Anticoagulation in Acute Coronary Syndrome and Beyond

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Objectives:
1. Describe the role of anticoagulant therapy in ACS management
2. List by mechanism of action the various anticoagulants potentially available in treating ACS
3. Discuss the different roles anticoagulants may plan in primary therapy and secondary prevention

Fibrin-linked platelet thrombosis in a coronary artery is at the pathologic root of myocardial infarction (MI), so it is reasonable that antithrombotic therapy is the foundation for the management of acute coronary syndrome (ACS). A number of agents have been studied, validated, and labeled by the United States Food and Drug Administration (FDA) for acute management of ACS and are therefore pertinent to emergency department (ED) care. Others have failed to demonstrate utility in acute management but may still have a role later in ACS care, such as in the cardiac catheterization laboratory. A group of novel oral agents may hold further promise of benefit in secondary prevention of ACS which, while not initiated in the ED, may impact ED management when the patient later presents for anginal symptoms or for other issues quite unrelated to coronary artery disease.

Anticoagulation is appropriate for patients deemed to be at intermediate or higher ACS ischemic risk. There are many options for anticoagulation in the upstream, ED environment, and the choice is impacted by many issues, including (1) emergency physician preference, (2) cardiologist preference, (3) perceived level of ischemic risk, (4) concern for hemorrhagic risk, (5) likely duration of therapy prior to angiography and possible revascularization, (6) logistical issues such as FDA labels and formulary inclusion, and (7) local standard of care.

Indirect and direct parenteral anticoagulants—unfractionated heparin, low-molecular-weight heparins, and bivalirudin—all have evidence-supported roles in the early medical and interventional management of ACS. After the acute phase, a generally prothrombotic state, due to persistent exposed prothrombotic material at the healing site of atherosclerotic plaque rupture and from the infarct-related artery and post–intravenous anticoagulant rebound hypercoagulability, persists. Effective management of this ongoing risk from the coagulation cascade requires an understanding of the data accrued for each option among this broad class of anticoagulant agents.

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Unfractionated heparin

Unfractionated heparin (UFH) exerts its anticoagulant effect by accelerating the action of circulating antithrombin III (AT-III), a proteolytic enzyme which inactivates Factor IIa (thrombin), Factor IXa, and Factor Xa. The UFH-AT-III complex prevents thrombus propagation but does not lyse existing thrombi. Conventional teaching in ACS pharmacology is that UFH has both early, through blocking Factor Xa which has an important impact of amplification of the clotting cascade, and a late anti-thrombin impact. Many cardiologists consider it an advantage that the effect of UFH can be readily and repeatedly measured—in the ED with the aPTT assay and in the cath lab with the activated clotting time (ACT). Still, the disadvantages of UFH are widely recognized—namely, its relatively poor bioavailability, which stems from its many nonproductive interactions with plasma proteins and endothelial cells, and its activation of the PF4 receptor on platelets. This may result in heparin-induced thrombocytopenia (HIT) and paradoxical pathologic thrombosis.

For many years now, the only “new” data on the use of UFH in ACS have been its use as a control agent vs newer anticoagulants such as low-molecular weight heparins and
bivalirudin. The initial, placebo-controlled support for UFH derives from six relatively small trials. In aggregate these studies suggest that the benefit of adding UFH to aspirin amounts to a statistically significant reduction in early, up to 30 days, depending on the study, death and MI of up to 54%.

The ACC/AHA Guidelines-recommended dosing for UFH in the acute management of ACS is as follows:

In ST-segment elevation myocardial infarction (STEMI) being managed with primary percutaneous coronary intervention (PCI): bolus of 40-60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/hr (maximum 1000 U), or successive boluses in the cath lab based on ACT monitoring and whether or not glycoprotein IIb/IIIa inhibitors are used.

In STEMI being managed with fibrinolysis: bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/hr (maximum 1000 U) initially adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 seconds).

