both studies[98,99] had a number of methodologic limitations, particularly in the selection of cases and control patients.

In summary, the ideal design to address the question of whether NSAIDs or COX-2 inhibitors increase bleeding on VKA is a randomized trial, and to our knowledge, such a trial has not been performed. To date, a number of observational studies have examined the question. Such studies, however, are subject to a number of important biases. Hence, although NSAIDs appear to increase the risk of upper GI bleeding on VKA, the low quality of the available evidence leaves uncertain whether or not COX-2 inhibitors increase in the rate of bleeding.

1.1.4 Risk of Bleeding and the Length of Time Relative to When Anticoagulant Therapy Started

In an RCT comparing warfarin with aspirin plus clopidogrel in patients with atrial fibrillation, 2,627 patients who had been on VKA already before the study and were randomized to continue with warfarin had a risk of major bleeding of 2.02%/yr, whereas the 744 warfarin-naïve patients had a risk of 2.92%/yr ($p = 0.028$ for interaction with the study treatment).[100] Six studies reported higher frequencies of bleeding early in the course of therapy.[12,41,60,63,101–103] In one of these studies,[60] the frequency of major bleeding decreased from 3%/mo the first month of outpatient warfarin therapy to 0.8%/mo during the rest of the first year of therapy, and to 0.3%/mo thereafter. It is plausible that many patients prone to bleeding for various reasons will discontinue the VKA therapy during the early phase of treatment, and those remaining on therapy therefore are perceived to tolerate the treatment better.

1.1.5 Bleeding Prediction Models

Investigators have developed models for estimating the risk for major bleeding during VKA therapy. These models are based on the identification of independent risk factors for VKA-related bleeding, such as a history of stroke, history of GI bleeding, age ≥ 65 years, and higher levels of anticoagulation.[12,41,51,55,69,104,105] Such prediction rules can be useful in clinical practice because although physicians' estimates of risk for anticoagulant-related bleeding are reasonably accurate during hospitalization, they are inaccurate during long-term outpatient therapy.[55,104]

Three prediction models have been validated in outpatients treated with warfarin. Beyth et al[55] identified four independent risk factors for bleeding: age > 65 years, history of GI bleeding, history of stroke, and one or more of four specific comorbid conditions. This Outpatient Bleeding Risk Index was validated in another cohort of patients treated in another city; the cumulative incidence of major bleeding at 48 months was 53% in high-risk patients (three or four risk factors), 12% in middle-risk patients (one or two risk factors), and 3% in low-risk patients (no risk factors).

Kuijer et al[69] developed another prediction model based on age, sex, and the presence of malignancy. In patients classified at high, middle, and low risk, the frequency of major bleeding was 7%, 4%, and 1%, respectively, after 3 months of therapy in patients with VTE.

Shireman et al[106] included eight variables—age of at least 70 years, gender, remote bleeding, bleeding during the index hospitalization, alcohol or drug abuse, diabetes, anemia, and antiplatelet therapy—in a risk score model for patients with atrial fibrillation. Major bleeding events occurred in 5.4%, 2.0%, and 0.9%, respectively, for the groups classified as high, moderate, and low risk. Furthermore, Gage et al[107] developed a bleeding risk score (HEMORR2HAGES- in analogy with the stroke risk score CHADS2) for patients with atrial fibrillation, by adding 2 points for a prior bleed and 1 point each for hepatic or renal disease, ethanol abuse, malignancy, older (age > 75 years), reduced platelet count or function, hypertension (uncontrolled), anemia, genetic factors, excessive fall risk, and stroke. The rate of bleeding requiring hospitalization per 100 patient-years of warfarin was 1.9 for 0 points, 2.5 for 1, 5.3 for 2, 8.4 for 3, 10.4 for 4, and 12.3 for 5 points or more.

The Outpatient Bleeding Risk Index[55] has been prospectively validated by others.[108–110] These prediction models should not be the sole criterion of deciding whether to initiate therapy, but may be helpful in the conjunction with other assessments, such as the patients functional and cognitive state, likelihood of adherence to therapy, risk of thromboembolism, and personal preference.[111] Clinicians can use these prediction models to help weigh the risks and benefits of therapy with VKA, potentially adjusting the intensity, type, or length of therapy or the frequency of INR monitoring. Clinicians can review these assessments at the initiation of therapy and periodically reassess throughout the course of therapy. It remains unclear whether assessment for the polymorphisms of cytochrome P450 to help identify patients at risk for bleeding during initiation of VKA therapy will enhance bleeding prediction models.[73–75,112]

1.2 Heparins

Heparin is usually given in low doses by subcutaneous injection to prevent venous thrombosis (prophylactic heparin), in higher doses to treat patients with acute VTE or with acute coronary syndromes (therapeutic heparin), and in very high doses in patients during open-heart surgery. In this chapter, we will only discuss bleeding associated with therapeutic heparin. (See the article by Geerts et al for a discussion of bleeding associated with prophylactic heparin). Heparin has the potential to induce bleeding by inhibiting blood coagulation, by impairing platelet function,[113] and by increasing capillary permeability.[114] Heparin can also produce thrombocytopenia, but this is rarely an important cause of bleeding.

1.2.1 Risk of Bleeding Compared to Control or Placebo

Few trials compared the risk of bleeding associated with therapeutic heparin to placebo or no treatment. Brandjes et al[115] conducted a trial in which 120 patients with proximal deep vein thrombosis were randomized to unfractionated heparin (UFH) by continuous IV infusion for 7 days plus acenocoumarol started at the same time as UFH or placebo infusion and acenocoumarol alone. There was no bleeding while the patients received UFH. The number of patients in the UFH arm was relatively small. To obtain a reasonable estimate of the bleeding incidence associated with UFH therapy for acute venous thrombosis, trials of UFH compared to other antithrombotics, *eg*, low-molecular-weight-heparin (LMWH), need to be considered. These are discussed later in this chapter.

A systematic review of patients with acute ST-segment elevation myocardial infarction by Collins et al[116] showed that without thrombolysis the risk of major hemorrhage increased from 0.7% with aspirin alone to 1.0% in combination with high-dose UFH but the risk did not increase with low-dose UFH (12,000 U). When studies with thrombolysis were included, high-dose UFH increased the risk from 1.1 to 2.3%.

In the International Stroke Trial,[117] the risk of intracranial and major extracranial bleeding during 14 days of treatment was 3.1% in patients who received UFH 12,500 U bid, compared to 0.6% in patients who received no treatment.

In the Fragmin in unstable coronary artery disease (FRIC) study,[118] patients with unstable angina or non–Q-wave myocardial infarction were randomized to either the LMWH dalteparin at a dose of 120 IU/kg subcutaneously bid or IV UFH (days 1–6) and then to either subcutaneous dalteparin 7,500 IU qd or placebo days 6–45. The rates of major bleeding during the chronic phase were very low and there was no difference between LMWH and placebo. In the Fragmin during instability in Coronary Artery Disease (FRISC) trial,[119] patients with unstable coronary artery disease received the same dalteparin regimen as in FRIC but compared with placebo from the beginning. The rate of major bleeding during the initial week was 0.8% with LMWH and 0.5% with placebo and during the following 5½ weeks 0.3% in both groups.

In the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) study,[120] dalteparin LMWH (5,000 IU or 7,500 IU based on patient's weight) or placebo was given bid subcutaneously for 3 months. The rate of major bleeding was increased with the LMWH, 3.3% vs 1.5%.

In conclusion, the incremental risk of major hemorrhage with UFH or LMWH varies between almost 0% and 2%, depending on the underlying disease, concomitant medication, the intensity and duration of treatment.

1.2.2 Determinants of Bleeding

Intensity of Treatment: It would make clinical sense that the bleeding rate should be related to the intensity of anticoagulation, as analyzed either by the prolongation of a test of hemostasis, *eg*, activated partial thromboplastin time (APTT) or the dose of heparin. Yet, such a relationship has been difficult to demonstrate.

In a study[121] evaluating prophylaxis in patients with recent-onset traumatic spinal cord injuries, the incidence of bleeding was significantly greater in patients randomized to receive heparin adjusted to maintain the APTT at 1.5 times control than compared with heparin at a fixed dose of 5,000 U bid during 7 weeks. The mean dose of heparin for the adjusted-dose regimen was 13,200 U bid. Bleeding occurred in seven adjusted-dose patients compared with none in the fixed-dose group.

In a blinded study by Hull et al,[122] 115 patients with proximal DVT were randomized to receive initial therapy with UFH subcutaneously or IV by continuous infusion. The mean APTT at 18 h after the start of therapy in the subcutaneous heparin group was 54.8 s compared to a mean of 71.8 s in the IV heparin group. There were two major bleeds in each group. If there were an effect of intensity of anticoagulation as measured by the APTT, then more bleeds in the IV heparin group would have been expected. However, the number of patients in this trial was relatively small.

In a second trial conducted by Hull et al,[123] 198 patients with DVT were randomized to UFH alone or UFH plus warfarin. A prescriptive heparin-dosing regimen was used in both arms to achieve a therapeutic APTT rapidly. Sixty-nine percent of patients receiving combined therapy had supratherapeutic APTT values compared with 24% of the single therapy group; yet no difference was detected in bleeding, 9% vs 12% respectively. Thus, there was no association between a supratherapeutic APTT and bleeding.

In a trial conducted by Raschke et al,[124] 115 patients requiring IV UFH for venous or arterial thromboembolism or for unstable angina were randomized to dosing with a weight-based nomogram or a usual care nomogram. The patients in the weight-based nomogram group had a higher rate of exceeding the therapeutic range in the first 24 h and a shorter time to achieve the range compared to the

standard group. Thus, presumably the intensity of their anticoagulation was greater in this protocol. Yet, during the early period of anticoagulation there were no major bleeds in the former group compared to one in the latter.

Anand et al[125] examined the relationship between the APTT and bleeding in 5,058 patients with acute coronary syndrome who received IV heparin in the Organization to Assess Strategies for Ischemic Syndromes (OASIS)-2 trial. For every 10-s increase in the APTT, the major bleeding was increased by 7% ($p = 0.0004$).

Finally, the results of Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO)-IIa and the Thrombolysis in Myocardial Infarction (TIMI) 9A studies in patients with ischemic coronary syndromes indicated that a 20% increase in the IV heparin dose above the 1,000 U/h that was used in the GUSTO I study increased the risk of ICH when combined with thrombolytic therapy.[126,127]

Method of Administering Heparin: The evidence for a relationship between the risk of bleeding and the method of administering heparin stems from RCTs in which UFH was either administered by continuous IV infusion or intermittent IV injection,[126–133] continuous IV heparin or subcutaneous heparin,[134–137] continuous IV heparin for about 10 days or a shorter course (4 to 5 days),[122,138] continuous IV heparin and VKA compared with VKA alone,[115] continuous IV heparin given on a weight-adjusted basis with a standard clinical approach (5,000-U bolus, 1,000 U/h),[124] and continuous IV heparin monitored using either the APTT or monitored using a heparin assay. In summary, there was an increased rate of major bleeding with intermittent IV heparin compared with continuous IV infusion. Continuous IV heparin and subcutaneous heparin injections were associated with a similar amount of bleeding; and continuous IV heparin for about 5 days or 10 days caused a similar amount of bleeding.

Patient Characteristics: Comorbid conditions, particularly recent surgery or trauma, are very important risk factors for heparin-induced bleeding.[132,139,140] This association was demonstrated in the study by Hull et al[140] in patients with proximal vein thrombosis. Patients without clinical risk factors for bleeding were treated with a starting dose of 40,000 U of UFH by continuous infusion, while those with well-recognized risk factors for bleeding (recent surgery, trauma) received a starting dose of 30,000 U. Bleeding occurred in 1 of 88 low-risk patients (1%) who received 40,000 U initially and 12 of 111 high-risk patients (11%) who received 30,000 U.

Early retrospective studies and a more recent case series[141] have documented aspirin as a risk factor for heparin-associated bleeding.[142] The risk of heparin-associated bleeding increases with concomitant thrombolytic therapy[5] or GP IIb/IIIa antagonists.[143,144] Renal failure, patient age, and sex have also been implicated as risk factors for heparin-induced bleeding in case series but the association with sex has not been consistent.[145,146] In an analysis of a randomized trial,[147] age > 70 years was associated with a clinically important increased risk of major bleeding.

1.2.3 Risk of Bleeding Compared to Other Anticoagulants

For the risk of bleeding of UFH or LMWH compared to fondaparinux, see Section 1.3 and specifically for VTE, Section 2.1.1.4; for ST-elevation myocardial infarction, Section 2.5.2; for unstable angina and non–ST-segment elevation myocardial infarction, Section 2.6.1; for percutaneous coronary intervention, Section 2.7.1. For the risk of bleeding compared to bivalirudin, see Section 1.4.1, Section 2.5.3, and Section 2.7.1; compared to lepirudin, see Section 1.4.2; compared to argatroban, see Section 1.4.3; compared to VKA, see Section 2.1.2.1; and for comparison of UFH with LMWH in VTE, see Section 2.1.1.2 and in ST-segment elevation myocardial infarction, Section 2.5.2.

1.3 Fondaparinux

The risk of major bleeding with fondaparinux compared to control can only be assessed with the lower dose of 2.5 mg/d, which is used in prophylaxis against VTE and for treatment of acute coronary syndromes. Two placebo-controlled RCTs have been performed. In the extended prophylaxis against VTE after surgery for hip fracture, 656 patients received open-label fondaparinux for the first week and were then randomized to another 3 weeks with fondaparinux or placebo.[148] The rate of major bleeding during the period after randomization was 2.4% with fondaparinux vs 0.6% with placebo ($p = 0.06$). There were no fatal or critical organ-hemorrhages and the difference was entirely due to events with a bleeding index of ≥ 2 (see Introduction).

In a study of prophylaxis against VTE in 849 medically ill patients randomized to fondaparinux or placebo for 6 to 14 days, major bleeding occurred in one patient (0.2%) in each group.[149] Furthermore, in a study on patients with ST-elevation myocardial infarction a subset of the population ($n = 5,658$) not considered eligible for treatment with heparin received fondaparinux or placebo for up to 8 days, and the rate of major bleeding was lower with fondaparinux (1.4% vs 2.0%).[150] Thus, the increase in risk of

major bleeding, not directly associated with the surgical site, appears to be extremely low during short-term treatment with fondaparinux at a dose of 2.5 mg/d. The higher dose of 7.5 mg/d, used for treatment of established VTE, has not been evaluated against placebo.

