Anticoagulants in Coronary Artery Disease

L. Veronica Lee, MD

KEYWORDS

• Anticoagulant • Acute coronary syndrome
• Acute myocardial infarction • Unstable angina • Therapy

Acute coronary syndromes, such as unstable angina (UA) and myocardial infarction (MI), are the result of plaque rupture and the formation of thrombus that occludes the coronary artery. The mechanism of thrombus formation has been a primary target of cardiovascular acute and preventive therapy for half a century. Thrombus formation is the result of the activation of thrombin, and activation and aggregation of platelets. Thrombin has a central role in thrombus formation because it can directly activate platelets, convert fibrinogen to fibrin, and activate factor XIIIa, which crosslinks fibrin forming a stable clot. Medical therapy for acute coronary syndromes has therefore been directed at inhibition of these two targets, thrombin and platelets, through combined therapy. Previously these agents have been referred to as antithrombotics, but because they have multiple affects beyond thrombin the term anticoagulation has been recommended by the current guidelines. The anticoagulants discussed are ones that have been used in clinical trials and are approved or anticipated for use in coronary artery disease.

Anticoagulants can be divided into unfractionated and low molecular weight heparin (LMWH) (enoxaparin, dalteparin, tinzaparin), direct thrombin inhibitors (argatroban, bivalirudin, inogatran, and lepirudin), heparinoids or synthetic heparins (danaparoid, fondaparinux), and the oral anticoagulant warfarin.

UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) is made primarily from porcine bowel or bovine lung and is composed of many different molecular weight glycosaminoglycans (5,000–30,000 d) with variable antithrombin activity. UFH indirectly inhibits thrombin by binding and causing a conformational change in antithrombin (also known as antithrombin III) increasing its activity against thrombin (factor IIa) 1000-fold and inactivating factor Xa and to a smaller degree factors IXa, XIa, and XIIa. UFH stabilizes and reduces further clot formation, but does not dissolve the thrombus nor does it have action against clot-bound active thrombin. The anticoagulant effect of UFH must be monitored using activated partial thromboplastin time (aPTT) to reach a prespecified target range by using a weight-adjusted nomogram that has been standardized for the health care center providing heparin therapy.[1–3] Body weight, age, sex, smoking, and diabetes are known to be factors that alter the degree of anticoagulation achieved with a specific dose of UFH.[1–5] UFH at high doses is primarily metabolized by the kidneys and should be adjusted if there is a reduction in creatinine clearance.[3]

UNFRACTIONATED HEPARIN IN ST SEGMENT ELEVATION MYOCARDIAL INFARCTION WITH FIBRINOLYTICS

Most of the trial data that support the use of UFH in ST segment elevation myocardial infarction (STEMI) is based on trials that did not use aspirin (ASA). These earlier trials supported the use of UFH and oral anticoagulants for reducing ultimate infarct size, reinfarction, and embolization, but this is not relevant to our current standard of care.[6–8] ASA is now routinely used, although there has

Division of Cardiology, Yale University School of Medicine, 789 Howard Avenue, FMP3, New Haven, CT 06437, USA
E-mail address: lveronica.lee@yale.edu

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not been a randomized controlled trial to directly evaluate the use of ASA with and without heparin in patients who had or did not have reperfusion therapy. When fibrinolytics are used a procoagulable state is created and coadministration or early administration of anticoagulants, such as heparin, is recommended with fibrin-specific fibrinolytics (eg, alteplase) because recurrent thrombosis has been demonstrated in their absence.[9] When fibrin-specific fibrinolytics are used, a procoagulable state is created that demonstrates a marked increase in fibrinopeptide A as a result of thrombin binding to soluble fibrin degradation products. Non–fibrin-specific fibrinolytics (streptokinase, anistreplase) do not demonstrate a benefit in the reduction of mortality or reinfarction with adjuvant treatment with UFH and are associated with an increased risk for hemorrhage.[10–14]

Fibrin-specific fibrinolytic trials have had variable results in part because of the difficulty in achieving adequate anticoagulation early with UFH without either under- or overshooting the desired target range established to achieve inhibition of the procoagulable state without increasing the risk for hemorrhage. The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the use of heparin with fibrin-specific fibrinolytics and select patients treated with non–fibrin-specific fibrinolytics who are at an increased risk for systemic embolization (atrial fibrillation, history of embolization, left ventricular thrombus, anterior or extensive MI).[15] UFH is to be administered as a 60 U/kg intravenous bolus (IVB) ($\leq$4000 U) followed by an intravenous infusion (IVF) of UFH at 12 U/kg/h ($\leq$1000 U/h). A target aPTT has been established as 50 to 70 seconds because other studies with more aggressive anticoagulation and a higher upper end target of anticoagulation resulted in increased hemorrhagic complications.[16–20] The length of treatment with UFH after MI has not been established. If a patient is at risk for embolization (atrial fibrillation, history of embolization, left ventricular thrombus, anterior or extensive MI, or heart failure) prolonged administration should be considered.[21]