In non-ST-segment elevation myocardial infarction (NSTEMI) ACS: bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/hr (maximum 1000 U) initially adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 seconds).

Dalteparin

Unfractionated heparin is a heterogeneous mixture of polysaccharide chains of molecular weights ranging from 5,000 to 30,000 Daltons. It is known that this chain weight has a direct impact on anticoagulant activity. Dalteparin and enoxaparin are “low-molecular-weight heparins” (LWMH), which are created through different, proprietary, enzymatic degradations of UFH to smaller chain lengths. The preponderance of LWMH chains retains the ability to link to AT-III and then to Factor Xa, impacting this amplification step in the clotting cascade and therefore inhibiting coagulation. Fewer LWMH chains have the stoichiometric capability to link to AT-III and the much larger thrombin (IIa) moiety, so the relative activity of LMWHs in therapeutic anticoagulation is much greater against Factor Xa than against thrombin.

Dalteparin, like its parent compound UFH, has been studied in a placebo-controlled trial in ACS patients. The FRISC study randomized 1,506 patients with NSTE-ACS to receive subcutaneous dalteparin or placebo twice daily for 6 days and then once a day for the next 35-45 days. Dalteparin was associated with a 63% risk reduction in death or MI during the first 6 days (4.8% vs. 1.8%, p < 0.001), which matched the favorable experience observed with UFH. A subsequent trial established dalteparin’s noninferiority to UFH in NSTE-ACS. Prolonged therapy with injectable anticoagulants after the patient’s discharge home after an episode of ACS has never gained much support in clinical practice, but the acute impact of dalteparin resulted in an FDA label for its use in ACS. The recommended dose of dalteparin for ACS in the ED is 120 IU per kg subcutaneous (SC) every 12 h (maximum 10,000 IU twice daily). Dalteparin is not specifically supported by the ACC-AHA Guidelines for use in ACS.

Enoxaparin

The LMWH enoxaparin, alternatively, is specifically supported by the most current ACC-AHA Guidelines for both NSTEMI and STEMI. For STEMI being managed with fibrinolytic therapy, enoxaparin is preferred over UFH (I-A). This recommendation is based on the EXTRACT TIMI-25 trial. EXTRACT was an international, double-blind, double-dummy comparison of enoxaparin versus UFH in 20,506 patients with STEMI who presented within 6 hours of symptom onset, and for whom fibrinolytic therapy was planned. A novel dosing regimen was used for enoxaparin, with dosing reductions both for advanced age and diminished renal function. The median treatment duration was 7 days for enoxaparin and 2 days for UFH. The primary endpoint for efficacy was death or nonfatal re-MI in 30 days.

The primary endpoint occurred in 12.0% of patients randomized to UFH and 9.9% of those receiving enoxaparin (17% relative risk reduction (RRR), p < 0.001). There was a small excess of overall major bleeding in the enoxaparin arm, (2.1% vs 1.4%, p < 0.001), but not of fatal bleeding or intracranial hemorrhage. Furthermore, 2,178 patients went on to PCI after lytic therapy, which occurred on randomized therapy if it occurred within 8 days (n = 2,178). Among patients who underwent PCI within 30 days of STEMI, the primary endpoint occurred in 10.7% of enoxaparin patients and in 13.8% of UFH patients (23% RRR, p < 0.001), with no difference in major bleeding.

