Minimizing the Risks of Anticoagulants and Platelet Inhibitors

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Thrombosis is a major contributor to the adverse outcomes associated with atherosclerotic disease. Acute coronary syndromes (ACS) result when intravascular thrombosis occurs at the site of an atherosclerotic plaque rupture. In this setting, the use of anticoagulants and platelet inhibitors is life-saving, but these agents also contribute additional risks for bleeding. The risks and benefits of antithrombotic therapy have been studied in large randomized clinical trials; however, clinicians must extrapolate from aggregate data when making therapeutic decisions for the individual. The validity of such extrapolation becomes less certain when factors encountered in practice differ from those observed in the trial setting.

The balance between risks and benefits of antithrombotic therapy in practice may be altered by factors across 3 domains: drug, patient, and provider. Although factors associated with these domains can independently influence outcomes, more commonly, it is the complex interplay of all 3 that ultimately determines the outcome of therapy in a given patient. This article will describe the common risks associated with antithrombotic therapy. In addition, factors that individually or in combination alter these risks will be explored with currently available agents approved for or studied in ACS (Figure 1). Finally, directions for optimizing the future safety of antithrombotic therapy will be discussed.

Anticoagulants and Platelet Inhibitors

A variety of anticoagulant and platelet inhibitor drugs have been approved for use in ACS patients (Table 1). These existing agents have unique pharmacological properties that influence both their comparative efficacy and safety as demonstrated in aggregate trial data and their safety as observed in clinical practice. The most frequently used anticoagulants in contemporary ACS care are unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). UFH is a heterogeneous mixture of polysulfated glycosaminoglycans that activates antithrombin through the formation of a heparin-antithrombin complex that, in turn, inhibits other coagulation factors. Although the clearance of UFH is not understood completely, it is thought to occur via the reticular endothelial system and, in high concentrations, via the kidneys. However, because of its protein-binding properties and combination of saturable and nonsaturable clearance, the effect of UFH can vary substantially. Accordingly, although an initial UFH dose can be estimated on the basis of patient weight, this approximation that must then be adjusted on the basis of activated partial thromboplastin time. The lack of linear relationship between dose, activated partial thromboplastin time, and clinical outcomes adds complexity to the optimal use of the drug. The half-life of UFH is on the order of 6 hours, which is intermediate among the anticoagulants; however, if uncontrolled bleeding occurs after UFH therapy, protamine is an effective, albeit not completely benign, antidote that reverses its anticoagulant effects.

Compared with UFH, LMWHs (eg, enoxaparin) have a specific inhibitory effect on thrombin and factor Xa. When given subcutaneously, enoxaparin demonstrates a more predictable steady state and slower clearance than UFH and requires no monitoring. LMWHs are cleared via the kidneys, so doses must be adjusted for weight and for renal function to avoid accumulation in patients with kidney disease. Several newer anticoagulants are also approved for use in ACS patients. Fondaparinux, a direct factor Xa inhibitor, mimics the binding of heparin to antithrombin III in a manner that is both selective and reversible. Fondaparinux is 80% renally cleared and is contraindicated in patients with creatinine clearance <30 mL/min. Fondaparinux is the longest acting of the anticoagulants, with a half-life approaching 24 hours. Bivalirudin, another newer anticoagulant, is a reversible direct thrombin inhibitor with additional mild antiplatelet activity. Bivalirudin is cleared by both proteolytic and renal mechanisms. It has a very short half-life, and in addition to its dual clearance, it is less likely than either fondaparinux or LMWH to accumulate in patients with renal insufficiency.

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Head-to-head comparisons of these agents in ACS patients have been the subject of several clinical trials. In these comparisons, LMWH demonstrates slightly greater efficacy and more bleeding than UFH. Fondaparinux and bivalirudin have similar or greater efficacy relative to either heparin, with less bleeding. The superior safety of fondaparinux and bivalirudin are also postulated as one reason these agents have better long-term outcome data.

The oral antiplatelet agents (aspirin and P2Y12 inhibitors) are often combined with anticoagulants in ACS care. Aspirin is a relatively weak antiplatelet agent that acts by irreversibly inhibiting platelet cyclooxygenase. The effects of aspirin are...
only reversed when new unaffected platelets enter the circulation, which occurs every 10 to 14 days. Aspirin also inhibits prostacyclin production in gastric endothelial cells and therefore carries a slightly greater risk for gastric ulcer formation than the P2Y₁₂ inhibitors. However, among patients at high risk for gastrointestinal ulceration, the use of prophylactic proton pump inhibition with aspirin has been demonstrated to be superior in preventing recurrent gastric side effects compared with switching to clopidogrel without a proton pump inhibitor. Aspirin, when tested against placebo, significantly reduces recurrent ischemic events by ~25% at a cost of an ~1% to 2% per year absolute increase in bleeding.