1.3.1 Determinants of Bleeding

In a metaanalysis of four studies on fondaparinux for postoperative prophylaxis against VTE the timing of the first injection was inversely related to the risk of major bleeding as well as to overt bleeding with a bleeding index of ≥ 2.0 ($p = 0.008$ for both).[151] In $> 10{,}000$ patients with acute coronary syndromes randomized to treatment with fondaparinux the point estimate for major bleeding was nonsignificantly higher in patients ≥ 65 years of age than in patients < 65 years of age (2.7% vs 1.4%) and significantly higher in patients with vs without revascularization within 9 days (4.2% vs 1.0%).[152]

1.3.2 Fondaparinux vs UFH or LMWH

Fondaparinux at a dose of 2.5 mg/d has been evaluated against UFH in patients with myocardial infarction (see Section 2.5.2) and at a dose of 7.5 mg/d against UFH in patients with pulmonary embolism (PE) [see Section 2.1.1.4] with similar rates of major bleeding in both treatment arms.

Fondaparinux at a dose of 2.5 mg/d has been evaluated against LMWH at a therapeutic dose (enoxaparin 1 mg/kg bid) in acute coronary syndromes (see Section 2.6.1) and the rate of major bleeding was significantly lower with fondaparinux (7.3% vs 9.0%, $p < 0.001$) without any loss of efficacy.[152] A metaanalysis of four RCTs with 7,344 patients has compared fondaparinux, 2.5 mg/d against a prophylactic dose of LMWH (enoxaparin 40 mg qd or 30 mg bid).[151] The rate of major bleeding was 2.7% with fondaparinux and 1.7% with LMWH ($p = 0.008$). There were no fatal or critical organ hemorrhages with fondaparinux vs two with LMWH. The difference in major bleeding was therefore based on events with a bleeding index of ≥ 2 and thus related to the surgical site. Finally, fondaparinux at a dose of 7.5 mg/d was compared with enoxaparin at a therapeutic dose of 1 mg/kg bid in patients with DVT (see Section 2.1.1.4) with similar rates of major bleeding.[153]

In conclusion, treatment with fondaparinux at a dose of 2.5 mg/d is associated with less bleeding than a therapeutic dose of LMWH and a similar risk of bleeding as UFH or prophylactic dose of LMWH. In the comparison with prophylactic dose of LMWH there is, however, a higher risk of surgical site bleeding with fondaparinux. Treatment with fondaparinux at a dose of 7.5 mg/d carries the same risk of bleeding as therapeutic dose of UFH or LMWH.

1.4 Direct Thrombin Inhibitors

The direct thrombin inhibitors (DTIs) bivalirudin and lepirudin have not been compared with placebo, and thus it is difficult to determine the increase in risk of bleeding that can be ascribed to these drugs.

1.4.1 Bivalirudin

In patients with ST-segment elevation myocardial infarction and initial thrombolytic therapy with streptokinase, bivalirudin was compared with UFH in the large RCT, The Hirulog and Early Reperfusion and Occlusion (HERO)-2 trial with $> 17{,}000$ patients.[154] There was a trend to more major bleeding and ICH with bivalirudin than with UFH (see Section 2.5.3). In contrast, for patients with percutaneous coronary intervention (PCI) pooled analysis of four RCTs with $> 11{,}000$ patients showed less major bleeding with bivalirudin compared to UFH (2.7% vs 5.8%, $p = 0.02$).[155] A recent RCT with almost 14,000 patients with acute coronary syndrome and invasive therapy also demonstrated less major bleeding with bivalirudin alone compared to UFH plus a glycoprotein IIb/IIIa-inhibitor (3.0% vs 5.7%; $p < 0.001$) without any loss of the effect.[156]

The dose of bivalirudin used in the large trials in myocardial infarction was mostly a bolus dose of 0.25 mg/kg followed by infusion of 0.5 mg/kg/h for 12 h and then 0.25 mg/kg/h.[154,157] The dose used in the trials in PCI was mostly a bolus of 0.1–1.0 mg/kg followed by infusion of 0.25–1.75 mg/kg/h throughout the procedure or escalating after the angiography and prior to the intervention.[154,156–160] It is thus not the absolute dose of bivalirudin that explains the more favorable outcome regarding bleeding in PCI than in myocardial infarction. The initial thrombolytic treatment in myocardial infarction may result in a hemostatically more compromised patient, and even lower doses of bivalirudin should be used in these patients.

1.4.2 Lepirudin

The hirudin derivative lepirudin has been studied in RCTs in patients with acute coronary syndrome or myocardial infarction and in prospective cohort studies with historical matched controls in patients with heparin-induced thrombocytopenia. In myocardial infarction lepirudin was compared with UFH as an adjunct after thrombolysis with streptokinase.[161] The 1,208 patients also received aspirin and lepirudin that was administered as an IV bolus dose of 0.2

mg/kg, followed by 0.5 mg/kg subcutaneously bid for 7 days. The rates of major bleeding were 3.3% with lepirudin and 3.5% with UFH, and the rates of ICH were 0.2% and 0.3%, respectively. In another trial, 10,141 patients with acute coronary syndrome received lepirudin 0.2 mg/kg, followed by 0.15 mg/kg/h for 72 h or UFH, all IV. Major bleeding occurred in 1.2% with lepirudin and 0.7% with UFH ($p = 0.01$).[162]

In patients with heparin-induced thrombocytopenia (as discussed in detail by Warkentin et al in this supplement). Lubenow et al[163] performed a pooled analysis of three prospective studies with lepirudin in a total of 91 patients. The dose used was a bolus of 0.4 mg/kg followed by infusion of 0.15 mg/kg/h. The historical controls ($n = 47$) had received VKA, aspirin, or no specific treatment. Major bleeding occurred in 14.3% of the patients treated with lepirudin and in 8.5% of the controls, but the difference was not statistically significant. In addition, Farner et al[164] compared data from 175 patients treated with lepirudin from the same studies as in the pooled analysis with data from 126 patients treated with danaparoid and reviewed retrospectively. Major bleeding was observed in 10.4% of those receiving lepirudin and 2.5% in those receiving danaparoid ($p = 0.009$).

In a retrospective analysis of 181 patients with heparin-induced thrombocytopenia treated with lepirudin, bleeding occurred in 20.4% of the patients.[165] Major bleeding was more frequent when the dose was > 0.07 mg/kg/h, when the treatment was long, or when the patient had moderate or severe renal impairment. In conclusion, lepirudin appears to be associated with an increased risk of major bleeding compared to UFH or danaparoid.

1.4.3 Argatroban

Argatroban has been compared with placebo in acute ischemic stroke[166] and in myocardial infarction.[167] In the stroke study 171 patients were randomized to argatroban, starting with a bolus dose of 100 μg/kg followed by an infusion of either 1 or 3 μg/kg/min and adjusted according to APTT, or to placebo for 5 days. The rate of symptomatic ICH was 3.4% with low-dose and 5.1% with high-dose argatroban vs 0% with placebo, which was not a statistically significant difference ($p = 0.18$) but only 171 patients were included. In a dose-ranging trial 910 patients in the Argatroban in Myocardial Infarction (AMI) trial received as an adjunct to streptokinase also argatroban or placebo and major bleeding was not increased in the experimental group.[167] It is difficult to evaluate how much argatroban increases the risk of bleeding based on these results.

Three RCTs have compared argatroban with UFH in patients with myocardial infarction and initial thrombolysis. In the Argatroban in Acute Myocardial Infarction (ARGAMI) study 127 patients were allocated in a 2:1 ratio to treatment with argatroban at a dose of 100 μg/kg bolus plus 3 μg/kg/min infusion for 72 h or to UFH.[168] The rate of bleeding complications was 19.5% with argatroban and 20% with UFH, and there was one ICH in the heparin group.

In the ARGAMI-2 trial, designed for 1,200 patients but discontinued after enrolling 600 due to lack of efficacy, high-dose argatroban was compared with UFH.[169] There were two major bleedings in the argatroban group vs 6 in the heparin group, with 2 ICHs among the latter. Minor bleeding occurred in 5.9% of the argatroban-treated patients and 8.3% of those receiving heparin. In the Myocardial Infarction with Novastan and TPA (MINT) trial 125 patients with myocardial infarction and initial thrombolysis were randomized to receive adjunct therapy with argatroban at a bolus dose of 100 μg/kg followed by an infusion of either 1 or 3 μg/kg/min or with UFH.[170] The rate of major bleeding was 2.6% with low-dose and 4.3% with high-dose argatroban vs 10% with UFH ($p = 0.29$ vs heparin).

Argatroban has also been evaluated in PCI. In an open-label study 152 patients received argatroban at a bolus dose of 250 or 300 μg/kg, followed by a 15-μg/kg/min infusion during the procedure together with the glyco-protein IIb/IIIa inhibitor abciximab or eptifibatide.[171] Two patients (1.3%) experienced major bleeding. A combined analysis has been performed of three studies with argatroban for PCI in patients with heparin-induced thrombocytopenia.[172] One of 91 patients experienced major bleeding.

The other major patient group for whom argatroban has been evaluated is heparin-induced thrombocytopenia. Lewis et al[173] published a pooled analysis of two prospective cohort studies in 882 patients with heparin-induced thrombocytopenia with or without thrombotic symptoms. The 185 historical controls, for whom the therapy consisted of stopping heparin and for some of them instead anticoagulation with VKA, were the same for the two studies. Argatroban was given at a dose of 1.7 to 2.0 μg/kg/min for 5 to 7 days. Major bleeding occurred in 6% of the patients treated with argatroban and 7% of the controls. Since the definition of major bleeding was similar to that in the studies on lepirudin, a rough comparison can be made to the favor of argatroban.

Determinants of bleeding have not been well characterized in the above-mentioned studies. Data from phase I indicate that patients with hepatic dysfunction have a clearance rate of one quarter compared to healthy volunteers and dose adjustments will be required.[174] In addition, the clearance

of argatroban in elderly men was 20% lower than in elderly women, but this difference may not be important. In conclusion, the risk of major bleeding with argatroban is similar or possibly lower than with UFH and probably lower than with lepirudin.

1.5 Thrombolytic Therapy

A comparison of the risk of major bleeding between trials is problematic due to the use of various definitions. Two commonly adopted definitions are the TIMI major bleeding criteria[175] and GUSTO severe bleeding criteria.[176] TIMI major bleeding criteria consist of (1) at least a 5 g/dL decrease in hemoglobin, (2) at least a 15% decrease in hematocrit, or (3) intracranial bleeding. GUSTO severe bleeding criteria are based on the following: (1) ICH, or (2) bleeding resulting in hemodynamic compromise. In addition, many studies have used their own variants for this definition. The most ominous hemorrhagic complication is ICH, which in some studies is split into primary hemorrhage and secondary transformation of ischemic stroke.

Determinants of Bleeding: The risk factors for major bleeding and intracranial bleeding differ somewhat with respect to the underlying disorder that is treated. In multivariable regression analysis of candidate risk variables in > 40,000 patients treated with thrombolytic therapy after myocardial infarction[177] advanced age, low body weight, prior cerebrovascular disease or hypertension, systolic and diastolic BPs, randomization to tissue plasminogen activator (tPA) (as opposed to streptokinase), and an interaction between age and hypertension were independent predictors of ICH. In patients receiving thrombolytic therapy for acute ischemic stroke leukoariosis,[178] pretreatment National Institute of Health Stroke Scale score[179,180] or clinical deficit,[181] brain edema,[180] early signs on CT of cerebral ischemia,[181,182] mass effect on CT before treatment,[180] and reduced pretreatment middle cerebral artery blood flow[183] have been identified as independent risk factors. In patients treated with recombinant prourokinase for ischemic stroke, a baseline glucose level of > 20 g/L was significantly associated with symptomatic ICH.[184] Conversely, hemostatic markers at baseline were not of any value for prediction of ICH.[179]

Independent predictors of mortality in patients with ICH after thrombolytic therapy were identified in the GUSTO-I trial as Glasgow coma score, time from thrombolysis to ICH, volume of ICH, and baseline clinical predictors of mortality.[185]

1.5.1. Patient Characteristics

Age, Sex, and Ethnicity: Old age was the strongest independent risk factor for ICH in the analysis of the population in the GUSTO-I trial,[177] in which 41,021 patients received either streptokinase or tPA. In a model for assessment of individual risk based on data from other trials, Simoons et al[186] found that age > 65 predicted for ICH with an OR of 2.2 (95% CI, 1.4–3.5). Gurwitz et al[187] analyzed data from an American registry of 71,073 patients with myocardial infarction. The adjusted OR for ICH was 2.71 (95% CI, 2.18–3.37) for the age group 65–74 years and 4.34 (95% CI, 3.25–5.45) for the age group ≥ 75 years. In the pooled analysis of the Assessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT)-3 and ASSENT-3 PLUS studies,[60] in which tenecteplase was evaluated with the addition of UFH or LMWH, old age was also a risk factor for ICH but only in the group treated with LMWH. The risk of major noncerebral hemorrhage increased by 40% for every 10-year increase of age in the ASSENT-2 population (OR, 1.20; 95% CI, 1.32–1.50),[61] and similarly in GUSTO-I (age 60 vs 50, OR, 1.30; 95% CI, 1.26–1.35).[62]

Female sex was also an independent risk factor for ICH in the analysis of the ASSENT-3 and ASSENT-3 PLUS studies[188] but not in GUSTO-I.[177] In the ASSENT-2 study[189] the highest risk of ICH was observed in females weighing ≤ 67 kg. Females also had a higher risk of noncerebral major bleeds (OR, 1.48; 95% CI, 1.26–1.74). Analysis of data from 16,648 patients in the International Tissue Plasminogen Activator/Streptokinase Mortality Study[190] showed that baseline characteristics included more risk factors in women than in men with myocardial infarction. However, after correction for all baseline characteristics, the incidence of hemorrhagic stroke was still higher among females with an OR of 2.90 (95% CI, 1.41–5.95). In the American registry[187] the adjusted OR for ICH in females was 1.59 (95% CI, 1.31–1.92). In the same population the adjusted OR for ICH was 1.70 (95% CI, 1.24–2.34) for African Americans compared to whites. This effect was also seen in GUSTO-I[191] (OR, 1.33; 95% CI, 1.12–1.57). None of these characteristics were independent risk factors for ICH after thrombolysis for stroke.[180–182]

BP and Weight: Diastolic BP was a stronger independent risk factor for ICH ($p = 0.0002$) than systolic BP ($p = 0.048$) in the analysis of GUSTO-I.[177] Simoons et al[186] found that hypertension on admission for myocardial infarction was independently associated with ICH with an OR of 2.0 (95% CI, 1.2–3.2). Based on data from the American registry, Gurwitz et al[187] concluded that systolic BP

of ≥ 140 mm Hg or diastolic BP of ≥ 100 mm Hg were independent risk factors for ICH after thrombolytic therapy for myocardial infarction. The adjusted ORs were 1.33 (95% CI, 1.04–1.69) for systolic BP of 140–159 mm Hg, 1.48 (95% CI, 1.14–1.92) for systolic BP of ≥ 160 mm Hg, and 1.40 (95% CI, 1.12–1.99) for diastolic BP of ≥ 100 mm Hg. Contrary to this, diastolic BP ≤ 70 mm Hg was a risk factor for major, noncerebral hemorrhage in the ASSENT-2 study[189] with OR 1.33 (1.14–1.54) with a similar finding in the GUSTO-I study[191] (OR 0.94 for diastolic BP 90 vs 80 mm Hg, 95% CI, 1.12–1.57).