UNFRACTIONATED HEPARIN IN ST SEGMENT ELEVATION MYOCARDIAL INFARCTION WITH PRIMARY PERCUTANEOUS INTERVENTION

Primary percutaneous intervention (PCI) routinely uses UFH to prevent thrombosis and acute vessel closure. A target activating clotting time (ACT) of 250 to 350 seconds is used. If glycoprotein receptor inhibitors are used the target range is reduced to 200 to 250 seconds.[22–24] Preprocedure and postprocedure heparin administration does not improve efficacy of PCI and is associated with an increased risk for hemorrhage and vascular complications.[25]

UNFRACTIONATED HEPARIN AND EARLY CONSERVATIVE THERAPY FOR UNSTABLE ANGINA/NON–ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

Early studies in patients who had UA and non–ST segment elevation myocardial infarction (UA/NSTEMI) with UFH and ASA demonstrated a 54% reduction compared with placebo in the composite endpoint of reinfarction or death during the first week of therapy and the addition of UFH to ASA versus ASA alone yielded a relative risk (RR) of 33% at follow-up during weeks 2 to 12.[26,27] The benefit to therapy is of short duration and there is evidence of a prothrombotic state once UFH is discontinued leading to the observed heparin rebound that has also been seen with other anticoagulants.[19,28–32] The now recommended weight-adjusted regimen is an initial 60 U/kg IVB (maximum 4000 U) followed by 12 U/kg/h IVF (maximum 1000 U/h) with an appropriate aPTT target range and nomograms for adjusting dose determined by local laboratory protocol that corresponds to anti-factor Xa concentration of 0.3 to 0.7 U/mL.[5] Dosing should be monitored every 6 hours until two measures are within the prespecified target range, then once daily with platelet count and hemoglobin measurement unless there is a clinical change that warrants additional testing of aPTT and blood counts (hypotension, recurrent ischemia, or suspected hemorrhage). Duration of UFH therapy for UA/NSTEMI has not been clearly defined.

UNFRACTIONATED HEPARIN AND EARLY INVASIVE THERAPY FOR ACUTE CORONARY SYNDROME

Unfractionated heparin has been used in PCI as the gold standard until more recent randomized clinical trials have been performed against newer agents. Results of these trials are discussed later under the particular agents. UFH remains the preferred choice if a patient is going to require emergent coronary artery bypass graft (CABG) (<24 h).

HEPARIN-INDUCED THROMBOCYTOPENIA

One of the obstacles to heparin therapy is heparin-induced thrombocytopenia (HIT), an immune-mediated reduction in platelets that occurs in 2.5% to 3.0% of patients who have prior exposure to heparin or exposure for approximately 4 days with a platelet count decline of 50% or greater.[33]

It is caused by antibodies that are formed against the unit formed by platelet factor 4 bound to heparin. HIT has been connected to both arterial and venous thrombosis. Delayed HIT has been seen with a median onset of 14 days after heparin has been stopped.[34] HIT is often underdiagnosed and it is recommended that daily platelet counts be made while on UFH; this is not needed for LMWH or the heparinoid fondaparinux.[35] In the case of a suspected or known history of HIT, anticoagulation should be changed to bivalirudin in patients who have STEMI. Patients who have a history of HIT have been able to have limited use of heparin during cardiopulmonary bypass with success after absence of HIT antibodies has been confirmed.[36–38]

LOW MOLECULAR WEIGHT HEPARINS

LMWHs come from depolymerized UFH and because of their similar smaller weights have a more reproducible antithrombin activity. Approximately 25% to 50% of a LMWH is long enough ($\geq$18 polysaccharides) to have both factor Xa and thrombin activity. LMWH has a greater effect on factor Xa than thrombin and cannot be measured using aPTT, although monitoring of Xa activity is possible. LMWH delivers a more uniform and predictable level of anticoagulation and has a lower association with HIT. LMWHs, because of their longer half-life, lack of reliance on aPTT measurement, and more reliable anticoagulant effect, can be given subcutaneously with less frequent dosing than UFH to achieve a similar benefit. Protamine is more effective in reversing the anticoagulant effects of UFH than LMWH. The prolonged anticoagulant effect with LMWH has been of importance clinically when anticoagulation is changed for an invasive procedure or in anticipation of surgery, as discussed later.