Per FDA label and ACC/AHA Guidelines, the recommended dose of enoxaparin in STEMI patients receiving lytic therapy is as follows: when serum creatinine < 2.5mg/dL in men and < 2.0mg/dL in women: if < 75 years of age, 30mg IV bolus, then 1.0mg/kg subcutaneously fifteen minutes later and every 12 hours thereafter; if > 75 years of age, omit bolus and administer 0.75mg/kg every 12 hours; if estimated creatinine clearance is < 30cc/min, change 12-hour dosing intervals to 24 hours.
In patients with NSTE-ACS, the most recent clinical trial evaluating enoxaparin is SYNERGY, which compared enoxaparin with UFH in patients with NSTE-ACS and high-risk features who were to be treated with an early invasive strategy. The dose of enoxaparin was 1mg/kg given SC every 12 hours, with a supplemental IV dose (0.3mg/kg) given in the event of PCI more than eight, but less than 12, hours after the last SC dose. The dose of UFH was an IV bolus of 60U/kg (up to 5000U), then an initial infusion of 12U/kg/hr (up to 1000U/hr), further adjusted with a goal of an activated partial thromboplastin time (aPTT) of 50-70sec. Patients with an estimated creatinine clearance of less than 30cc/min were excluded. All other treatment, including clopidogrel, GPIs, beta-blockers, statins, etc., was left to the discretion of the treating physician, although compliance with the 2002 Guidelines was encouraged.

Overall, 92% of the patients underwent diagnostic angiography, and approximately half of those underwent PCI; 19% of the 10,027 patients underwent coronary artery bypass grafting (CABG), a high proportion probably attributable to the advanced age of the subject population of which one-quarter were 75 years and older. There was no baseline or procedural intensity differences between the two groups. Median time from randomization to catheterization was 22 hours, although some 8-10 hours typically elapsed between presentation and randomization, which potentially impacts the applicability of this study to ED management. The primary efficacy endpoint failed to show superiority of enoxaparin, although noninferiority criteria (at a 10% margin) were satisfied; 14.0% of the enoxaparin patients had death or MI by 30 days, while 14.5% of the UFH patients met the endpoint (hazard ratio, 0.96; 95% CI, 0.86, 1.06). The safety endpoint was less clear-cut, with the enoxaparin patients experiencing a statistically significant increase in TIMI major bleeding (9.1% vs 7.6%, p = 0.008), but a nonsignificant excess of GUSTO severe bleeding (2.7% vs 2.2%, p = 0.08) and red cell transfusions (17.0% vs 16.0%, p = 0.16). At least some of the excess bleeding was attributable to crossover from enoxaparin to UFH at the time of PCI in this unblinded study, once more reinforcing the need for good communication and collaboration between emergency physicians and cardiologists. It should be noted that the dosing interval for enoxaparin should be doubled from 12 to 24 hours if creatinine clearance, which can be readily estimated in the ED, is less than 30cc/min. The 2007 ACC/AHA Guidelines for NSTE-ACS recommend the use of enoxaparin at a 1-A level.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide with the AT-III binding site of UFH. Because of its small and uniform chain size, the fondaparinux-AT-III complex can bind only Factor Xa, and not thrombin, so fondaparinux has no measurable antithrombin activity. It is also thought to be associated with a very, very low rate of PF4 activation and hence rare, if any, HIT risk. The OASIS-6 trial was an international, double-blind, double-dummy comparison of fondaparinux versus placebo or UFH in 12,092 patients with STEMI who presented within 12-24 hours of symptom onset. Patients with serum creatinine > 3.0mg/dL were excluded. Patients selected by their treating physician to receive STEMI management in which no UFH would ordinarily be given, such as fibrinolytic therapy with streptokinase or no reperfusion therapy, were randomized to receive either fondaparinux or placebo (Stratum I, n = 5,658). Patients selected for fibrinolysis with a fibrin-specific agent, for primary PCI, or for no reperfusion therapy but with anticoagulation, were randomized to either fondaparinux or UFH (Stratum II, n = 6,434). The study dose of fondaparinux was 2.5mg IV at randomization, then 2.5mg SC daily thereafter. The median treatment duration was 8 days for fondaparinux in Stratum I and, in Stratum II, 7 days for fondaparinux and 45 hours for UFH. The primary endpoint for efficacy was death or nonfatal re-MI at 30 days.