In multivariable logistic regression analysis of characteristics of the patients in the GUSTO-I trial,[177] lower body weight was associated with ICH ($p = 0.0001$), and major hemorrhage in general was also predicted by this characteristic.[191]

Preexisting Disease: A history of stroke or cerebrovascular disease in general was identified as a risk factor for ICH after thrombolysis for myocardial infarction, both in the GUSTO-1 study[177] ($p = 0.0001$) and in the American registry (adjusted OR, 1.90; 95% CI, 1.37–2.65).[187] Diabetes was instead a risk factor for symptomatic hemorrhagic transformation after thrombolysis in patients with ischemic stroke in the Multicenter Acute Stroke Trial-Europe (MASTE-E).[182] Likewise, baseline glucose > 200 mg/dL predicted for ICH in a trial with intraarterial prourokinase for a similar population,[184] with a RR of 4.2 (95% CI, 1.04–11.7).

1.5.2 Thrombolytic Agent; Concomitant Drugs

A recent metaanalysis found no statistically significant difference in the risk of hemorrhage between different agents in patients treated with thrombolysis for ischemic stroke.[192] For patients with myocardial infarction the results have been different. Alteplase (tPA) resulted in a higher risk of ICH than streptokinase, according to a multivariate analysis performed by Simoons et al[186] (OR, 1.6; 95% CI, 1.0–2.5). Likewise, in a combined analysis[193] of the Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico (GISSI)-2[194] and the Third International Study on Infarct Survival (ISIS-3)[195] there were more cerebral hemorrhages after tPA (0.6%) than after streptokinase (0.3%) [$p < 0.00001$]. The total number of patients randomized in these two studies was > 48,000. A borderline significant effect ($p = 0.046$) in the same direction was also found in the GUSTO-1 trial[177] with > 41,000 patients. Comparisons between streptokinase and tPA, both given as IV infusion and tenecteplase, reteplase, lanoteplase (all tPA derivatives) or saruplase (single chain urokinase plasminogen activator), all given as a bolus injection, did not show any reduction of ICH with the latter (Table 3).

In a metaanalysis of studies on thrombolysis in ischemic stroke,[192] a higher dose of thrombolytic therapy was associated with an increase in fatal ICH (OR, 3.25; 95% CI, 1.32–7.97). Analysis of data from the American registry on myocardial infarction[187] attributed an increased risk of ICH to a dose of tPA > 1.5 mg/kg. A dose finding study with tPA, TIMI-II,[196] showed a higher incidence of ICH with 150 mg than with 100 mg ($p < 0.01$). In TIMI 10B[197] a clear dose response on ICH was found between doses of 30 mg, 40 mg, and 50 mg of tenecteplase. However, in the parallel ASSENT-1 trial,[198] the incidence of ICH was 0.94% in the 30-mg group and 0.62% in the 40-mg group ($p = 0.4$). In both studies the rate of ICH decreased after protocol amendments with a reduction of the dose of heparin for patients weighing ≤ 67 kg and adjustments according to the APTT using a nomogram.

In the GISSI-2[194] and ISIS-3[199] trials, which had a multifactorial design, there was no difference in the rate of ICH between those without and with heparin (see Section 2.5.2). In the ISIS-2 trial[200] with > 17,000 patients and a multifactorial design, addition of aspirin to streptokinase did not result in an increased rate of ICH or of other bleeding requiring transfusion. A metaanalysis[201] found that addition of glycoprotein IIb/IIIa blockers to the combination of thrombolytic therapy, aspirin, and heparin increased the risk of major bleeding by 69% (95% CI, 38–109%).

2.0 Risk of Bleeding and Clinical Disorders

2.1 VTE

2.1.1 Initial Therapy

Initial Thrombolytic Therapy vs Anticoagulant Therapy Alone in Patients With Acute DVT or PE: Metaanalyses have combined the results of the mostly small RCTs that have compared various thrombolytic regimens with anticoagulant therapy alone in patients with acute DVT.

In patients with acute DVT, Watson and Armon[202] estimated the RR for "significant bleeding" (excludes very minor bleeding and ICH) to be 1.7 (95% CI, 1.04–2.9) with use of thrombolytic therapy (Table 4).[202] There were 2 (0.6%) ICHs among those who received thrombolytic therapy and none among those who received anticoagulant therapy alone (Table 4).[202]

In patients with PE, Wan and colleagues[203] estimated the OR for major bleeding to be 1.4 (95% CI, 0.8–2.5) with use of thrombolytic therapy (Table 4).

Table 3—*Rate of ICH After Thrombolytic Therapy for Myocardial Infarction With Different Thrombolytic Agents: Clinical Description and Results (Section 1.5.2)**

Study	Patients, No.	Streptokinase		Alteplase†		Anistreplase		Tenecteplase + UFH	Reteplase + UFH	Lanoteplase + UFH	Saruplase + UFH
		Without UFH	With UFH	Without UFH	With UFH	Without UFH	With UFH				
GISSI2/Int Study[346]	20,891	0.3	0.2	0.4	0.4						
ISIS-3[195]	41,299	0.25	0.22	0.72§	0.59§	0.71	0.40				
GUSTO-I[191]	41,021		0.49/0.54*		0.72‖						
GUSTO III[347]	15,059				0.87				0.91		
ASSENT-2[348]	16,949				0.94			0.93			
ASSENT-3[349]	6,095							0.88/0.93‡			
COBALT[350]	7,169				0.81/1.12§						
InTIME II[351]	15,078				0.64					1.12 (p = 0.0004)	
COMPASS[352]	3,089		0.3								0.9 (p = 0.038)
INJECT[353]	6,010		0.37					0.77			

*Administered subcutaneously or IV.
†Alteplase administered as IV infusion or IV injections.
‡Tenecteplase combined with enoxaparin or UFH.
§Streptokinase vs alteplase, with or without UFH (p = 0.00001).
‖p = 0.046.

There were 2 (0.5%) ICHs in those who received thrombolytic therapy and 1 (0.3%) among those who received anticoagulant therapy alone.[203] The absolute rate of major bleeding both in patients who did, and did not, receive thrombolytic therapy was about sixfold higher in the trials that included patients with severe PE compared to those that excluded such patients, and there was a trend to a higher proportional risk of major bleeding with thrombolytic therapy vs anticoagulant therapy in those trials (OR, 2.0; 95% CI, 1.0–3.9) than in the trials that excluded patients with major PE (OR, 0.7; 95% CI, 0.2–1.9).[203]

The absolute frequency of major bleeding with thrombolytic therapy in these two metaanalyses of randomized trials was lower than has been reported in a registry of catheter directed thrombolytic therapy for DVT (11%; 54/743)[204] and for systemic thrombolytic therapy for PE (22%; 66/304 [9% in the absence of thrombolytic therapy in the same registry]).[205] In conclusion, thrombolytic therapy appears to be associated with a 1.5- to twofold increase in the risk of major bleeding compared with anticoagulant therapy alone in patients with acute VTE.

UFH vs LMWH for Initial Treatment of DVT or PE: Trials that have evaluated acute treatment of VTE with different heparin regimens have generally compared fixed-dose LMWH with adjusted-dose UFH given IV[206–216] or subcutaneously[217–219] (Table 5). The results of these studies, not including the two most recent studies that are noted below in which heparin was given subcutaneously,[217,219] have been combined in a number of recent metaanalyses.[220–222] In the most recent metaanalysis, which included studies in which heparin was given IV (17 studies; 3,517 patients) and subcutaneously (2 studies; 107 patients), LMWH was associated with less major bleeding than UFH (OR, 0.57; 95% CI, 0.39–0.83).[222] Since that metaanalysis was performed, two large studies have compared subcutaneous weight-adjusted UFH (adjusted to APTT results in one study[219] and in fixed doses without APTT monitoring in the other;[217] total of 705 UFH patients) with LMWH and found no difference in the frequency of major bleeding and almost identical efficacy with the two types of heparin (Table 5).

Direct Comparisons Among LMWH Regimens for Initial Treatment of VTE: Once-daily and twice-daily administrations of the same LMWH have been directly compared in six studies (the same total daily dose of LMWH has not always been compared within studies).[223–228] A metaanalysis of five of these studies[224–228] that had unconfounded comparisons found no increase in major bleeding with once-daily

Table 4—*Initial Thrombolytic Therapy vs Anticoagulant Therapy Alone in Patients With Acute DVT or PE: Clinical Description and Results (Section 2.1.1.1)*

Study/yr	Type of Publication	Participants	Interventions	Follow-up	Outcomes and Results
Wan et al[203]/2004	Metaanalysis of 11 RCTs involving 248 patients	Acute PE	Thrombolytic therapy (urokinase [2 studies], streptokinase [4 studies, intrapulmonary in 1 study], tPA [5 studies]); various doses; given for 0.5–72 h	3–30 d	Major bleeding: Thrombolytics: 34/374 Heparin: 23/374 OR (95% CI) 1.4 (0.8–2.5)* Intracranial bleeding: Thrombolytics: 2/374 Heparin: 1/374 OR (95% CI) 1.0 (0.4–3.0)* Major bleeding was approximately sixfold higher in five studies that included patients with major PF, compared to the six studies that did not.
Watson and Armon[202]/2004	Metaanalysis of 12 RCTs involving 668 patients	Acute DVT (symptoms ≤ 7 d)	Thrombolytic therapy (urokinase [3 studies], streptokinase [5 studies], tPA [4 studies]); various doses, various routes, various durations, vs anticoagulation	1.5–30 d	Significant bleeding: Thrombolytics: 44/440 Control: 18/228 RR (95% CI) 1.7 (1.04–2.9) Intracranial bleeding: Thrombolytics: 2/459 Control: 18/242 RR (95% CI) 1.7 (0.21–14)

*Heterogeneity, $p < 0.1$.

treatment (OR, 1.2; 95% CI, 0.4–3.2).[229] Outpatient and inpatient administration of LMWH (3 preparations were used) was compared in a single study of 201 patients: 2 major bleeds occurred in each group.[230] Tinzaparin and dalteparin, each given once daily, have been compared for outpatient treatment of VTE in a study of 497 patients; 5 major bleeds occurred in the tinzaparin group and 2 occurred in the dalteparin group ($p = 0.44$).[231]

Fondaparinux vs UFH or LMWH: The synthetic pentasaccharide, fondaparinux, has been evaluated for acute treatment of PE and DVT (Matisse studies).[153,232] In the Matisse-PE trial, 2,213 patients were treated with a single subcutaneous dose of fondaparinux (7.5 mg for 50 to 100 kg) or IV UFH (APTT ratio 1.5 to 2.5) for at least 5 days using an open-label design.[232] Major bleeding occurred in 1.3% (14/1,103) of fondaparinux, and 1.1% (12/1,110) of UFH-patients during the initial treatment period.[232]

In the Matisse-DVT trial, 2,205 patients were treated with a single subcutaneous dose of fondaparinux (7.5 mg if 50 to 100 kg) or twice-daily subcutaneous LMWH (enoxaparin 1 mg/kg) for at least 5 days using a blinded design.[153] Major bleeding occurred in 1.1% (12/1,098) of fondaparinux and 1.2% (13/1,107) of LMWH patients during the initial treatment period.[153]

2.1.2 Long-term Treatment of VTE

VKAs, overlapped initially with heparin therapy (UFH or LMWH preparations), have been the standard long-term treatment for VTE. Linkins and colleagues[233] performed a metaanalysis of 33 prospective studies (10,757 patients in 29 RCTs and 4 cohort studies, performed from 1990 to 2001) to assess the clinical impact of bleeding in patients with VTE who were treated with VKA therapy (target INR, 2.0–3.0). During the first 3 months of treatment, the rate of major bleeding was 2.1% and the rate of fatal bleeding was 0.37%. Of 275 major bleeds during the total duration of follow-up, 37 were fatal for an overall case-fatality of 13%. Case-fatality with ICH was 46% and for major extracranial bleeds was 10%. Extracranial bleeds, which accounted for 81% of major bleeding episodes, caused about two thirds of the deaths from bleeding. Although the risk of bleeding was higher during the first 3 months of anticoagulant therapy than subsequently, case fatality with major bleeding was similar during the acute and long-term phases of treatment.[233]

Long-term Treatment With UFH or LMWH vs VKAs: There have been 15 RCTs in patients with VTE in which VKAs were compared with various subcutaneous heparin regimens, usually over a

Table 5—*LMWH vs UFH for the Initial Treatment of VTE: Clinical Description and Results (Section 2.1.1.2)**