LOW MOLECULAR WEIGHT HEPARIN AND ST SEGMENT ELEVATION MYOCARDIAL INFARCTION AND FIBRINOLYTICS

Trials suggest that there is a benefit when using LMWH as compared with UFH with nonspecific fibrinolytics (eg, streptokinase) with improved clinical outcomes.[39] Benefit has also been found when used in STEMI patients treated with fibrin-specific fibrinolytics and LMWH versus UFH.[40–45] A large meta-analysis of more than 27,000 patients receiving enoxaparin used a combined primary efficacy and safety endpoint of mortality and reinfarction within 30 days of initial STEMI and found a reduction in the enoxaparin-treated group as compared with the UFH group (11.1% versus 12.9%, odds ratio [OR] 0.84, 95% CI 0.73–0.9).[46] Major hemorrhage occurred more frequently in the enoxaparin group as compared with UFH treated patients (2.6% versus 1.8%), which translates into a decrease in 21 deaths or reinfarctions for an increase of four nonfatal major hemorrhages. Increased hemorrhage risk was found in patients 75 years or older and with reduced renal function.

LOW MOLECULAR WEIGHT HEPARIN AND EARLY CONSERVATIVE THERAPY FOR UNSTABLE ANGINA/NON–ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

There are eight major randomized trials that have explored the effect of LMWH as an alternative therapy of UFH in UA/NESTMI patients. Most data from trials comparing UFH and LMWH are with enoxaparin. Trials with dalteparin and nadroparin did not demonstrate improved efficacy for death and reinfarction.[28,47,48] Enoxaparin was found to decrease mortality and nonfatal MI event rates in five of six trials, when analyzed together demonstrating an OR of 0.91 (95% CI 0.83–0.99).[49–54] Hemorrhage rates are in general more prominent in LMWH as compared with UFH heparin, but these are primarily minor and related to the injection site.[40,41] Because none of these studies directly compared the different LMWHs the presence or absence of a class effect cannot be determined in these dissimilar trials that allowed open-label use of anticoagulants before randomization, and different doses, study designs, and populations. The exception is the Enoxaparin Versus Tinzaparin (EVET) (n = 436) trial that compared enoxaparin and tinzaparin in patients who had UA/NSTEMI with LMWH administered for 7 days. There was a decreased rate of the composite endpoint of death, nonfatal MI, or recurrent angina present at 7 days that persisted to the 6-month endpoint in the enoxaparin group as compared with tinzaparin (6 month 22.5% versus 44.0%, $p<.001$) without a difference in hemorrhage.[55,56] Other studies that did not directly compare LMWH to UFH but used placebo are not discussed here.[57]

LOW MOLECULAR WEIGHT HEPARIN AND EARLY INVASIVE THERAPY FOR ACUTE CORONARY SYNDROME

LMWH during PCI cannot be monitored by ACT and in earlier trials UFH was used during PCI for a target ACT greater than 350 seconds with LMWH being stopped before CABG successfully.[50,58,59] The Superior Yield of the New Strategy

of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial (n = 9978) studied high-risk UA/NSTEMI patients during PCI randomized to receive either enoxaparin or UFH.[54] Although there was no significant difference in efficacy, there was a significant increase in TIMI-defined major hemorrhage (9.1% versus 7.6%, $p = .008$) that post hoc seemed related to the use of UFH in enoxaparin patients at PCI.[60] It is therefore suggested that anticoagulant therapy not be changed if possible during PCI until this can be evaluated further.[26] The guidelines suggest that if substitution is necessary that LMWH be stopped approximately 8 hours before PCI and UFH use and that LMWH be discontinued 24 hours before CABG when possible to minimize hemorrhage.

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors directly bind to thrombin and inactivate at least one of its active sites. Unlike heparin they do not require a cofactor to work, can inactivate clot-bound thrombin, are less affected by circulating inhibitors than heparin (eg, platelet factor 4), and inhibit thrombin activation of platelets. They also interact less with circulating plasma proteins. Hirudin was the first to be developed as a recombinant protein derived from the one produced from the salivary gland of the medicinal leech (*Hirudo medicinalis*). Hirudin blocks thrombin's action by binding to the substrate (fibrinogen binding) and catalytic sites. Hirulog, now known as bivalirudin, is a peptide analog that binds thrombin at the same two sites as hirudin.[61] Argatroban is an arginine derivative that competitively binds the catalytic site of thrombin. It is approved for use in patients who have heparin-induced thrombocytopenia, but is not recommended for use in ACS in the current guidelines.[62,63] The dose of argatroban is given as a continuous infusion of 2 μg/kg/m and then adjusted according to aPTT or ACT. It is hepatically metabolized. Oral direct thrombin inhibitors have not been successful to date in cardiac patients; ximelagatran, the last tested, was associated with an increase in MI and severe liver damage.