The P2Y₁₂ inhibitors (ticlopidine, clopidogrel, prasugrel, and ticagrelor) have a stronger inhibitory effect on the platelet than aspirin. Ticlopidine, the first of the ADP receptor blockers, requires twice-daily dosing owing to its short half-life and is rarely used in practice because of uncommon but serious side effects (eg, thrombocytopenia purpura and bone marrow suppression). Clopidogrel and prasugrel are "prodrugs" that require activation in the liver via the cytochrome P450 system. Because of a 1- versus 2-step activation process, prasugrel is more consistent than clopidogrel, with fewer potential drug interactions. Ticagrelor, the newest P2Y₁₂ inhibitor (awaiting approval), demonstrates strong and reversible inhibition of platelet activation. Unlike its predecessors, ticagrelor does not require conversion to its active form, but it requires twice-daily dosing owing to its short half-life.

In terms of efficacy, the addition of clopidogrel to aspirin reduces ischemic events by ~20% at a cost of an ~1% to 2% per year absolute increase in bleeding above that associated with aspirin alone. This association of increased bleeding with dual-antiplatelet therapy appears to be lessened if the dose of aspirin is reduced to 100 mg or less per day. The combination of prasugrel and aspirin recently was shown to be ~20% more effective than clopidogrel and aspirin for reducing ischemic events. Once again, however, this increased efficacy came at a cost of an ~1% absolute increase in bleeding. In subgroup analysis, certain high-risk subgroups (age ≥75 years, weight <60 kg, or history of stroke or transient ischemic attack) had a less favorable balance between safety and efficacy with prasugrel. In another recent study, the comparative efficacy of ticagrelor and aspirin showed similar reductions in ischemic events (~17%) versus clopidogrel but with only a minor associated increase in bleeding events.

The intravenous antiplatelet agents are also components of ACS care, particularly for patients undergoing percutaneous intervention. Glycoprotein IIb/IIIa receptor inhibitors block the final common pathway of platelet activation but carry a risk for thrombocytopenia and bleeding. The small-molecule inhibitors eptifibatide and tirofiban are reversible and short-acting; however, both are renally cleared and require dose adjustment in the setting of chronic kidney disease. Abciximab is a Fab fragment that targets the glycoprotein IIb/IIIa receptor and is specifically used in percutaneous coronary intervention. Timing is important in optimizing risk-benefit for these potent antiplatelet agents, which have the greatest impact at the time of percutaneous intervention.

Finally, the oral anticoagulant warfarin, although not specifically indicated for ACS care, is often used concurrently for other indications in ACS patients (eg, atrial fibrillation, mechanical valves, left ventricular thrombus, or deep venous thrombosis). Warfarin is a racemic mixture of isomers that inhibits synthesis of vitamin K–dependent coagulation factors. The effective dose of warfarin varies significantly among individuals, in part owing to genetic variations in its receptor and metabolism via the cytochrome P450 system. Its metabolism is further influenced by interactions with other drugs, vitamins, and dietary intake. These factors, along with the narrow therapeutic window of warfarin, make individualized dosing and ongoing monitoring of prothrombin time necessary.

Warfarin use alone increases the risk of bleeding to ~13% per year, and risks are highest among new users and the elderly. Patients taking warfarin therapy are excluded from many ACS clinical trials, so data on risks of combined
### Table 1. Antithrombotics and Platelet Inhibitors

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<th>Drug Class</th>
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<td><strong>Anticoagulants</strong></td>
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| UFH                         | Clearance: Dose-dependent hepatic and enzymatic (RES); renal at high doses  
Half-life: ~6 h  
Dosing issues: Weight adjustment; rebound effects after cessation; requires monitoring of aPTT; highly variable response due to protein binding, clearance  
Thrombocytopenia/HIT: ~1-5%; monitor platelet counts  |
| Enoxaparin                  | Clearance: Dose-independent renal; some hepatic  
Half-life: ~7 to 24 h  
Dosing issues: Weight adjustment, consideration of lean vs total body weight, renal function adjustment  
Thrombocytopenia/HIT: Yes, lower risk than with UFH  |
| Fondaparinux                | Clearance: Dose-independent renal  
Half-life: ~17 to 24 h  
Dosing issues: Once-per-day dosing, excellent bioavailability, contraindicated if CrCl <30 mL/min  
Thrombocytopenia/HIT: No  |
| Bivalirudin                 | Clearance: 80% proteolysis, 20% renal  
Half-life: ~30 min; reversible  
Dosing issues: None, renal  
Thrombocytopenia/HIT: Yes, rare  |
| Glycoprotein IIb/IIIa agents| Absciximab  
Clearance: Protease degradation of monoclonal antibody  
Half-life: ~10 to 30 min; long-acting  
Dosing issues: None; slow reversibility (~48 h, some effect persists for 1-2 wks)  
Thrombocytopenia: Yes, modest  |
| Eptifibatide                | Clearance: 50% renal  
Half-life: ~2.5 h; short-acting  
Dosing issues: Renal adjustment, 25% protein binding; fast reversibility (2-4 h)  
Thrombocytopenia: Yes, rare  |
| Tirofiban                   | Clearance: 65% renal  
Half-life: ~2 h; short-acting  
Dosing issues: Renal adjustment; 65% protein binding; fast reversibility (4-8 h)  
Thrombocytopenia: Yes, rare  |
| Oral antiplatelet agents    | Aspirin  
Biological half-life: ~6 days  
Platelet inhibition at standard dosing: + (weak)  
Drug interactions: None  
Special issues: Gastric irritation  |