Nearly one-quarter of the patients in OASIS-6 received no reperfusion therapy. Overall, the primary endpoint was significantly reduced in the group receiving fondaparinux compared to control therapy (11.2% vs 9.7%, RRR 14%, p = 0.008), with a significant and persistent reduction in mortality at 9, 30, and 180 days. Fondaparinux was superior to the comparator in both strata, but the subset of Stratum II patients undergoing primary PCI received no benefit compared to UFH (8.5% of fondaparinux patients with primary endpoint, vs 8.2% with UFH). At least some of this deficiency in primary PCI was due to guiding catheter thrombus in patients instrumented on fondaparinux monotherapy, a problem similar to that reported in OASIS-5, which studied NSTE ACS patients. There was a tendency towards fewer major

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bleeding complications with fondaparinux in OASIS-6.16 The OASIS-5 trial considered the possible role of fondaparinux in NSTE-ACS.17 The OASIS-5 investigators compared a control strategy of enoxaparin 1.0mg/kg SC twice daily, once daily if creatinine clearance was < 30cc/min, coupled with UFH at the time of PCI if performed more than 6 hours after the last enoxaparin dose, versus a strategy of fondaparinux 2.5 mg SC daily, one-third the venous thrombosis treatment dose, with more fondaparinux or UFH at the time of PCI. The OASIS-5 trial was designed and powered as a noninferiority trial. After enrollment of about 60% of the 20,078 NSTE-ACS patients in the study, the protocol was amended to allow more UFH in the catheterization laboratory. This was in response to the finding that catheter-associated thrombus was reported three times more frequently (0.9% vs 0.3%) in the fondaparinux arm than in the enoxaparin arm,17 but given the findings of increased bleeding in the SYNERGY study among patients who received both enoxaparin and UFH,15 the change may have negatively impacted the safety profile of enoxaparin in this double-blind, double-dummy study.

In OASIS-5, only about two-thirds of the patients underwent diagnostic angiography; just over half of these had PCI and the CABG rate overall was under 10%. The primary ischemic outcome (death, MI, or refractory ischemia) at 9 days showed no difference between the two groups (5.8% with fondaparinux, 5.7% with enoxaparin; hazard ratio for fondaparinux, 1.01; 95% CI, 0.90, 1.13), but met the noninferiority margin of 18.5%. At 30 days and at 6-month follow-up, patients receiving fondaparinux experienced a nonsignificant trend towards better composite ischemic outcomes, although the single endpoints of death at 30 days (p = 0.02) and 180 days (p = 0.05), and of stroke at 180 days (p = 0.04) significantly favored fondaparinux. In the safety analysis of OASIS-5, major bleeding was much less common in the fondaparinux arm at 9 days (2.2% vs 4.1%; hazard ratio 0.52, p < 0.001), driving a net benefit, defined as primary ischemic composite plus major bleeding, which favored fondaparinux (7.3% vs 9.0%; hazard ratio 0.81; 95% CI, 0.73, 0.89; p < 0.001).17

Fondaparinux is not labeled for use in ACS in the US. In the ACC-AHA Guidelines for both STEMI, not managed with primary PCI, and NSTE-ACS, it is a reasonable option especially in patients with high bleeding risk.7,9

### Bivalirudin

Bivalirudin is an intravenous direct thrombin inhibitor. It does not require the intercession of AT-III to impact the clotting cascade. It affects only Factor IIa (thrombin). Bivalirudin is approved by the FDA as a catheterization laboratory anticoagulant. There is evidence from both a large NSTE-ACS trial (ACUITY) and a contemporary STEMI primary PCI trial that bivalirudin is an effective anticoagulant with a bleeding risk lower than indirect anticoagulants.16,17 However, from ACUITY (NSTE-ACS) and from HORIZONS (STEMI), there is no clear evidence that initiation of bivalirudin in the ED is associated with, nor is it necessary for, improved ischemic outcomes. For example, in HORIZONS, 66% of the patients undergoing primary PCI who were randomized to receive bivalirudin actually received UFH in the ED, without apparent decrement in the overall benefit of bivalirudin.19 In the ACC/AHA Guideline recommendations for NSTE-ACS, bivalirudin receives a I-B recommendation, while in primary PCI for STEMI, it is graded at I-C.7,9

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### Secondary prevention and newer oral anticoagulants

Warfarin has been effective in some studies of post-ACS patients,2,19-22 but other studies have shown either no efficacy benefit over ASA alone or worrisome bleeding risks which outweigh ischemic benefit.23-25 The negative benefit-risk balance of warfarin is cited in the absence of support for routine use in secondary prevention in the current ACS guidelines.