DIRECT THROMBIN INHIBITORS AND ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

Small clinical trials HIT, TIMI-5, and TIMI-6 suggested that direct thrombin inhibition in STEMI receiving either fibrin-specific or nonspecific fibrinolytics suggested a benefit as compared with treatment with UFH.[64,65] After an increased rate of intracranial hemorrhage in both treatment arms in GUSTO-IIA and TIMI-9a caused the trials to be halted, further evaluation of hirudin was performed at a lower dose in GUSTO-IIb (also included UA/NSTEMI and PCI), TIMI-9B, and HIT-4.[31,66] There were no significant differences found in the primary efficacy endpoints or hemorrhage in these trials.

Hirulog (bivalirudin) in the HERO pilot trial of STEMI patients receiving fibrinolytics therapy with streptokinase and ASA demonstrated an increase in TIMI grade 3 flow without an increase in hemorrhage with bivalirudin.[67] HERO-2, which compared bivalirudin with UFH in STEMI treated with streptokinase, demonstrated a significant reduction in reinfarction at 96 hours (1.6% bivalirudin versus 2.3% UFH) and a trend toward increased major hemorrhage (0.7% versus 0.5%, $p = .07$) and intracranial hemorrhage (0.6 % versus 0.4 % $p = .09$). The ACC/AHA guidelines (2004) have recommended that bivalirudin be considered as a reasonable therapy in patients treated with streptokinase and with a history of HIT to heparin therapy.[15] Dosing of bivalirudin is to include an initial IVB of 0.25 mg/kg followed by a continuous IVF of 0.5 mg/kg/h for 12 hours and then dose reduction to 0.25 mg/kg/h for 36 hours. The dose of bivalirudin should be adjusted in renal insufficiency and if during the first 12 hours an aPTT is greater than 75 seconds.

PCI was evaluated in the HORIZON study (n = 3600) in STEMI patients randomized to treatment with UFH and GP IIb/IIIa inhibitors or bivalirudin and "provisional" GP IIb/IIIa inhibitors.[68,69] Bivalirudin was given in an IVB of 0.75 mg/kg followed by a continuous IVF of 1.75 mg/kg/h until post-PCI. There was no significant difference in the primary efficacy endpoint of death, reinfarction, ischemic target vessel revascularization, or stroke (5.4% versus 5.5%). Non-CABG major hemorrhage was less in the bivalirudin group, however (4.9% versus 8.3%).

There are limited data with argatroban from the MINT trial (n= 125) in which STEMI patients treated with alteplase were randomized to receive either argatroban or UFH.[70] There was improved attainment of TIMI 3 flow especially in patients presenting late (>3 hours) and a reduction in major hemorrhage in the argatroban group compared with UFH. Clinical efficacy could not be assessed in this preliminary study.

DIRECT THROMBIN INHIBITORS AND EARLY CONSERVATIVE STRATEGY NON–ST SEGMENT ELEVATION MYOCARDIAL INFARCTION AND UNSTABLE ANGINA

GUSTO IIB evaluated 8011 patients who had suspected NSTEMI treated with ASA and then

randomly assigned to either intravenous hirudin (0.1 mg/kg IVB and 0.1 mg/kg/h IVF for 3 to 5 days) or UFH.[17] At 30 days the primary efficacy endpoint of death, nonfatal MI, or reinfarction was reduced in the hirudin group 9.1% versus 8.3% in the UFH group, respectively (OR 0.90, $p = .22$). The Organization to Assess Strategies for Ischemic Syndromes (OASIS-2) trial (n = 10,141) used the middle dose found in their pilot to again assess the benefit of hirudin (0.4 mg/kg IVB and 0.15 mg/kg/h IVF) versus UFH (5000 IU IVB plus 15 U/kg/h IVF) administered for 72 hours in patients who had UA/NSTEMI.[71] The composite efficacy endpoint of death or new infarction was decreased in the hirudin group (3.6 %) versus the UFH group (4.2%) at 7 days (RR 0.84, $p = .06$), but more transfusions were required in the hirudin group (1.2% versus 0.7% with heparin, $p = .014$). At present bivalirudin is not recommended for UA/NSTEMI treated conservatively.