Study/yr	Treatment	No. of Patients	Bleeding†	
			Major	Fatal
Duroux[207]/1991	Nadroparin SC bid (weight adjusted)	85	2 (2.4%)	0
	IV heparin APTT ratio 1.5 to 2.0	81	4 (4.9%)	0
Faivre	CY222 5,000 IU IV, followed by 155 IU/kg SC bid	35	0	NR
et al[354]/1987	IV heparin 5,000 U followed by 250 U SC bid APTT adjustment	35	3 (8.6%)	NR
Prandoni	Nadroparin SC bid (weight adjusted)	85	1 (1%)	0
et al[213]/1992	IV heparin APTT ratio 1.5 to 2.0	85	3 (4%)	0
Hull	Tinzaparin 175 Xa U/kg SC qd vs	213	1 (0.5%)	0
et al‡[210]/1992	IV heparin APTT ratio 1.5 to 2.5	219	11 (5.0%)	2 (0.9%)
Lopaciuk	Nadroparin 92 Xa U/kg SC bid	74	0	0
et al[218]/1992	SC heparin APTT ratio 1.5 to 2.5	72	1 (1%)	0
Simonneau	Enoxaparin 1 mg/kg SC bid	67	0	0
et al[214]/1993	IV heparin APTT ratio 1.5 to 2.5	67	0	0
Lindmarker	Dalteparin 200 Xa U/kg SC qd	101	0	0
et al[212]/1994	IV heparin APTT ratio 1.5 to 3.0	103	0	0
Fiessinger	Dalteparin 200 Xa U/kg SC qd	127	0	0
et al[208]/1996	IV heparin APTT ratio 1.5 to 3.0	133	2 (2%)	0
Levine	Enoxaparin 1 mg/kg SC bid	247	5 (2%)	2 (0.8%)
et al§[211]/1996	IV heparin APTT 60 to 85 s	253	3 (1%)	0
Koopman	Nadroparin SC bid (weight adjusted)	202	1 (0.5%)	0
et al§[355]/1996	IV heparin APTT ratio 1.5 to 2.0	198	4 (2%)	2 (1%)
Columbus	Reviparin 3,500 to 6,300 Xa U SC bid (weight-adjusted)	510	16 (3%)	0
Study§[216]/1997	IV heparin APTT ratio 1.5 to 2.5	511	12 (2%)	2 (0.4%)
Simonneau	Tinzaparin 175 Xa U/kg SC qd	304	0	0
et al‖[215]/1997	IV heparin APTT ratio 2.0 to 3.0	308	1 (0.3%)	1 (0.3%)
Decousus	Enoxaparin 1 mg/kg SC bid	195	7 (3.6%)	1 (0.5%)
et al[206]/1998	IV heparin APTT ratio 1.5 to 2.0	205	8 (3.9%)	1 (0.5%)
Kirchmaier	Certoparin 8,000 IU SC bid	128	1 (0.8%)	0
et al[356]/1998	IV Certoparin	128	9	1 (0.8%)
	IV heparin APTT ratio 2.0 to 3.0	131	4	0
Harenberg	Certoparin 8,000 IU SC bid	265	4 (1.5%)	0
et al[209]/2000	IV heparin APTT ratio 2.0 to 3.0	273	12 (4.5%)	2 (0.7%)
Breddin	Reviparin 7,000–12,600 IU SC qd	388	1 (0.3%)	0
et al[223]/2001	Reviparin 7,000–12,600 IU SC qd for 21 d	374	1 (0.3%)	0
	IV heparin APTT ratio 1.5 to 2.5	375	2 (0.5%)	0
Merli	Enoxaparin 1 mg/kg SC bid	312	4	0
et al[226]/2001	Enoxaparin 1.5 mg/kg SC qd	298	5	1
	IV heparin APTT ratio 1.5 to 2.5	290	6	0
Riess	Certoparin 8,000 IU SC bid for 12 d	627	6 (1.0%)	0
et al[357]/2003	IV heparin APTT ratio 1.5 to 2.5	593	5 (0.8%)	0
Kakkar	Bemiparin 115 IU/kg SC od	126	0	0
et al[242]/2003	IV heparin APTT ratio 1.5 to 2.5	126	1 (0.8%)	0
Galilei	Nadroparin 85 IU/kg SC bid	360	3	0
Investigators[219]/2004	IV heparin 4,000–6,000 U; followed by 12,500 U if < 50 kg, 15,000 U if 50–70 kg, 17,500 U if > 70 kg SC bid APTT 50–90 s	360	4	1
Kearon	LMWH (dalteparin or enoxaparin) 100 IU/kg SC bid	352	5	1
et al§[217]/2006	heparin 333 U/kg; followed by 250 U/kg SC bid (no adjustment)	345	4	0

*SC = subcutaneous.
†No. per approximately 3 mo.
‡Blinded.
§Included home treatment with LMWH (and UFH[217]).
‖PE.

3-month period (Table 6).[234–249] Higher intensities of anticoagulation (*ie*, INR of 2.6 to 4.4) were evaluated in earlier studies,[234,238,239] than in more recent trials (*ie*, INR of 2.0 to 3.0).[15,235–237,240–247,249] The higher-intensity regimens were consistently associated with more total bleeding than the comparison arms, with a similar trend for major bleeding (Table 6).

Table 6—*UFH or LMWH vs VKAs for Long-term Treatment of VTE: Clinical Description and Results (Section 2.1.2.1)**

Study/yr	Treatment	No. of Patients	Bleeding†	
			Major	Fatal
Bynum and Wilson[234]/1979	Warfarin (INR 2.6–4.4)	24	4 (16.7)	0
	Heparin (5,000 U SC bid)	24	0	0
Hull et al[239]/1979	Warfarin (INR 2.6–4.4)	33	4 (12.1)	0
	Heparin (5,000 U SC bid)	35	0	0
Hull et al[238]/1982	Warfarin (INR 2.6–4.4)	53	3 (5.7)	0
	Heparin (~ 10,000 U SC bid)	53	0	0
Pini et al[247]/1994	Warfarin (INR 2.7)	94	12 (12.8)	0
	Enoxaparin (4,000 IU SC qd)	93	3 (3.2)	0
Das et al[235]/1996	Warfarin (INR 2.0–3.0)	55	0	0
	Dalteparin (5,000 IU SC qd)	50	0	0
Hamann[237]/1998	Phenprocoumon (INR 2.0–3.0)	100	2 (2)	NR
	Dalteparin (5,000 IU SC qd)	100	0	
Lopaciuk et al[244]/1999	Acenocoumarol (INR 2.0–3.0)	95	2 (2.1)	0
	Nadroparin (85 IU/kg SC qd)	98	1 (1.0)	0
Gonzalez-Fajardo et al[236]/1999	Warfarin (INR 2.0–3.0)	80	2 (2.5)	0
	Enoxaparin (4,000 IU SC od)	85	1 (1.2)	0
Veiga et al[249]/2000	Acenocoumarol (INR 2.0–3.0)	50	2 (4.0)	1
	Enoxaparin (4000 IU SC qd)	50	1 (2.0)	0
Lopez-Beret et al[245]/2001	Acenocoumarol (INR 2.0–3.0)	77	4.7 (5.2)	0
	Nadroparin (approximately 102 IU/kg SC bid)	81	0	0
Meyer et al[246]/2002	Warfarin (INR 2.0–3.0)	75‡	12 (16)	6
	Enoxaparin (150 IU/kg SC qd)	71‡	5 (7.0)	0
Hull et al[240]/2000	Warfarin (INR 2.0–3.0)	239	2 (0.8)	NR
	Tinzaparin (175 IU/kg SC qd)	233	1 (0.4)	
Hull et al[241]/2003	Warfarin (INR 2.0–3.0)	368	17 (4.6)	NR
	Tinzaparin (175 IU/kg SC qd)	369	12 (3.3)	
Lee et al[243]/2003	Warfarin (INR 2.0–3.0)	335‡	12 (3.6)§	0
	Dalteparin (200 IU/kg SC qd first month) 150 IU/kg SC qd 2nd–6th mo	338‡	19 (5.6)§	1 (0.3)
Kakkar et al[242]/2003	VKA (INR 2.0–3.0)	246	1 (0.4)	0
	Bemiparin 3,500 IU od	111	1 (0.9)	1 (0.9)

*NR = not reported. See Table 5 for abbreviation not used in the text.
†Data are presented as No. per approximately 3 mo (%).
‡All patients had cancer.
§Six-month follow-up.

The 12 most recent of these studies compared VKA therapy at a targeted INR of 2.0 to 3.0 with widely differing regimens of three LMWH preparations (Table 6).[235–237,240–247,249] The daily LMWH dose was as low as 4,000 IU[236,247] to as high as 200 IU/kg,[243,245] approximately a 3.5-fold difference. Two metaanalyses of studies that compared LMWH with VKA, each given for 3 months after initial heparin therapy, have been performed.[248,250] In the analysis by Iorio and colleagues,[250] which includes seven studies[235,236,240,244,245,247,249] and a total of 1,379 patients, there was a trend toward less bleeding with long-term LMWH therapy (OR, 0.45; 95% CI, 0.2–1.1). Importantly, in a metaregression analysis the relative frequency of major bleeding with LMWH therapy was dose dependent, varying from an OR of ~ 0.2 at a dose of ~ 4,000 IU/d to an OR of ~ 0.7 at a dose of ~ 12,000 IU/d ($p = 0.03$ for relationship between daily dose of LMWH and major bleeding).[250]

UFH vs LMWH: In a study of 80 patients that compared 10,000 U UFH with 5,000 IU dalteparin, each administered subcutaneously bid for 3 months after acute VTE, there were no episodes of major bleeding.[251]

Different Durations of Treatment With VKA: Five randomized trials have compared 4 weeks[252–254] or 6 weeks[255,256] with 3 months[252–254] or 6 months[255,256] and three have compared 3 months[255,257,258] with 6 months[255,257] or 12 months[257,258] of VKA (INR ~ 2.0 to 3.0) for the treatment of VTE. Following the initial phase of treatment during which all patients were treated with active drug, major bleeding occurred infrequently without convincing evidence of more bleeding with the longer durations of therapy.[253–256,258] Three RCTs have evaluated long-term VKA for the prevention of recurrent VTE following an acute episode.[37,259,260] Schulman et al[260] randomized 227

patients to regimens of either 6 months or 4 years of anticoagulation (INR, 2.0 to 2.85) after a second episode of VTE. Major bleeding occurred more frequently in patients who were treated with long-term anticoagulation (2.4% vs 0.7% per patient-year); however, 6 of the 10 major bleeds in the long-term treatment group occurred in the first 6 months of therapy.[260,261] Kearon et al[259] randomized 162 patients with a first episode of unprovoked VTE to remain on warfarin (INR, 2.0 to 3.0), or to receive placebo, for a further 2 years after an initial 3 months of anticoagulation. Major bleeding occurred in 3 of the long-term therapy patients during an average of 10 months of follow-up (3.8 vs 0% per patient-year).[259] Ridker et al[37] compared low-intensity warfarin therapy (INR 1.5–2.0) with placebo in 508 patients who had completed at least 3 months of initial warfarin treatment with INR 2.0–3.0; major bleeding occurred in 5 warfarin patients (0.9% per patient-year) and 2 placebo patients (0.4% per patient-year).

A metaanalysis by Ost and colleagues[10] of 15 studies, including 10 of the previously noted studies,[37,252–259,262] estimated the rate of major bleeding to be 1.1% per patient-year (18 episodes in 1,571 years) during the extended phase of anticoagulation (INR, 2.0–3.0) compared with 0.6% per patient-year (9 episodes during 1,497 years) without anticoagulation (RR of 1.80; 95% CI, 0.72–4.51).[10]

Different Intensities of VKA: One small study has compared two intensities or VKA therapy (equivalent to an INR of ~ 2.2 vs INR of 2.6–4.5) for the first 3 months following initial heparin therapy.[15] The frequency of major bleeding was similar in the low- and high-intensity groups (2/47 vs 2/49), but there was less total bleeding with the less intense regimen (2/47 [4.3%] vs 11/49 [22%]).[15]

Kearon et al[39] compared in a blinded trial warfarin therapy with INR 1.5–1.9 and INR 2.0–3.0 for long-term prevention of recurrent unprovoked VTE in 738 patients who had completed at least 3 months of initial treatment with INR 2.0–3.0; there was no difference in the frequency of major bleeding between the two groups during an average of 2.4 years of follow-up (INR 1.5–1.9 vs INR 2.0–3.0: 1.1% vs 0.9% per patient-year; hazard ratio, 1.2 [95% CI, 0.4–3.0]).[39]

Oral Direct Thrombin Inhibitor: In a long-term treatment study, 18 months of ximelagatran (subsequently withdrawn), 24 mg bid was compared with placebo in 1,224 patients with DVT or PE who had completed 6 months of initial treatment with VKAs.[262] There was no apparent increase of major bleeding with the oral thrombin inhibitor (0.7% per year; hazard ratio 1.2 [95% CI, 0.4–3.8]).

2.2 Atrial Fibrillation

VKA vs Placebo or vs Antiplatelet Agents: A number of RCTs and metaanalyses of RCTs have consistently demonstrated the efficacy of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation.[23–25,44,100,263–280] Overall, the rates of warfarin-related bleeding in these studies have been low (Table 7). Hart et al[269] conducted a metaanalysis of six trials that compared adjusted-dose warfarin to placebo or control. The rate of ICH was 0.3%/yr with warfarin and 0.1%/yr with placebo. This difference was not statistically significant. The RR for major extracranial hemorrhage was 2.4 (95% CI, 1.2–4.6), absolute increase of 0.3%/yr for warfarin patients. The analysis by Hart et al[269] also examined five trials that compared adjusted-dose warfarin with aspirin. The RR of ICH for warfarin vs aspirin was 2.1 (95% CI, 1.0–4.6).[269]

Segal et al[277] conducted a metaanalysis of five trials that compared warfarin to placebo. The OR for major hemorrhage for patients on warfarin compared to placebo was 2.35 (95% CI, 1.20–4.24). The rate of major hemorrhage on placebo was 0.7 per 100 person-years compared to 1.3 per 100 person-years on warfarin.