In the phase II ESTEEM trial, however, ximelagatran, an oral direct thrombin inhibitor, plus ASA was significantly more effective than ASA monotherapy in reducing the composite endpoint of death, nonfatal reinfarction, and severe recurrent ischemia in a high-risk population randomized within 14 days after an acute event. The risk reduction was evident within the first month and the difference was maintained, or even increased, over six months of treatment.26 In contradistinction to warfarin trials, major bleeding was not significantly increased in the ximelagatran-treated groups relative to placebo, although the cumulative risk for total bleeding (major and minor) was higher in the ximelagatran groups. Nonetheless, the ESTEEM data were widely interpreted as providing clear evidence that a non-warfarin oral anticoagulant might actually prevent new coronary events in a secondary prevention setting. Ximelagatran was
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subsequently found to be associated with hepatotoxicity which prevented its approval and widespread adoption with further study truncated.

Besides ximelagatran, there are other oral non-warfarin anticoagulants which have potential utility in the longer term management of coronary artery disease, and they are these same agents being studied in stroke prevention in atrial fibrillation: rivaroxaban, apixaban, and dabigatran. All three drugs are being considered as adjuncts to dual antiplatelet therapy in secondary prevention for patients after an episode of ACS.

The ATLAS ACS-TIMI 46 trial was a dose-ranging study designed to find the best dose of rivaroxaban in ACS. Patients were stratified by the choice of background antiplatelet therapy, dual antiplatelet therapy or ASA monotherapy. Rivaroxaban caused significant and dose-dependent increases in bleeding, with the biggest increase in patients receiving dual antiplatelet therapy. Although there were no overall significant differences in the primary endpoint of death, MI, stroke, or severe recurrent ischemia requiring revascularization, there was a significant benefit observed in the group of patients who received aspirin monotherapy.27

Apixaban was studied in the Dose Ranging Study to Evaluate Safety and Efficacy of Apixaban in Patients with a Recent Acute Coronary Syndrome (APPRAISE-1), in which apixaban combined with ASA or dual antiplatelet therapy (ASA+clopidogrel) for 6 months post-ACS led to reduced ischemic events but also increased bleeding in a dose-dependent fashion.28 Similar outcomes were found among patients taking ASA or dual antiplatelet therapy.

Dabigatran is being studied in secondary prevention for ACS in the ongoing REDEEM trial.

Conclusion

It is clear that treating patients with ACS using anticoagulant therapy requires the clinician to understand multiple potential regimens. Evaluation of anticoagulant strategies is an active, ongoing area of investigation. It is difficult to draw conclusions that one anticoagulant strategy is to be preferred over another based on study in which dosing, treatment duration, timing, and concomitant medical and interventional therapy vary. A number of acceptable anticoagulant strategies can be recommended, but preferences for one strategy over another may be elusive on a global basis. It is better to seek prospective agreement among all the stakeholders in ACS care, emergency physicians, hospitalists, noninterventional cardiologists, and interventional cardiologists, within a specific institution and to develop evidence-based, Guidelines-consistent protocols which can be readily referenced and used to minimize the chance of medication errors and double anticoagulation administration when personal preferences are superimposed on an already-initiated treatment plan. It is often best, if sometimes politically challenging, for emergency physicians to take the lead in developing these approaches.

References


28. ESC 2008 presentation of APPRAISE-1.