DIRECT THROMBIN INHIBITORS AND EARLY INVASIVE STRATEGY NON–ST SEGMENT ELEVATION MYOCARDIAL INFARCTION AND UNSTABLE ANGINA

A subset of patients in the GUSTO IIB trial (n = 1410) were treated with PCI and were found with hirudin to have a benefit in death and reinfarction rates versus UFH with a small increase in hemorrhage.[72] REPLACE 2 found bivalirudin (0.75 mg/kg IVB followed by 1.75 mg/kg/h IVF) to be non-inferior at one year compared with UFH (65 U/kg IVB) in patients undergoing elective or urgent PCI treated with provisional GP IIb/IIIa inhibition.[73–75] The Acuity trial compared in a 2 × 2 open-label randomized factorial design the use of UFH versus enoxaparin with and without GP IIb/IIIa inhibition with and without upstream bivalrudin.[76] PCI was done using an early invasive approach with a mean time to PCI of 4 hours. Non-inferiority was demonstrated in the heparin versus bivalirudin groups receiving GP IIb/IIIa inhibitors for the 30 day composite endpoints of ischemia or major bleeding. Non-inferiority in the composite endpoints was also found in the group receiving bivalirudin alone compared with the group receiving heparin and GP IIb/IIIa inhibitors with less hemorrhage (3.0% versus 5.7%, $p<.001$, RR 0.53, 95% CI 0.43–0.65) and statistically significant superiority in clinical outcome at 30 days (10.1% versus 11.7%, respectively, $p = 0$ .015, RR 0.86, 95% CI 0.77–0.97). Thienopyridine before PCI demonstrated a 7.0% composite endpoint reduction in the bivalirudin alone group (9.1% without thienopyridine) versus 7.3% in the heparin plus GP IIb/IIIa inhibition (7.1% without thienopyridine). Bivalirudin is approved for UA/NSTEMI in patients who have a planned early invasive strategy, including PCI. It is recommended that in patients who have delayed PCI or early ischemia who are using bivalirudin or heparin, a thienopyridine or GP IIb/IIIa inhibitor should be given before PCI to achieve the most benefit.[26] Unlike the heparins there are few data and there is no specific protocol for controlling the increase in hemorrhage associated with changing therapy at the time of PCI.

HEPARINOIDS

Fondaparinux, which is a synthetic heparin pentapeptide, has direct action on antithrombin that specifically inhibits factor Xa. In the setting of hemorrhage protamine can be used to reverse UFH and LMWH, but not fondaparinux, which requires transfusion of fresh frozen plasma to restore coagulation factors. Danaparoid is a combination of heparin, chondroitin, and dermatan sulfates and as a result can be used in patients who have HIT with less than 10% cross-reactivity.[77] The synthetic heparin fondaparinux was used in OASIS-6 (n = 12,000) in two different groups. In one group UFH was not indicated (majority had streptokinase fibrinolysis) and patients were randomized to receive fondaparinux (2.5 mg/d for 8 days) or placebo, and in the other group heparin was indicated (primary PCI, fibrin-specific fibrinolysis, or no reperfusion) and patients were randomized to receive UFH (24–48 hours) or fondaparinux (2.5 mg/d for 8 days).[78] Both groups compared with no heparin or UFH demonstrated a significant reduction in death and nonfatal reinfarctions at 30 days (9.7% versus 11.2%, hazards ratio 0.86, 95% CI 0.77–0.96). Both endpoint reductions of mortality and nonfatal reinfarctions were independently significant at 30 days. Analysis of the separate groups did not find a significant difference in patients who required heparin therapy because of a trend toward worse clinical outcomes in patients who had primary PCI (increase in catheter thrombosis, abrupt closure, dissection, and lack of flow). In the group of patients who did not require heparin the benefit seen may have been the result of the prolonged anticoagulation. Based on current data use in primary PCI is contraindicated and use with fibrinolysis requires further evaluation.

OASIS 5 was designed to evaluate the use of enoxaparin (1.0 mg/kg subcutaneously twice a day, with renal dosing for creatinine clearance less than 30 mL/min) versus fondaparinux (2.5 mg subcutaneously every day) for a mean of 6 days in ACS patients (n = 20,078) undergoing PCI.[79] Initially PCI was performed with UFH (65 U/kg with GP IIb/IIIa inhibitor, 100 U/kg