More recently, two metaanalyses[279,280] have evaluated the RR and benefits of oral anticoagulant therapy vs antiplatelet therapy in patients with atrial fibrillation. Oral anticoagulant therapy was associated with increased major bleeding (1.45 OR,[279] and 1.71 hazard ratio[280]); the increased risk of oral anticoagulant therapy was offset by reduced nonfatal stroke (OR 0.68),[279] all strokes (hazard ratio 0.55),[280] and all cardiovascular events (hazard ratio 0.71).[280] The analysis by Taylor et al[279] did not include the Stroke Prevention in Atrial Fibrillation (SPAF) I and III studies[23,278] or the European Atrial Fibrillation Trial study.[66] The analysis by van Walraven et al[280] used the pooled individual patient data from six published trials in 4,052 patients with a mean age of 72 years, comparing oral anticoagulants with aspirin for atrial fibrillation. Oral anticoagulant therapy was associated with increased major bleeding (hazard ratio 1.71, absolute increase 0.9 events per 100 patient-years, $p = 0.02$); the corresponding hazard ratios and absolute increases in rates per 100 patient-years for all hemorrhagic stroke were 1.84 and 0.2 ($p = 0.19$) and for fatal bleeding were 2.15, and 0.2 ($p = 0.32$). This analysis concluded that treating 1,000 patients with atrial fibrillation for 1 year with oral anticoagulants rather than aspirin would prevent 23 ischemic strokes while causing nine additional major bleeds.[280]

In an attempt to improve the effectiveness of antiplatelet therapy, aspirin was combined with clopidogrel and compared with warfarin in the Atrial

Table 7—*Atrial Fibrillation: Clinical Description and Results (Section 2.2.1.1)**

Study/yr	Treatment	Patients, No.	Bleeding†	
			Major	Fatal
Petersen et al[276]/1989	Warfarin (INR 2.8–4.2)	335	NR	1 (0.3)
	Aspirin (75 mg)	336	NR	0
	Placebo	336	NR	0
Special report[278]/1990	Warfarin (INR 2.0–3.5)	201	1.7	NR
	Aspirin (325 mg)	192	0.9	NR
	Placebo	195	1.2	NR
Boston[263]/1990	Warfarin (INR 1.5–2.7)	212	8 (3.8)	1 (0.5)
	No medication	208	8 (3.8)	1 (0.5)
Connolly et al[264]/1991	Warfarin (INR 2.0–3.0)	187	5 (2.7)	2 (1.1)
	Placebo	191	1 (0.5)	0
SPAF II[281]/1994	Warfarin ≤ 75 yr (INR 2.0–4.5)	358	1.7	NR
	Aspirin ≤ 75 yr	357	0.9	NR
	Warfarin > 75 yr (INR 2.0–4.5)	197	4.2‡	NR
	Aspirin > 75 yr	188	1.6	NR
EAFT[44]/1995	Warfarin (INR 2.5–4.0)	225	13 (2.8)	3 (0.6)
	Placebo	230	3 (1.3)	1 (0.4)
	Aspirin (300 mg)	404	6 (1.5)	2 (0.5)
Veterans Affairs[266]/1992	Warfarin (INR 1.4–2.8)	260	6 (2.3)	0
	Placebo	265	4 (1.5)	1 (0.4)
SPAF III[23]/1996	Warfarin (INR 1.2–1.5) plus aspirin (325 mg)	521	13 (2.4)	3 (0.6)
	Warfarin (INR 2.0–3.0)	523	12 (2.1)	2 (0.4)
Morocutti et al[272]/1997	Warfarin (INR 2.0–3.5)	454	6.0	1.0
	Indobufen	462	1.0	0
Gulløv et al[24]/1999,[268]/1998	Warfarin (INR 2.0–3.0)	170	1.1	0.3
	Warfarin (1.25 mg)	167	0.8	0
	Warfarin plus aspirin (1.25 mg + 300 mg)	171	0.3	0
	Aspirin (300 mg)	169	1.4	0.3
Pengo et al[274]/1998	Warfarin (INR 2.0–3.0)	153	2.6	NR
	Warfarin (1.25 mg)	150	1.0	NR
Hellemons et al[270]/1999	Phenprocoumon/acenocoumarol (INR 2.5–3.5)	131	0.5	NR
	Phenprocoumon/acenocoumarol (INR 1.1–1.6)	122	1.4	NR
	Aspirin (150 mg)	141	1.4	NR
Yamaguchi[25]/2000	Warfarin (INR 1.5–2.1)	60	0	NR
	Warfarin (INR 2.2–3.5)	55	6.6§	NR
Pengo et al[273]/2003	Warfarin (target INR, 2)	52	1.2	0
	Warfarin (target INR, 3)	55	2.0	0.8
Pérez-Gómez et al[275]/2004	Warfarin intermediate risk (INR 2.0–3.0)	237	1.80	0
	Triflusal intermediate risk	242	0.35	0
	Warfarin plus triflusal intermediate risk	235	0.92	0.18
	Warfarin high risk (INR 2.0–3.0)	259	2.13	0
	Warfarin plus triflusal high risk	236	2.09	0.17
ACTIVE W[100]/2006	Warfarin (INR 2.0–3.0)	3,371	2.21	0.26
	Aspirin (75–100 mg) and clopidogrel	3,335	2.42	0.17
SPORTIF III[282]/2003	Warfarin (INR 2.0–3.0)	1,703	1.8	0.3
	Ximelagatran (36 mg bid)	1,704	1.3	0.2
SPORTIF V[283]/2005	Warfarin (INR 2.0–3.0)	1,962	3.1	0
	Ximelagatran (36 mg bid)	1,960	2.5	0.1

*Boston = Boston Aerea Anticoagulation Trial for Atrial Fibrillation Investigators; EAFT = European Atrial Fibrillation Trial; SPAF = Stroke Prevention in Atrial Fibrillation; ACTIVE = Atrial fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events; SPORTIF = Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation; see Table 6 for expansion of abbreviation.

†Data are presented as % per year or No. (%) unless otherwise indicated.

‡$p = 0.04$.

§$p < 0.01$.

fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W)[100] [Table 7]. The study population consisted of 6,706 patients with atrial fibrillation and at least one more risk factor for stroke. The annual rate of major bleeding was similar, 2.21% in the warfarin group and 2.42% in the aspirin-clopidogrel group. ICH occurred at an annual rate of 0.36% in the warfarin group and 0.12% in the aspirin-clopidogrel group ($p = 0.036$), but the rate of minor bleeding was lower in the warfarin group (11.4%) than in the aspirin-clopidogrel group (13.6%) [$p = 0.0009$]. The annual rate of fatal

bleeding was low in both groups, 0.26% in thewarfarin group and 0.17% in the aspirin-clopidogrel group. An interaction was identified between anticoagulation therapy already at entry into the study and major bleeding. Thus, patients with experience from VKA therapy did generally better on warfarin than on aspirin-clopidogrel with the reverse result in warfarin-naïve patients.[100]

Because ≥ 50% of patients with atrial fibrillation are > 75 years old, the risk-benefit of oral anticoagulant therapy in this clinical subgroup is of particular interest. One study (SPAF II)[281] raised concern that the risk for warfarin-related bleeding, especially ICH, may be substantially increased in patients ≥ 75 years. The annual rate of major bleeding while receiving warfarin was 2.3%, compared with 1.1% for patients receiving aspirin 325 mg/d. However, the rate of major warfarin-related bleeding was 4.2% in patients ≥ 75 years old, compared with 1.7% in younger patients; the corresponding annual rates for ICH were 1.8% and 0.6%, respectively. The reason why these rates are substantially higher than those observed in the other clinical trials of warfarin in patients with atrial fibrillation is likely related to the intensity of anticoagulant therapy: virtually all ICHs in SPAF II, as in the other clinical trials, were associated with an INR > 3.0.[281] In contrast, in the SPAF III trial (targeted INR, 2.0–3.0), the mean age was 71 years and the annual rate of ICH was 0.5%.[23] In conclusion, stroke prophylaxis in atrial fibrillation with VKA confers an increased risk of major hemorrhage compared to aspirin, but the absolute increase is < 1%/yr.

VKA vs Oral Thrombin Inhibitor: The oral thrombin inhibitor ximelagatran was compared with warfarin in two large RCTs.[282,283] In a prespecified pooled analysis, the annual rate of major and minor bleeding was 38.7% in the warfarin group and 31.7% in the ximelagatran group ($p < 0.0001$). Ximelagatran was subsequently withdrawn from all trials due to hepatic adverse events. Another oral thrombin inhibitor, dabigatran, is at present under evaluation vs warfarin in a trial that will recruit at least 18,000 patients.

Low vs Moderate Intensity of VKA: Two trials have evaluated a fixed low dose of warfarin (1.25 mg/d) in atrial fibrillation.[263,268,274] These trials were stopped early because of the SPAF III trial[23] results that demonstrated that low-intensity warfarin (*ie*, INR < 1.5) was insufficient for stroke prevention. The rates of major bleeding were low in these studies (Table 7).

The risk of warfarin therapy at a targeted INR of approximately 2 vs INR of approximately 3 has been evaluated in two randomized trials in patients with atrial fibrillation.[25,273] Yamaguchi[25] compared warfarin therapy at a targeted INR of 1.5–2.1 with warfarin therapy at a targeted INR of 2.2–3.5. Major bleeding occurred in 6 of 55 patients in the conventional-intensity group (annual rate 6.6%), compared with none of the 60 patients (0%) in the low-intensity group ($p = 0.01$). The 6 patients with major bleeding were all elderly (mean, 74 years) and older than the other 109 patients without major bleeding (mean, 66 years) [$p < 0.01$].

Pengo et al[273] compared warfarin therapy with INR target 2 (low intensity) vs INR target 3 (moderate intensity) in 103 patients with mitral stenosis and atrial fibrillation. Major bleeding and ICH occurred in three and zero patients (1.2%/yr and 0%/yr), respectively, in the low-intensity group and in five and three patients (2.0%/yr and 1.2%/yr), respectively, in the moderate-intensity group. Two of the ICHs were fatal. In both studies the number of patients was too small to allow for any conclusions about the relative effectiveness of the different intensities of anticoagulation.

A systematic review[265] compared the rates of stroke, intracranial bleeding, and major bleeding from studies of patients treated in actual clinical practice with the pooled data from RCTs. Patients in clinical practice were older and had more comorbid conditions than the patients in clinical trials. Nevertheless, the rates of ischemic stroke were similar between clinical practice and the clinical trials (1.8 and 1.4 per 100 patient-years, respectively), as were the corresponding rates of ICH (0.1 and 0.3 per 100 patient-years, respectively) and major bleeding (1.1 and 1.3 per 100 patient-years, respectively).[265] There was a higher rate of minor bleeding in clinical practice (12.0 per 100 patient-years) than in clinical trials (7.9 per 100 patient-years) [$p = 0.002$].

UFH and VKA vs LMWH in Cardioversion of Atrial Fibrillation: For atrial fibrillation with a duration of > 48 h, common practice has been to provide prophylaxis against systemic embolism with a VKA for 4 weeks before and after cardioversion. The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) study[284] evaluated the possibility to omit the long treatment with VKA before cardioversion by excluding a thrombus in the left atrial appendage with transesophageal echocardiography (TEE). Patients without evidence of a thrombus were treated with UFH if they were hospitalized or with warfarin as outpatients for < 24 h before the cardioversion, followed by 4 weeks of warfarin afterwards. This strategy was feasible in 425 of 619 patients (69%). In the control arm, 603 patients received standard anticoagulation with warfarin for 4 + 4 weeks without TEE. Major bleeding was observed in 0.8% in the TEE group and in 1.5% in the control group. Major or minor bleeding

occurred in 2.9% in the TEE group and in 5.5% in the control group ($p = 0.03$). The results from a follow-up trial (ACUTE II) have not been reported yet.

In the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial,[285] the treatment was streamlined further, comparing UFH and the VKA phenprocoumon with LMWH alone, in 496 patients with or without the TEE strategy. Enoxaparin was initially given at a dose of 1 mg/kg bid for 3–8 days, followed by 40 mg (body weight < 65 kg) or 60 mg (body weight ≥ 65 kg) for the rest of the study period. Major bleeding occurred in 2.4% of the 212 patients treated with UFH and phenprocoumon compared to 0.8% among the 216 patients treated with enoxaparin.[285]

In conclusion, stroke prophylaxis in atrial fibrillation using VKA confers a risk of major hemorrhage and ICH that is higher than with placebo or aspirin but the difference is small in absolute numbers. The risk of bleeding is similar with warfarin as with the combination of aspirin and clopidogrel. LMWH appears to cause less bleeding than VKA for the short-term anticoagulation in association with cardioversion.

2.3 Prosthetic Heart Valves

Four metaanalyses have examined studies including only patients with prosthetic heart valves on long-term VKA therapy.[286–289] Three of the analyses aimed at evaluating risks and benefits of a combination of VKA and antiplatelet agent vs anticoagulant alone and included five,[286] 10,[288] and 11 studies,[287] respectively. In the metaanalysis by Cappelleri et al,[286] the combined regimen increased the risk of any hemorrhage by 65% and of major hemorrhage by 49%, but only the former difference was statistically significant. The metaanalysis by Massel and Little[288] was updated in 2003 by Little and Massel,[287] adding one more study to the material. The risk of major hemorrhage was increased by the addition of antiplatelet regimens ($p = 0.003$), and when one of the trials with a higher intensity in the group treated with VKA alone was excluded the difference increased further ($p = 0.0003$). There was evidence that 100 mg of aspirin compared to higher doses provided a safer combination. A metaanalysis by Pouleur and Buyse,[289] based on six trials evaluating the efficacy and safety of adding dipyridamole to anticoagulant therapy, showed that the risk of hemorrhage was identical in the two groups.

The studies included in these analyses differed regarding the targeted intensity of anticoagulation (in many of the studies based on a best guess of the reagents used to perform the prothrombin time), the antiplatelet agent (aspirin or dipyridamole), and the dose of aspirin (100, 500, or 1,000 mg), which increases the heterogeneity of the findings. These trials are described in greater detail below.

Bleeding rates in patients receiving different regimens with long-term VKA therapy for prosthetic heart valves have been reported from 15 randomized clinical trials.[16–19,78–80,290–297] The targeted intensity of oral anticoagulant therapy was not defined with the INR in the first five trials.[291–294,297]

In all 10 randomized trials of long-term VKA therapy in patients with mechanical heart valves since 1990, the targeted intensity of anticoagulation was reported using the INR.[16–19,78–80,290,295,296] The rates of major bleeding reported in these trials (Table 8) is, however, based on somewhat different definitions, and the time within the target INR range varied from 35 to 86%. Altman et al[17] failed to define major bleeding,[17] and Pruefer et al[296] failed to provide numerical data by treatment group. Four trials compared different intensities of VKAs.[16,19,290,295,296] Saour et al[19] randomized patients to either warfarin therapy at a targeted INR of 2.65 or very-high-intensity warfarin therapy (targeted INR, 9.0). The rate of major bleeding in the former treatment arm was 3.3% compared with 7.2% in the latter arm during 3.5 years of follow-up ($p = 0.27$). In the trial conducted by Acar et al,[290] 380 patients were randomized to treatment with acenocoumarol at a targeted INR of 2.0–3.0 or the same medication at a targeted INR of 3.0–4.5. The rate of major bleeding in the lower-intensity group was 9.0% compared with 12.0% in the higher-intensity group > 2.2 years ($p = 0.29$). In a trial conducted by Pengo et al,[16] 205 patients were randomized to treatment with either warfarin or acenocoumarol at a targeted INR of 2.5–3.5 or the same medications at a targeted INR of 3.5–4.5 and followed for a mean of 3 years. The rate of major bleeding was 3.8% in the former group compared with 11% in the latter group ($p = 0.019$). In the German Experience with Low Intensity Anticoagulation (GELIA) study by Hering et al,[295] 2,735 patients were randomized to treatment with VKAs, about 90% of which was phenprocoumon, at a targeted INR of 2.0-3.5, or 2.5-4.0, or 3.0-4.5 for a mean of 2.5 years. Among the 2,024 patients with the prosthesis in the aortic position, there was a trend to more severe bleedings with higher intensity, 0.28%, 0.47%, and 0.78%, respectively ($p = 0.14$). Among the 553 patients with the prosthesis in the mitral position, the pattern was in the opposite direction, 0.92%, 0.46%, and 0.24%, respectively ($p = 0.36$), but the number of events was very small.