without) in the enoxaparin arm if more than 6 hours from last dose because there was a lack of data and the FDA had not approved enoxaparin for PCI. OASIS 5 was revised after there was found to be more catheter-related thrombus in the fondaparinux arm during PCI to include UFH IVB at the operator's discretion. Non-inferiority was demonstrated at 9 and 30 days for the composite endpoint of death, MI, or refractory ischemia. There was a significant decrease in mortality at 30 days (295 fondaparinux versus 352 enoxaparin, $p = .02$) and at 180 days, and in the combined endpoint of reinfarctions, stroke, and death at 180 days ($p = .007$). Major hemorrhage was significantly lower in fondaparinux group (2.2%) versus enoxaparin (4.1%, $p<.001$), although this may have to do with the crossover to UFH in the enoxaparin group, which was associated with increased hemorrhage in SYNERGY. Fondaparinux has been recommended in the treatment of UA/NSTEMI with the use of UFH 50 to 60 U/kg intravenously during PCI, although further evaluation is warranted because UFH use was not prespecified and controlled in OASIS 5.[26] UFH is still preferred in patients who may require CABG within 24 hours.

WARFARIN: LONG-TERM ANTICOAGULATION AND ORAL ANTICOAGULANTS

Although there have been attempts to find a substitute for warfarin as an oral anticoagulant, warfarin remains the only approved option for cardiac use. Warfarin is composed of S and R enantiomers and when strongly bound to protein, chiefly albumin, is inactive. If warfarin is displaced from the proteins that bind it activity is increased. The S form, more physiologically active, is metabolized in the liver by the CYP2C9 enzyme system, which is inducible by medications. Warfarin inhibits the vitamin K–dependent coagulation factors II, VII, IX, and X, and inhibitor proteins C and S increasing factors VIII and V activity. The effect of warfarin does not reach full potency until 36 to 72 hours after the first dose is given and factor II levels are reduced. Typically a higher dose of warfarin is given the first 2 days of therapy (2–5 mg at bedtime).[80–82] Higher doses have been found to lead to a hypercoagulable state from initial effects on protein C and a falsely elevated international normalized ratio (INR) through isolated effects on the extrinsic pathway and factor VII without complete inhibition of intrinsic pathways. As a result heparin therapy is typically recommended to overlap for 4 to 5 days when initiating therapy to prevent protein C–related effects and allow for complete inhibition of the intrinsic pathway. A black box warning has been added to labeling by the FDA because of the association of warfarin and hemorrhage and death. Risk factors for hemorrhage include increasing age, female, hypertension, diabetes, liver or renal disease, alcoholism, malignancy, anemia, diarrhea, heart failure, fever, prior hemorrhage (eg, intracranial, active gastrointestinal), bleeding disorder (platelet or coagulation disorder, concomitant medications affecting platelets or coagulation factors), prior stroke, genetic variations in hepatic enzyme pathway, prior hemorrhage on therapeutic warfarin, noncompliance, abnormal INR or difficult-to-regulate INR. If the INR is less than 5.0 but above the desired target range then the risk for hemorrhage is lower and withholding a dose and decreasing the subsequent dose should be sufficient to attain a therapeutic INR in target range with close monitoring.[83] If the INR is between 5.0 and 9.0, however, then there is a 1% risk for hemorrhage within the next 30 days that remains even after the anticoagulation has been corrected.[84] If there is no active bleeding and the INR is between 5.0 and 9.0, holding the dose with or without oral vitamin K is recommended.[85] INR greater than 9.0 without bleeding should have warfarin therapy stopped temporarily and oral vitamin K administered. If there is active bleeding on warfarin therapy warfarin should be stopped, and intravenous vitamin K and fresh frozen plasma administered.[86–91] If the hemorrhage is more emergent prothrombin complex or recombinant human factor VIIa can be administered.

Warfarin requires careful monitoring so that the predetermined target INR is reached and not exceeded. Any changes in a patient's diet or over-the-counter or prescription medications that affect vitamin K levels require increased vigilance for side effects, alterations in INR, and appropriate adjustment of warfarin dosing. A meta-analysis demonstrated in more than 50,000 patients that INR is outside of the target range 64% of the time with self-monitoring achieving the best rates at 72%.[92]

Currently warfarin is not indicated for patients who have a diagnosis of ACS, unless there is a secondary indication. Secondary indications include left ventricular thrombus, left ventricular aneurysm, atrial fibrillation, mechanical valve replacement, and so forth. There are numerous trials that have been performed in STEMI patients comparing ASA to the addition of warfarin to ASA with different INR target ranges from high to low intensity (<1.5–4.8). Of the trials that demonstrated benefit to warfarin therapy after STEMI (WARIS II, APRICOT-2, ASPECT-2) there was often difficulty maintaining target range INR, high discontinuation rates, and increased bleeding.[93–96] Patients were also not treated with newer antiplatelet agents, which limits the applicability of data from these

Table 1
Summary of 2007 anticoagulant for therapy of ST segment elevation myocardial infarction, American College of Cardiology/American Heart Association guideline update

Reperfusion/PCI/Supportive	Dosing	Evidence
Reperfusion with fibrinolytic	IV anticoagulant ≥48 h (max 8 d)	Class I, Level C
IV anticoagulation ≥48 h	Avoid UFH, reduce HIT	Class I, Level A
UFH dosing for maximum 48 h	60 U IVB per kg (maximum 4000 U) followed by IV infusion of 12 U/kg/h (maximum 1000 U/h) adjust to aPTT of 1.5–2.0 times control (approximately 50–70 s)	Class I, Level C
Enoxaparin (Cr<2.5 mg/dL men, <2.0 women)	<75 y old IVB 30 mg and SC 1.0 mg/kg q 12 h start 15 min after IVB	Class I, Level A
Duration of hospitalization or for maximum 8 days	≥75 y old No IVB, SC 0.75 mg/kg q 12 h CrCl<30 mL/min SC 1.0 mg/kg q 24 h	
Fondaparinux (Cr<3.0 mg/dL) Duration of hospitalization or for maximum 8 days	First dose 2.5 mg IV then 2.5 mg SC once daily	Class I, Level B
Post-PCI	Dosing to adjust if GPIIb/IIIa receptor inhibitor given for UFH and enoxaparin	Class I, Level C
PCI with prior UFH	Bolus with UFH to support procedure Bolus with bivalirudin to support procedure	Class I, Level C Class I, Level C
PCI with prior enoxaparin	Within 8 h: no additional enoxaparin Within 8–12 h: 0.3 mg/kg enoxaparin IV	Class I, Level B
PCI with prior fondaparinux	Anti-IIa anticoagulant adjusting if GPIIb/IIIa receptor inhibitor given	Class I, Level C
Fondaparinux in PCI	Not to be used alone as anticoagulant because of increase in catheter thrombosis	Class III, Level C
Supportive therapy for STEMI (no reperfusion)	IV or SC UFH or SC LMWH for ≥48 h or ambulatory	Class IIa, Level C
LMWH Fondaparinux	For more than 48 h and up to 8 d to reduce HIT as dosed above for patients treated with fibrinolytics	Class IIa, Level C Class IIa, Level B

Data from Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. J Am Coll Cardiol 2008;51:172–209.

trials to current standard of care, such as for patients receiving stents and clopidogrel.

Although there is a possible theoretic advantage to long-term anticoagulation with warfarin or subcutaneous LMWH after discontinuation of intravenous anticoagulation (eg, prothrombotic state noted post–intravenous anticoagulant therapy and exposed prothrombotic material at healing site of infarct-related artery) data have not supported long-term use.[97,98] In the setting of UA there are limited trial data; however, two study groups have suggested benefit in reduction of ischemic events with a small increased risk for hemorrhagic complications in some patient groups (ATACS, OASIS, OASIS 2) from warfarin after UA.[99–101] Currently our approach to patients who have UA/NSTEMI has changed to include an early invasive strategy with stent placement and the use of newer antiplatelet agents, such as clopidogrel. Clopidogrel is frequently used in patients who are allergic to ASA who in the past might have been recommended to receive warfarin. As a result warfarin should only be used in the setting of a secondary indication, and when adding antiplatelet therapy post-stent with ASA and clopidogrel assessment of hemorrhagic risk and careful

Table 2
Intravenous anticoagulants for unstable angina/non–ST segment elevation myocardial infarction from American College of Cardiology/American Heart Association guidelines

Drug	Initial Medical Treatment	Received Initial Treatment	Did not Receive Initial Treatment	After PCI
Bivalirudin	0.1 mg/kg bolus, 0.25 mg/kg/h infusion	0.5 mg/kg bolus, increase infusion to 1.75 mg/kg/h	0.75 mg/kg bolus, 1.75 mg/kg/h infusion	No additional treatment or continue infusion for up to 4 h
Dalteparin	120 IU/kg SC every 12 h (maximum 10,000 IU twice daily)	IV GP IIb/IIIa planned: target ACT 200 s using UFH No IV GP IIb/IIIa planned: target ACT 250–300 s for HemoTec; 300–350 s for Hemochron using UFH	IV GP IIb/IIIa planned: 60–70 U/kg of UFH No IV GP IIb/IIIa planned: 100–140 U/kg of UFH	No additional treatment
Enoxaparin	LD of 30 mg IV bolus may be given 1 mg/kg SC every 12 h; extend dosing interval to 1 mg/kg every 24 h if estimated creatinine clearance less than 30 mL per min	Last SC dose less than 8 h: no additional therapy Last SC dose greater than 8 h: 0.3 mg/kg IV bolus	0.5–0.75 mg/kg IV bolus	No additional treatment
Fondaparinux	2.5 mg SC once daily. Avoid for creatinine clearance less than 30 mL/min	50–60 U/kg IV bolus of UFH is recommended by the OASIS 5 investigators	50–60 U/kg IV bolus of UFH is recommended by the OASIS 5 investigators	No additional treatment
Unfractionated heparin	LD of 60 U/kg (max 4000 U) as IV bolus IV infusion of 12 U/kg/h (max 1000 U/h) to maintain aPTT at 1.5 to 2.0 times control (approximately 50–70 s)	IV GP IIb/IIIa planned: target ACT 200 s No IV GP IIb/IIIa planned: target ACT 250–300 s for HemoTec; 300–350 s for Hemochron	IV GP IIb/IIIa planned: 60–70 U/kg No IV GP IIb/IIIa planned: 100–140 U/ kg	No additional treatment