Four trials have addressed the addition of aspirin to VKAs. In a blinded trial, Turpie et al[79] compared warfarin (INR, 3.0–4.5) with warfarin plus 100 mg aspirin. The rate of major bleeding was 10.3% in the

Table 8—*Prosthetic Heart Valves: Clinical Description and Results (Section 2.3)*

Study/yr	Treatment	No. of Patients (Patient-Years)	Bleeding†		
			Major	Fatal	Intracranial
Saour et al[19]/1990	Warfarin (INR 2.65)	122 (421)	1.0	0	0
	Warfarin (INR 9.0)	125 (436)	2.1	0.5	0.5
Turpie et al[79]/1993	Warfarin (INR 3.0–4.5) plus placebo	184 (~ 462)*	4.1	0.7	0.7
	Warfarin (INR 3.0–4.5) plus aspirin 100 mg	186 (~ 462)*	5.2	0.6	1.5
Altman et al[80]/1996	Acenocoumarol (INR 2.0–3.0) plus aspirin 100 mg	207 (416)	3.6	0.5	0.2
	Acenocoumarol (INR 2.0–3.0) plus aspirin 650 mg	202 (366)	5.2	0.3	0.3
Acar et al[290]/1996	Acenocoumarol (INR 2.0–3.0)	188 (414)	4.1	0.2	0.5
	Acenocoumarol (INR 3.0–4.5)	192 (422)	5.5	0.2	0.7
Pengo et al[16]/1997	Warfarin (INR 2.5–3.5)	104 (333)	1.2 ($p < 0.05$)	0	0.3
	Warfarin (INR 3.5–4.5)	101 (289)	3.8	0.3	0.3
Meschengieser et al[18]/1997	Acenocoumarol (INR 2.5–3.5) plus aspirin 100 mg	258 (529)	1.1	0	0
	Acenocoumarol (INR 3.5–4.5)	245 (471)	2.3	0.2	0.6
Laffort et al[78]/2000	VKA (INR 2.5–3.5)	120 (120)	8.3 ($p = 0.02$)	3	0
	VKA (INR 2.5–3.5) plus aspirin 200 mg	109 (109)	19.2	3	0
Hering et al[295]/2005	VKA (INR 2.0–3.5)	857 (2,205)	0.41	NR	NR
	VKA (INR 2.5–4.0)	870 (2,142)	0.47	NR	NR
	VKA (INR 3.0–4.5)	850 (2,073)	0.68	NR	NR

*Approximate values estimated from mean follow-up.
†Data are presented as %/yr.

warfarin alone group compared with 12.9% in the warfarin plus aspirin group after 2.5 years of follow-up ($p = 0.43$). Altman et al[80] compared two different doses of aspirin (100 mg daily vs 650 mg daily) in patients receiving acenocoumarol at an INR of 2.0–3.0 followed for an average of 24.1 and 21.7 months, respectively. The rate of major bleeding in the lower-dose aspirin group was 7.2% compared with 9.4% in the higher-dose group ($p = 0.4$). Meschengieser et al[18] compared acenocoumarol alone (INR, 3.5-4.5) with a combination of acenocoumarol at a lower intensity (INR, 2.5-3.5) plus 100 mg aspirin. The rate of major bleeding was 4.5% in the monotherapy group compared with 2.3% in the combination therapy group after a median follow-up of 23 months ($p = 0.27$). The trial of Laffort et al[78] is unique in its homogeneity, since only patients with St. Jude medical valve prosthesis in the mitral position were included. Treatment with VKAs alone (INR, 2.5-3.5) was compared with a combination of VKA and aspirin (200 mg daily) for 1 year, starting immediately after surgery. This may explain the high rate of major bleeding which was 8.3% with monotherapy and 19.2% with the combination ($p = 0.02$).

Table 8 shows the annual bleeding rates regarding major, fatal, or ICH. Cannegieter et al[30] reported the results of a retrospective study in 1,608 patients who received VKA therapy for mechanical heart valves. The rate of intracranial and spinal bleeding was 0.57%/yr and the rate of major extracranial bleeding was 2.1%/yr. Cannegieter et al[298] also published the results of a metaanalysis of 46 studies (randomized trials and case series) of patients who received VKAs for mechanical valves. The incidence of major bleeding was 1.4%/yr.[298]

In conclusion, the addition of aspirin to VKA increases the risk of major hemorrhage compared with VKA alone for prophylaxis against thromboembolism in patients with mechanical heart valves. The risk of hemorrhage using VKA alone increases with the intensity of treatment.

2.4 Ischemic Cerebral Vascular Disease

2.4.1 Acute Stroke

UFH, LMWH, VKA, Aspirin: Direct Comparisons of Any of the Four: Approximately 20 mostly small studies have compared early anticoagulant therapy with control in patients with acute ischemic stroke. Gubitz and colleagues[299] conducted a Cochrane systematic review that summarized the results of studies that were published by 1999 (approximately 23,000 patients). The trials in this overview evaluated UFH, LWMH, heparinoid, oral anticoagulants, and direct thrombin inhibitors administered in differing doses (*eg*, prophylactic doses for VTE, therapeutic doses for stroke); and by different routes (*eg*, subcutaneously or IV). The review found that acute anticoagulation had the following effects on the risk of bleeding: (1) increased symptomatic intracranial bleeding approximately 2.5-fold (an excess of 9 per 1,000 patients) and (2) increased major extracranial bleeding approximately threefold (an excess of 9 per

Table 9—*Risk of Intracranial and Major Extracranial Bleeding (14 Days) for Subcutaneous Heparin in Acute Ischemic Stroke: Clinical Description and Results (Section 2.4.1.1)

Treatment	Patients, No.	Total†	Bleeding†		
			Intracranial	Extracranial	Fatal
Heparin 12,500 U bid plus aspirin 300 mg qd	2,430	75 (3.1)	42 (1.7)	33 (1.4)	10 (0.4)
Heparin 5,000 U bid plus aspirin 300 mg qd	2,431	39 (1.6)	19 (0.8)	20 (0.8)	9 (0.4)
Heparin 12,500 U bid	2,426	76 (3.2)	43 (1.8)	33 (1.4)	12 (0.5)
Heparin 5,000 U bid	2,429	26 (1.1)	16 (0.7)	10 (0.4)	9 (0.4)
Aspirin 300 mg qd	4,858	49 (1.0)	26 (0.5)	23 (0.5)	13 (0.3)
Control	4,859	29 (0.6)	15 (0.3)	14 (0.3)	5 (0.1)

*From the International Stroke Trial.[117]
†Data are presented as No. (%).

1,000 patients). As the International Stroke Trial[117] with > 19,000 patients accounted for > 75% of patients in the analysis, it will be considered further.

In the International Stroke Trial,[117] patients with acute ischemic stroke were treated with aspirin (300 mg/d), subcutaneous UFH (5,000 U bid or 12,500 U bid), both, or neither (Table 9). Heparin was associated with a dose-dependent increase of both intracranial and extracranial bleeding (all major bleeds: control 0.6%; heparin 5,000 U bid, 1.1%; heparin 12,500 U bid, 3.2%), which at the higher doses more than offset the antithrombotic benefit. Patients who had the highest risk of recurrent ischemic stroke also had the highest risk of ICH. For example, in patients with acute ischemic stroke and atrial fibrillation, although the frequency of hemorrhagic stroke after 14 days was 2.1% (32 of 1,557 patients) with heparin therapy (either dose) compared with 0.4% (7 of 1,612 patients) without heparin therapy, there was no difference in the combined end point of recurrent ischemic or hemorrhagic stroke. More recently, the Therapy Of Patients with Acute Stroke (TOPAS) study[300] compared four doses of a LMWH (certoparin) in 400 patients with ischemic strokes and found a trend toward more major bleeding with the highest dose compared to the three lower doses combined (9.0% vs 2.0%).

UFH or LMWH vs Antiplatelet Agents: Four trials[117,301–303] have compared anticoagulants with antiplatelet agents in patients within 14 days of acute ischemic stroke. Investigators compared UFH[117,303] and LMWH[301,302] in low doses[117,303] or high doses[117,301,302] with aspirin[117,301,302] or aspirin and dipyridamole.[303] Three trials[117,301,303] included cardioembolic and noncardioembolic strokes, whereas one study[302] was confined to cardioembolic strokes. Berge and Sandercock[304] have combined the findings of these four studies, with data from 16,558 patients (88% from the IST)[117] in a Cochrane systematic review. The review found that compared to antiplatelet therapy, anticoagulants increase symptomatic ICH 2.3-fold (an excess of 10 per 1,000 patients) and increase major extracranial hemorrhages 1.9-fold (an excess of 5 per 1,000 patients treated). The increase in major bleeding with anticoagulants was mostly confined to high-dose regimens.[304]

In a randomized double-blind placebo-controlled study of direct thrombin inhibition in acute ischemic stroke, argatroban at a bolus dose of 100 μg/kg, followed by continuous IV infusion at 3 μg/kg/min (high dose, n = 59) or 1 μg/kg/min (low dose, n = 58), significantly prolonged APTT without increasing ICH or major bleeding at 30 days.[166] Symptomatic ICH occurred at 5.1% with high-dose argatroban compared to 3.4% with low-dose argatroban and 0% with placebo ($p \leq 0.18$). There were no significant differences in asymptomatic ICH between groups. The study was not sufficiently powered to evaluate efficacy.

In conclusion, UFH or LMWH given within 14 days of ischemic stroke increases the risk of intracranial and extracranial hemorrhage approximately twofold compared to aspirin or placebo. The magnitude of the increased risk is dose dependent.

Thrombolytic Therapy vs Placebo: Thrombolytic therapy improves the functional outcome in acute ischemic stroke, but it increases the risk of death and cerebral hemorrhage. Wardlaw[305] identified 17 RCTs of thrombolytic therapy vs control in 5,216 patients (including provisional data from the Altepase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS] A and B and Recombinant Prourokinase in Acute Cerebral Thromboembolism [PROACT] II trials[184]). Eight trials tested recombinant tissue plasminogen activator (rt-PA) in 2,889 patients involving 56% of all data. Most of the data were from trials testing thrombolysis up to 6 h after stroke. Overall there was an

increase in the odds of symptomatic ICH (OR, 3.53; 95% CI, 2.70–4.45) (slightly less with rt-PA) and death (OR, 1.85; 95% CI, 1.48–2.3) within the first 10 days of thrombolytic therapy despite a significant reduction (OR, 0.83; 95% CI, 0.73–0.94) in patients with a poor functional outcome at the end of follow-up.[305]

A pooled analysis of individual patient data (n = 2,775) from six controlled trials of IV tPA vs placebo[306] reported hemorrhage in 82 (5.9%) rt-PA patients and 15 (1.1%) controls ($p < 0.0001$); hemorrhage was not associated with delay from stroke onset to start of treatment but it was associated with rt-PA treatment ($p = 0.0001$) and with age ($p = 0.0002$).

Addition of antiplatelet therapy to thrombolytic therapy in the setting of acute cerebral ischemia increased the risk of hemorrhage without providing additional benefit. For example, a *post hoc* analysis of the Multicenter Acute Stroke Trial-Italy (MAST 4)[307] comparing streptokinase plus aspirin (n = 156) with streptokinase alone (n = 157) found that the combined regimen significantly increased the risk of early death (day 3–10), which was mainly cerebral (OR, 2.0; 95% CI, 1.3–3.7) and was associated with hemorrhagic transformation (OR, 2.2; 95% CI, 1.0–5.0). Thus, thrombolytic therapy for acute cerebral ischemia within 3 h of symptoms onset is associated with improved long-term functional outcomes, but the severity of initial deficit and the presence of early ischemic changes on CT scan are associated with increased risk of hemorrhagic infarction.

2.4.2 Secondary Prophylaxis After Ischemic Stroke

VKA vs Aspirin: A Cochrane systematic review comparing VKA vs aspirin as secondary prophylaxis after stroke of arterial origin included 5 trials with 4,076 patients.[308] The RR of major bleeding with VKA was 1.27 (95% CI, 0.79–2.03) for low intensity treatment (INR, 1.4–2.8), 1.19 (95% CI, 0.59–2.41) for moderate intensity (INR, 2.1–3.6), and 9.0 (95% CI, 3.9–21) for high intensity (INR, 3.0–4.5). In the largest of these trials, the Warfarin-Aspirin Recurrent Stroke Study (WARSS),[309] warfarin adjusted to an INR of 1.4 to 2.8 was compared with aspirin at a dose of 325 mg in 2,206 patients. The annual rate of major hemorrhage was 2.2% with warfarin and 1.5% with aspirin (OR, 1.48; 95% CI, 0.93–2.44), and there were significantly more minor hemorrhages with warfarin (20.8% vs 12.9%; OR, 1.61; 95% CI, 1.38–1.89).

One study that compared warfarin (INR, 2.0–3.0) with aspirin at a dose of 1,300 mg/d after transitory ischemic attack or stroke caused by an intracranial arterial stenosis in 569 patients[310] was discontinued prematurely due to safety concerns. The annual rate of major hemorrhage was 1.8% with aspirin compared to 5.0% with warfarin (hazard ratio, 0.39; 95% CI, 0.18–0.84). In conclusion, secondary prophylaxis with warfarin after noncardiogenic stroke is associated with a higher risk of major hemorrhage than with aspirin, particularly in patients with intracranial arterial stenosis.

2.5 ST-Segment Elevation Myocardial Infarction

2.5.1 Thrombolytic Therapy

A metaanalysis published in 1994 addressing the risk of ICH induced by thrombolytic therapy included all studies with at least 1,000 patients randomized.[311] Compared to placebo, thrombolytic therapy was associated with four additional strokes per 1,000 patients during the first 2 days. Two of the four strokes resulted in early death and one of the four caused moderate-severe disability. These proportions were similar in the more recent GUSTO I trial.[312] The mortality rate of ICH in patients treated with thrombolysis after myocardial infarction was 60% at 30 days and, in addition, 27% of the patients became disabled.[312] In a model for evaluation of individual risk of ICH based on data from other trials, Simoons et al[186] concluded that thrombolytic therapy (with streptokinase) in a patient without additional risk factors for bleeding yielded a probability of ICH of 0.26%. For each additional risk factor present, such as old age, low body weight, and hypertension, the probability increased to 0.96%, 1.32%, and 2.17% for 1, 2, and 3 additional factors.[186] The risk of major, fatal, and intracranial hemorrhage associated with thrombolytic therapy in the large placebo-controlled studies of myocardial infarction is shown in Table 10.