Data from Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. J Am Coll Cardiol 2008;51:172–209.

Table 3
Summary of anticoagulant therapy unstable angina/non–ST segment elevation myocardial infarction from American College of Cardiology/American Heart Association guidelines

Evidence	Therapy	Evidence
Early invasive/conservative	Anticoagulant in addition to antiplatelet therapy without delay at presentation	Class I, Level A
Early invasive choice of anticoagulant	Enoxaparin	Class I, Level A
	UFH	Class I, Level A
	Bivalirudin	Class I, Level B
	Fondaparinux	Class I, Level B
Conservative therapy choice of anticoagulant	Enoxaparin	Class I, Level A
	UFH	Class I, Level A
	Fondaparinux	Class I, Level B
Conservative therapy at increased risk for hemorrhage	Fondaparinux	Class I, Level B
Conservative without CABG in 24 h	Enoxaparin or fondaparinux preferred over UFH	Class IIa, Level B
Conservative therapy duration of anticoagulation	UFH for 48 h or enoxaparin or fondaparinux for hospitalization or up to 8 days	Class I, Level A
Anticipated CABG		
UFH	Continue UFH preoperatively	Class I, Level B
Enoxaparin	Discontinue 12–24 h before CABG and change to UFH	Class I, Level B
Fondaparinux	Discontinue 24 h before CABG and change to UFH	Class I, Level B
Bivalirudin	Discontinue 3 h before CABG and change to UFH	Class I, Level B
Post–uncomplicated PCI	Discontinue anticoagulant therapy	Class I, Level B
Post-PCI: medical management	No significant obstructive coronary artery disease at discretion of clinician	Class I, Level C
UFH	Continue for at least 48 h or until discharge	Class I, Level A
Enoxaparin	Continue duration of hospitalization or maximum of 8 days	Class I, Level A
Fondaparinux	Continue duration of hospitalization or maximum of 8 days	Class I, Level B
Bivalirudin	Discontinue or reduce dose to 0.25 mg/kg/h for a maximum of 72 h	Class I, Level B
Conservative therapy with no additional angiography or stress testing	UFH for 48 h or fondaparinux or enoxaparin continue duration of hospitalization or maximum of 8 days	Class I, Level A

Data from Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. J Am Coll Cardiol 2008;51:172–209.

monitoring are recommended until further studies can assess combination therapy.

SUMMARY

Anticoagulant therapy has evolved greatly in the past allowing for more options than before, and a better understanding of the risk and benefit of using these medications has been achieved through elaborate clinical trials. We have achieved better control of UFH through weight-adjusted nomograms and found other agents that achieve a longer, more predictable level of anticoagulation. Newer agents also have been able to directly affect clot-bound thrombin. We are now in need of further investigation into the interaction of antiplatelet and anticoagulant agents with our newer invasive therapies to improve efficacy and safety.

In addition, further investigation into procedures for crossover therapy that is still necessary at times, especially when CABG is required, and methods to further reduce hemorrhage perioperatively in the presence of the newer antiplatelet agents are needed.

Present clinical guideline recommendations are summarized in **Table 1** for STEMI and in **Tables 2** and **3** for UA/NSTEMI. Long-term anticoagulation with an oral agent is not recommended at present unless there is a compelling secondary reason, such as left ventricular thrombus, left ventricular aneurysm, atrial fibrillation, mechanical valve replacement, and so forth. Careful monitoring for bleeding and dose reduction after an assessment of hemorrhagic risk should be performed. Future oral anticoagulants that have more predictable anticoagulation have yet to be found, although the oral once a day rivaroxaban (Xarelto) has just recently had promising data released when used in symptomatic venous thromboembolic disease.

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