The most common severe, noncerebral hemorrhages appear to be related to procedures–coronary artery bypass surgery (0.3%) or groin hematoma (0.2%).[189] Nonprocedure-related severe bleedings are GI (0.3%) or retroperitoneal (0.2%).[191] These rates were obtained from the GUSTO-I study, which also indicated that patients with moderate or severe bleeding had a higher 1-month mortality than the total study population (20% vs 7%), as well as a higher rate of serious complications such as reinfarction (27% vs 4%), cardiogenic shock (30% vs 6%), tamponade (19% vs < 1%), or stroke (22% vs 1%).[62] In conclusion, thrombolytic therapy for ST-segment elevation myocardial infarction is associated with a twofold to threefold increase of major bleeding and intracranial hemorrhage.

Table 10—*Myocardial Infarction and Thrombolytic Therapy: Clinical Description and Results (Section 2.5.1)**

Study/yr	Treatment	No. of Patients	Bleeding		
			Major	Fatal	Intracranial
GISSI-1[358]/1991	Streptokinase 1.5 MU/1 h	5,860	NR	NR	0.14
	Placebo	5,852	NR	NR	0
ISIS-2[200]/1988	Streptokinase 1.5 MU/1 h	4,300	0.5†	NR	0.05
	Streptokinase and aspirin 160 mg	4,292	0.5†	NR	0.1
	Aspirin 160 mg	4,295	0.2	NR	0
	Placebo	4,300	0.3	NR	0
ISAM[359]/1986	Streptokinase 1.5 MU/1 h	859	NR	NR	0.5
	Placebo	882	NR	NR	0
EMERAS[360]/1993	Streptokinase 1.5 MU/1 h	2,234	1.0‡	NR	0.6§
	Placebo	2,259	0	NR	0.1
USIM[361]/1991	Urokinase 1 MU twice/1 h	1,128	0.44	NR	0.2
	Placebo	1,073	0.37	NR	0.1
LATE[362]/1993	Alteplase 100 mg/3 h	2,836	0.78	0	2.3
	Placebo	2,875	0.45	0	1.2
ASSET[363]/1988	Alteplase 100 mg/3 h	2,516	1.4	NR	0.3
	Placebo	2,495	0.5	NR	0.1
AIMS[364]/1988	Anistreplase 30 U/5 min	502	NR	NR	0.4
	Placebo	502	NR	NR	1.0

*Data are presented as % unless otherwise indicated. See Table 6 for abbreviation not used in the text.
†Streptokinase groups combined vs nonstreptokinase, $p < 0.001$.
‡$p < 0.0001$.
§$p < 0.05$.

2.5.2 Heparin, LMWH, and Fondaparinux

Addition of UFH to thrombolytic therapy in the early large trials did not increase the risk of ICH.[313] The rate of ICH was 0.3% with streptokinase alone, 0.2% with streptokinase and heparin, 0.4% with tPA alone, and 0.4% with tPA and heparin. The dose of heparin was 12,500 U subcutaneously bid. In later trials the rate of ICH was between 1% and 2%. The reason was probably excessive dosing of heparin, which was left to the discretion of the investigators. Weight-adjusted doses of 18 U/kg/h, as recommended for VTE, or additional heparin during more commonly performed rescue angioplasty resulted in daily doses > 30,000 U. The protocol had to be amended with a reduction of the heparin dose, after which a decline in the risk of ICH was seen in all three trials: TIMI-9B 1.87% before vs 1.07% after amendment,[314] GUSTO-IIB 0.92% before vs 0.71% after,[315] and TIMI-10B 2.8% before vs 1.16% after.[197]

In 1996, Collins et al[116] performed a metaanalysis of 26 studies with 73,000 patients that compared UFH, given subcutaneously or IV, with placebo. In the 7 studies with low-dose heparin (mean 12,000 U) there was no major bleeding. With UFH given at a high dose, the risk of major bleeding doubled compared to placebo (2.3% vs 1.1%, $p = 0.01$). When only trials, in which aspirin was given were selected, the rate of major bleeding was 1.0% with UFH compared to 0.7% with placebo ($p < 0.0001$). The reporting of major bleeding in the early studies was usually incomplete and the definitions varied widely.

A recent metaanalysis of 14 trials evaluated the efficacy and safety of UFH vs placebo, LMWH vs placebo, or UFH vs LMWH for patients with ST-segment elevation myocardial infarction and treated with aspirin and thrombolysis.[316] In the UFH trials this drug was given IV and in all trials the patients were also treated with thrombolysis and aspirin. In 4 trials with 1,239 patients UFH did not increase the risk of major bleeding compared to placebo (OR, 1.21; 95% CI, 0.67–2.18), but there was a small, nonsignificant increase in ICH (OR, 2.3; 95% CI, 0.6–9.0). In 4 trials with 16,943 patients LMWH increased the risk of major bleeding compared to placebo (OR, 2.70; 95% CI, 1.07–4.52) as well as the risk of ICH (OR, 2.2; 95% CI, 1.1–4.5). In the 6 trials with 7,098 patients with a direct comparison of LMWH vs. UFH there was a nonsignificant increase in the risk of major bleeding with LMWH (OR, 1.30; 95% CI, 0.98–1.72), no difference in ICH (OR, 1.18; 95% CI, 0.74–1.87) but there was a significant increase of minor bleeding (OR, 1.26; 95% CI, 1.12–1.43).

The largest study by far in this metaanalysis was the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE) trial[317] with > 15,000 patients that compared the LMWH reviparin to placebo. There was a significant excess of major bleed

ing with reviparin (0.9% vs 0.4%, $p < 0.001$) and a nonsignificant excess of ICH (0.3% vs 0.1%).

Théroux and Welsh[318] performed a metaanalysis, specifically comparing the LMWH enoxaparin and UFH. There was again a nonsignificant excess of major bleeding with enoxaparin (OR, 1.34; 95% CI, 0.97–1.87) and a significant increase of minor bleedings, but no difference in the incidence of ICH (OR, 1.00). The incidence of major bleeding was significantly higher when enoxaparin followed thrombolysis with tPA or tenecteplase than when it followed treatment with streptokinase ($p = 0.032$).

The CLARITY-TIMI 28 trial[319] was not included in these analyses. In this study 2,860 patients were randomized to receive clopidogrel or placebo, and it was to the discretion of the investigator to give any of the LMWHs or UFH. Since the distribution was very even between these two alternatives, the authors performed an analysis of the effect and safety after adjustment for all possible confounders. The rates of TIMI major bleeding and ICH were similar in the LMWH and UFH groups (1.6% vs 2.2% and 0.6 vs 0.8%, respectively). The rates of TIMI major bleeding in the subsets receiving active treatment with clopidogrel (LMWH 1.8% vs UFH 1.9%), who had PCI during hospitalization (LMWH 0.8% vs UFH 1.7%), who received a glycoprotein IIb/IIIa inhibitor (LMWH 2.7% vs UFH 1.6%), or who had a reduced glomerular filtration rate (LMWH 2.6% vs UFH 2.7%) were similar (all p values nonsignificant).[319] A small study comparing two different LMWHs, enoxaparin and tinzaparin, did not identify any significant difference in the risk of serious bleeding.[320]

In the OASIS 6 trial[150] with $> 12{,}000$ patients with ST-elevation myocardial infarction, randomization was to fondaparinux or placebo in patients for whom heparin was not considered indicated (stratum 1) and otherwise to fondaparinux or UFH (stratum 2). Fondaparinux was given at a dose of 2.5 mg subcutaneously qd for up to 8 days and UFH was given IV for up to 48 h. The rate of ICH was 0.2% in the groups with fondaparinux as well as in the placebo/UFH groups. Major bleeding occurred in 1.4% of fondaparinux-treated patients in stratum 1 compared to 2.0% with placebo ($p = 0.07$) according to criteria used in the OASIS 5[152] and in 1.0% vs 1.6% ($p = 0.6$), respectively, using the TIMI definition. In stratum 2, major bleeding was observed in 2.1% of patients receiving fondaparinux compared to 2.3% with UFH (nonsignificant) according to OASIS criteria, or in 1.1% in each group by the TIMI criteria. Finally, fatal bleeding occurred in 0.6% of patients treated with fondaparinux vs 0.8% of patients receiving placebo/UFH.

Thus, fondaparinux given once daily subcutaneously appears to be at least as safe as UFH given IV, in spite of longer duration of treatment. Between the heparins, UFH appears to be safer than LMWH as an adjunct to thrombolytic therapy.

2.5.3 DTIs vs Heparin

A metaanalysis of 11 RCTs between 1995 and 1999 with 35,970 patients compared the effect and safety of DTIs and UFH.[321] The analysis was based on individual patient data. Overall there was a nonsignificant reduction of ICH with DTIs compared to UFH (0.11% vs 0.16%; OR, 0.72; 95% CI, 0.42–1.13), and there was a significant reduction of major bleeding (1.9% vs 2.3%; OR, 0.75; 95% CI, 0.65–0.87).

However, the results differed when the DTIs were separated into the three classes: hirudin, bivalirudin, and small direct DTIs (Table 11). Hirudin, including desirudin and lepirudin, is an irreversible large, bivalent DTI; bivalirudin is a reversible large, bivalent DTI whereas the small DTI argatroban, efegatran, and inogatran are reversible and univalent, only attaching to the active site pocket of thrombin. None of these agents require the cofactor activity of antithrombin. Results from the GUSTO IIa[126] and r-Hirudin for Improvement of Thrombolysis (HIT)-III study,[322] which were not included in the metaanalysis, support the finding that hirudin confers a higher risk of bleeding than UFH (1.3% vs 0.7% ICH in GUSTO IIa, 2.7% vs 0.0% ICH in HIT-III, and 3.4% vs 1.9% major bleeding in HIT-III).

Another metaanalysis[323] compared bivalirudin with UFH, based on data from six trials with 5,674 patients, mainly undergoing elective PCI but some also with acute coronary syndromes. Again, there was a reduction of in-hospital major hemorrhage with bivalirudin (OR, 0.41; 95% CI, 0.32–0.52), corresponding to 58 fewer events per 1,000 treated patients.

Table 11—*Acute Coronary Syndromes and Adjunct Anticoagulant Therapy (Section 2.5.3)**

Hirudin	Bivalirudin	Small DTIs	UFH	OR (95% CI)
Major bleeding, %				
1.7			1.3	1.28 (1.06–1.55)
	4.2		9.0	0.44 (0.34–0.56)
		0.7	1.3	0.55 (0.25–1.20)
ICH, %				
0.14			0.17	0.80 (0.44–1.45)
	0.04		0.09	0.47 (0.04–5.20)
		0.0	0.27	0.10 (0.00–2.11)

*Metaanalysis based on individual patient data.[321]

Subsequent to this metaanalysis, HERO-2[154] enrolled > 17,000 patients with ST-elevation myocardial infarction evaluating 1.5 million units of streptokinase and either bivalirudin or UFH in a bolus dose before and a 48-h IV infusion after thrombolysis. There was a trend to increased risk of severe bleeding with bivalirudin compared to UFH (0.7% and 0.5%, respectively; p = 0.07) and of ICH (0.6% and 0.4%, respectively; p = 0.09) and there was a significantly higher rate of moderate and mild bleeding (OR, 1.32; 95% CI, 1.00–1.74; and OR, 1.47; 95% CI, 1.34–1.62, respectively). These results contradict those from the metaanalysis by Kong et al,[323] but in the latter there were only two small studies with patients suffering from myocardial infarction and the dose of bivalirudin was generally lower in those studies.

In conclusion, the irreversible DTI hirudin and its closest derivatives confer an increased risk of bleeding compared to UFH in patients with ST-segment elevation myocardial infarction. In patients with unstable angina, bivalirudin or the small DTIs appear to be safer than UFH.

2.5.4 Secondary Prophylaxis With Anticoagulant Agents

Several recent metaanalyses have examined addition of a VKA to the standard secondary antithrombotic prophylaxis after myocardial infarction with aspirin. Rothberg et al[82] performed a metaanalysis of 10 trials with 5,938 patients treated for an average of 1.9 years. The annual incidence of major bleeding was higher in patients with warfarin added to aspirin than in those with aspirin alone (rate ratio 2.5, 95% CI, 1.7–3.7). Hart et al[77] found in a metaanalysis of 6 trials with 3,874 patients that addition of warfarin to aspirin more than doubled the risk of ICH compared to aspirin alone (RR 2.4; 95% CI, 1.2–4.8).

Anand and Yusuf[324] conducted a metaanalysis of trials evaluating VKA in patients with coronary artery disease. Trials were stratified based on the intensity of the VKA and on the use of aspirin. In 16 trials (10,056 patients) of high-intensity therapy (INR, 2.8-4.8), the reduction in mortality and thromboembolic complications was offset by a sixfold increase (95% CI, 4.4- to 8.2-fold) in major bleeding. For moderate-intensity therapy (INR, 2-3) vs control (four trials, 1,365 patients), the RR for major bleeding was 7.7 (95% CI, 3.3-18). For moderate-to-high-intensity therapy (INR ≥ 2) vs aspirin (seven trials, 3,457 patients), there was a RR of 2.4 (95% CI, 1.6-3.6) for increase in major bleeding. For low-intensity therapy (INR < 2.0) and aspirin vs aspirin alone (three trials, 8,435 patients), the RR for major bleeding was 1.3 (95% CI, 1.0-1.8) with no significant reductions in mortality or cardiovascular events.

The most recent metaanalysis by Andreotti et al[325] included 16 trials with 25,307 patients and found that adding VKA to aspirin did not significantly increase the incidence of ICH. In studies with INR target 2 to 3 the increased risk of major bleeding (OR, 2.32; 95% CI, 1.63–3.29), corresponding to number needed to harm = 100, did not offset the reduction in major events (all death, myocardial infarction, thromboembolic stroke; OR 0.73, 95% CI 0.63–0.84), corresponding to number needed to treat = 33.

There are 13 published randomized trials[326–340] of long-term VKA therapy in patients with acute myocardial infarction (Table 12). These 13 trials compared the following regimens: anticoagulant therapy was compared with placebo or control (n = 7),[327–329,333,335–339] anticoagulant therapy vs aspirin (n = 1),[331] anticoagulant therapy vs aspirin or placebo (n = 1),[330] fixed low doses of warfarin (1 mg or 3 mg) combined with aspirin vs aspirin alone (n = 1),[326] anticoagulant therapy alone or combined with aspirin vs aspirin alone (n = 2),[334,340] and anticoagulant therapy combined with aspirin vs aspirin (n = 1).[332] The frequency of major bleeding ranged from 0 to 10% and fatal bleeding ranged from 0 to 2.9%.

Smith et al[339] reported the results of a randomized trial that renewed interest in the long-term use of VKA after myocardial infarction. The targeted INR was 2.8 to 4.8. Five patients in the warfarin group (0.8%) had ICH, and three of these were fatal. Eight (1.3%) warfarin-treated patients experienced major extracranial bleeds. There were no major bleeds in the placebo group.

In a trial conducted by the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT)-1 investigators,[327] patients who had sustained a myocardial infarction were randomized to either VKA at a targeted INR of 2.8 to 4.8 or placebo. The mean follow-up was 37 months. Seventy-three patients (4.3%) in the anticoagulant group experienced major bleeding compared with 19 placebo-treated patients (1.1%). Three extracranial bleeds in the anticoagulant group were fatal; all were GI in origin. Cerebral hemorrhage was more common in patients who had been treated with VKA (17 cases, 1%), 8 of which were fatal, compared with 2 cerebral hemorrhages in placebo-treated patients, none of which were fatal. The rate of major bleeding in the anticoagulant-treated group was 1.5%/yr compared with 0.2%/yr in the placebo-treated group. This difference was statistically significant.[327]

Table 12—*Ischemic Heart Disease and VKA: Clinical Description and Results (Section 2.5.4)**

Study/yr	Treatment	Patients, No.	Bleeding	
			Major	Fatal
Sixty-Plus Reinfarction Study Research Group[337]/1980,[338]/1982	Acenocoumarin or phenprocoumon (INR 2.2–5.0)	439	18 (4.1)	6 (1.4)
	Placebo	439	1 (0.2)	1 (0.2)
EPSIM Group[331]/1982	Oral anticoagulants†	652	21 (3.2)	8 (1.2)
	ASA (500 mg tid)	651	5 (0.8)	4 (0.6)
Breddin et al[330]/1980	Phenprocoumon (INR 2.0–5.0)	320	NR	0
	ASA (500 mg tid)	317	NR	0
	Placebo	309	NR	0
Meuwissen et al[336]/1969	Phenprocoumon (INR 1.9–5.0)	68	0	0
	Placebo	70	0	0
Loeliger et al[335]/1967	Phenprocoumon (INR 2.0–5.0)	128	1 (0.8)	0
	Placebo	122	1 (0.8)	1 (0.8)
Bjerkelund[328]/1957,[329]/1963	Dicumarol (INR 1.3–2.1)	138	20 (14.5)	4 (2.9)
	No treatment	139	5 (3.6)	1 (0.7)
Harvald et al[333]/1962	Dicumarol (INR 1.5–2.1)	145	28 (19.3)	1 (0.7)
	Placebo	170	0	0
Smith et al[339]/1990	Warfarin (INR 2.8–4.8)	607	13 (2.1)	3 (0.5)
	Placebo	607	0	0
ASPECT[327]/1994	Nicoumalone/phenprocoumon (INR 2.8–4.8)	1,700	73 (4.3)‡	11 (0.6)§
	Placebo	1,704	19 (1.1)	0
CARS[326]/1997	Warfarin 3 mg (INR 1.2) + ASA 80 mg	3,382	75 (2.2)	NR
	Warfarin 1 mg (INR 1.0) + ASA 80 mg	2,028	42 (2.1)	NR
	ASA 160 mg	3,393	57 (1.7)	NR
ASPECT-2[340]/2002	ASA 80 mg	336	3 (1)	NR
	Phenprocoumon/acenocoumarol (INR 3.0–4.0)	325	3 (1)	NR
	Phenprocoumon/acenocoumarol (INR 2.0–2.5) + ASA 80 mg	332	7 (2)	NR
CHAMP[332]/2002	Warfarin (INR 1.5–2.5) + ASA 81 mg	2,522	1.28/100 patient-yr	NR
	ASA 162 mg	2,537	0.72/100 patient-yr	NR
WARIS II[365]/2002	Warfarin (INR 2.8–4.2)	1,216	0.68/patient-yr	5 (0.4)
	Aspirin 160 mg	1,206	0.17/patient-yr	0
	Warfarin (INR 2.0–2.5) + aspirin 75 mg	1,208	0.57/patient-yr	6 (0.5)

*Data are presented as No. (%) unless otherwise indicated. Sixty-plus = Sixty-Plus Reinfarction Study Research Group; ASA = aspirin; see Table 6 for expansion of abbreviation.
†A number of different oral anticoagulants.
‡$p < 0.01$.
§Median INR at 6 months of treatment. Warfarin was given as a fixed dose (1 mg or 3 mg).

The Coumadin-Aspirin Reinfarction Study (CARS)[326] compared long-term treatment using fixed low doses of warfarin (1 mg or 3 mg) combined with aspirin, 80 mg, to treatment with aspirin alone (160 mg) using a randomized, blinded study design. The median follow-up was 14 months. The median INR values 4 weeks and 6 months after beginning treatment were 1.27 and 1.19, respectively, for patients receiving 3 mg of warfarin with 80 mg of aspirin. Major hemorrhage, including those related to invasive procedures, occurred in 75 patients (2.0%/yr) receiving 3 mg of warfarin with 80 mg of aspirin, 42 patients (1.7%/yr) given 1 mg of warfarin with 80 mg of aspirin, and 57 patients (1.5%/yr) receiving aspirin alone. For spontaneous major hemorrhage (not procedure related), annual rates were 1.4% in the group receiving 3 mg of warfarin plus 80 mg of aspirin, 1.0% in the group receiving 1 mg of warfarin plus 80 mg of aspirin, and 0.74% in the group receiving 160 mg of aspirin alone.[326]

The Combination Hemotherapy and Mortality Prevention (CHAMP) study[332] compared the efficacy of warfarin (target INR, 1.5-2.5) with 81 mg of aspirin to 162 mg of aspirin alone in patients after myocardial infarction and who were followed for a median of 2.7 years. In the CHAMP study[332] major bleeding occurred more frequently in the combination therapy group than in the aspirin-alone group (1.28 events vs 0.72 events/100 patient-years; $p < 0.001$).

The ASPECT-2 trial[340] compared 80 mg of aspirin, high-intensity (INR, 3.0-4.0) VKA or combination of 80 mg of aspirin and moderated intensity (INR, 2.0-2.5) VKA in patients who had survived acute coronary events; the median follow-up was 12 months. Major bleeding rates were 1%, 1%, and 2% per patient-year in the aspirin, warfarin, and combination groups, respectively. The frequency of minor bleeding was 5%, 8%, and 15% per patient-year in the aspirin, warfarin, and combination groups, respectively.

The Warfarin Aspirin Reinfarction Study (WARIS)-II trial[334] compared the efficacy and safety of warfarin (target INR, 2.8-4.2), aspirin (160 mg), and the two combined (75 mg of aspirin with warfarin with target INR of 2.0-2.5) in a long-term, randomized, open multicenter study involving 3,606 patients after acute myocardial infarction (1,202 in each treatment group). The mean duration of follow-up was 4 years. Major nonfatal bleeding occurred in 0.62% of patients per treatment year in both warfarin groups and in 0.17% of patients receiving aspirin ($p < 0.001$). In conclusion, secondary prophylaxis after ST-segment elevation myocardial infarction with VKA increases the risk of major hemorrhage by 1–2%/yr compared to aspirin or placebo.

2.6 Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

2.6.1 Heparin, LMWH, and Fondaparinux

A metaanalysis published in 2003 that included 7 studies with > 11,000 participants randomized to UFH or LMWH[341] found no difference in major bleeds (RR 1.00; 95% CI, 0.80–1.24) or minor bleeds (RR 1.40; 95% CI, 0.66–2.90). Subsequently, a systemic overview of studies comparing the LMWH enoxaparin and UFH was performed.[342] Individual patient data were available from three trials and aggregate data from another three trials. Again, no significant difference in blood transfusion (OR, 1.01; 95% CI, 0.89–1.14) or major bleeding (OR, 1.04) was identified.

The OASIS-5 trial[152] compared fondaparinux 2.5 mg daily and the LMWH enoxaparin 1 mg/kg bid, both drugs injected subcutaneously, in > 20,000 patients. Patients treated with fondaparinux had a lower rate of major bleeding after 9 days, 2.2%, than those treated with enoxaparin, 4.1% ($p < 0.001$). This was reflected by a lower death rate during the first 30 days (2.9% vs 3.5%, $p = 0.02$). This difference was also true for major bleeding requiring surgical intervention, retroperitoneal hematoma, bleeding requiring transfusions, and bleeding associated with death at the end of the study (180 days). The authors also noted that patients with major bleeding during the hospitalization, irrespective of the allocated treatment, had a higher death rate (13.2% vs 2.8%) and a higher rate of other serious events (reinfarction: 11.9% vs 36%; stroke: 3.5% vs 0.7%) than those without bleeding. Whether this is due to interruption of all antithrombotic therapy to control the bleeding or to other mechanisms remains unclear. There was no difference in ICH between the treatment groups.[152] It may be that the therapeutic dose of enoxaparin, contrasting with the dose of fondaparinux used for prophylaxis against VTE in studies on orthopedic surgery, was responsible for the increased bleeding. If that is so, however, it then remains to be demonstrated that a lower, prophylactic dose of enoxaparin would retain the same efficacy.

In conclusion, for the same efficacy in unstable angina or non–ST-segment elevation myocardial infarction, fondaparinux at a dose of 2.5 mg/d causes less bleeding than a therapeutic dose of LMWH. The risk of major bleeding with LMWH and UFH is of the same magnitude.

2.6.2 DTIs vs Heparin

The metaanalyses discussed above[321,323] also included patients with unstable angina or non–ST-segment elevation myocardial infarction (see Section 2.5.3).

2.7 Percutaneous Coronary Intervention

2.7.1 Comparisons of UFH, LMWH, and DTIs

In a pooled analysis of heparin vs bivalirudin, specifically in patients with PCI, Ebrahimi et al[155] identified four trials with 11,638 patients. The incidence of major bleeding was reduced from 5.8% with UFH to 2.7% with bivalirudin ($p = 0.02$). Many of the patients had also received treatment with gpIIb/IIIa inhibitors.

Sinnaeve et al[343] evaluated the results of PCI with heparin or DTIs as anticoagulant in a database of 35,970 patients from 11 RCTs. In the PCI trials major bleeding was observed in 7.5% of the patients treated with UFH and in 2.6% of the patients receiving a DTI ($p < 0.0001$). In the trials that primarily enrolled patients with acute coronary syndrome and who ended up having PCI performed, the incidence of major bleeding was the same with the two types of drugs, before, on the day of the procedure, and afterwards.

Subsequent to these pooled analyses, two major trials have been completed and published. Montalescot et al[344] compared the LMWH enoxaparin at a dose of 0.5 mg or 0.75 mg/kg with UFH adjusted to achieve a target activated clotting time of 300–350 s in 3,528 patients with elective PCI. The primary end point, major or minor bleeding during the first 48 h and not related to coronary artery bypass graft, occurred in significantly more patients on UFH (8.5%) than in patients receiving 0.5 or 0.75 mg/kg of LMWH (5.9 and 6.5%, respectively). This was primarily driven by a difference in major bleeding, which occurred at a rate of 2.8% with UFH and at 1.2% in each of the LMWH groups, a reduction by 57%. The risk of bleeding was increased by the use of a glycoprotein IIb/IIIa-inhibitor (40% of patients), age of 75 years or more, and by female sex.

Stone et al[156] compared heparin plus a glycoprotein IIb/IIIa-inhibitor with bivalirudin plus a glycoprotein IIb/IIIa-inhibitor or bivalirudin alone in 13,819 patients with unstable angina or non-ST-elevation myocardial infarction who were undergoing invasive treatment. In the heparin group there was an equal distribution between the use of UFH or LMWH. In the bivalirudin alone-group, 9% of the patients received a glycoprotein IIb/IIIa-inhibitor due to procedural complications. The primary end point major bleeding not related to coronary artery bypass graft during 30 days occurred in 5.7% of the heparin-combined group, 5.3% in the bivalirudin-combined group, and in 3.0% in the bivalirudin-alone group ($p < 0.001$). There was a similar pattern for all major bleeding, blood transfusions, access-site hemorrhage, and retroperitoneal hematoma, whereas ICH occurred in only three patients in each group. Bivalirudin monotherapy reduced the risk of bleeding in all subgroups analyzed, and the benefit was achieved without a loss of efficacy.

In conclusion, for patients undergoing PCI, anticoagulation with LMWH causes less bleeding than with UFH. Bivalirudin alone is safer and as effective as bivalirudin or heparin in combination with a glycoprotein IIb/IIIa-inhibitor.

2.7.2 VKA and Aspirin vs Dual Antiplatelet Therapy

Rubboli et al[345] conducted a metaanalysis of four trials with 2,436 patients treated with a VKA and aspirin or with the combination of aspirin and a thienopyridine after coronary stenting with a follow-up of 30 days. There was a nonsignificant reduction of major bleeding with dual antiplatelet therapy (RR 0.36; 95% CI, 0.14–1.02) and a benefit in efficacy, assessed as the composite end point of death, myocardial infarction, and need for revascularization.

3.0 Overall Comparisons

So far there is no anticoagulant agent that, across all indications, is safe regarding major hemorrhage. Comparisons between different drugs may yield different RRs depending on the selected intensity of treatment, concomitant or antecedent anticoagulant, antiplatelet or thrombolytic drugs, characteristics of the patient population, and also the condition that is being treated, as in the following examples:

- LMWH is safer than UFH in the treatment of acute VTE, but UFH appears safer than LMWH as an adjunct after thrombolytic therapy for ST-segment elevation myocardial infarction.
- Fondaparinux is safer than LMWH in unstable angina or non–ST-segment elevation myocardial infarction, but LMWH causes less surgical-site related bleeding after orthopedic surgery.
- Bivalirudin is safer than UFH in unstable angina, non-ST-elevation myocardial infarction, or PCI but appears to have higher bleeding risk than UFH in ST-segment elevation myocardial infarction.

It remains to be demonstrated that an antithrombotic agent can be effective without increasing the risk of hemorrhage in any of the conditions discussed in this article.

Finally, the risk of hemorrhage must, in clinical practice, be weighed against the reduction of thromboembolic events. The latter can be of differing severity, and strict comparison of numbers is not always sufficient, for example, when the thromboembolic events are transitory ischemic attacks or DVT vs life-threatening hemorrhage. Conversely, major hemorrhage consists to a large extent of GI hemorrhage that requires hospitalization and transfusion but without any late sequelae, which to a certain degree is acceptable in the prevention of stroke.

Conflict of Interest Disclosures

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