### Table 1. Continued

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<th>Drug Class</th>
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| Clopidogrel | Biological half-life: 5–6 days  
Platelet inhibition at standard dosing: Onset of action 2–4 h with loading doses of 300–600 mg; ++ (stronger)  
Drug interactions: Some via cytochrome P450  
Special issues: Prodrug requiring conversion (2-step process; 95% inactive)  |
| Prasugrel   | Biological half-life: 5–10 days  
Platelet inhibition at standard dosing: +++ (strongest)  
Drug interactions: None identified  
Special issues: Prodrug requiring conversion (more efficient 1-step process). Caution with prior stroke, age ≥75 y, weight <60 kg, propensity to bleed  |
| Warfarin    | Biological half-life: ~6 to 30 h; varies by clotting factor  
Drug interactions: Many drugs (ie, Cipro, digoxin, amiodarone) and foods (leafy greens)  
Special issues: Delayed onset of action; warfarin skin toxicity  |

RES indicates reticular-endothelial system; aPTT, activated partial thromboplastin time; and CrCl, creatinine clearance.

therapy are limited. Observational data demonstrate a higher rate of bleeding with triple therapy than with antiplatelet therapy alone. Warfarin is still the most effective agent in many settings, so its use in combination with other antithrombotics is often unavoidable.

**Risks of Antithrombotic Therapy**

The most common complication of antithrombotic therapy is bleeding. In-hospital major bleeding occurs in 3% to 15% of trial and registry ACS populations. The definition of “major” bleeding varies across clinical trials and registries; however, most definitions include intracranial hemorrhage, large drops in hemoglobin (>3 mg/dL), bleeding with hemodynamic consequences, bleeding that requires medical intervention or transfusion, and bleeding-related death.

Regardless of definition, major bleeding is associated with higher mortality in a dose-dependent manner. Patients with hemodynamically significant bleeding are at greatest risk of in-hospital mortality compared with those with asymptomatic blood loss or minor bleeding. Major bleeding also increases the adjusted hazard of death at 30 days in ACS patients by >5-fold (adjusted hazard ratio 5.37, 95% confidence interval 3.97 to 7.26) and continues to increase the risk of death by 50% from 30 days to 6 months (adjusted hazard ratio 1.54, 95% confidence interval 1.01 to 2.36).

The early hazard associated with bleeding is clear, yet an association between bleeding and long-term mortality also exists. A time-dependent analysis compared the long-term risks associated with in-hospital bleeding or recurrent ischemia in an ACS population and found that recurrent ischemic events were associated with a 3.1-fold increased risk for death.
that was limited to the first 30 days, whereas major bleeding
was associated with a continued 3.5-fold higher risk at 1
year.\textsuperscript{47} Potential explanations for short-term mortality include
a direct effect of the bleeding event (ie, intracranial hemor-
rhage or hemodynamic collapse), insufficient hemoglobin or
volume loss, or effects of transfusions (ie, inflammatory and
cogulation activation). The long-term association with mor-
tality may be from residual confounding or issues in process
of care (ie, cessation of antithromboses in response to
bleeding). ACS patients who have a major bleed are 50\% less
likely to be discharged with prescriptions for either aspirin or
clopidogrel, and many are still not taking these evidence-
based therapies at 6 months.\textsuperscript{48}

Another less common complication of antithrombotic ther-
apy is thrombocytopenia. In ACS populations, thrombocyto-
penia (platelet count $<150,000/\text{mm}^3$) occurs in 13\% of
patients, and moderate thrombocytopenia (platelet count
$<100,000/\text{mm}^3$) occurs in $\approx 1\%$.\textsuperscript{49} This complication may
arise from heparin-induced thrombocytopenia (HIT), glyco-
protein IIb/IIIa inhibitor–associated platelet consumption, or
nonimmune causes. Regardless of origin, thrombocytopenia
is associated with mortality, major bleeding, and ischemic
complications.\textsuperscript{50}

HIT is a hypersensitivity reaction to heparin mediated via
an IgG antibody to platelet factor 4. This IgG/heparin/platelet
factor 4 complex binds to platelets and cross-links their
receptors, which causes platelet activation and thrombosis.
Both UFH and LMWH cause HIT; however, LMWH is less
antigenic. Bivalirudin and fondaparinux, despite weak bind-
ing to the platelet factor 4 antigen, have not been demon-
strated to cause HIT. In the CATCH (Complications After
Thrombocytopenia Caused by Heparin) registry, 36\% of
patients receiving heparin developed thrombocytopenia
(platelet count $<150,000/\text{mm}^3$ or a reduction in platelet count
of $>50\%$ from baseline). Often, these patients were not
identified until after a thrombotic complication occurred. Of
those patients who were evaluated, 20\% to 25\% had HIT.\textsuperscript{51}
Because of the prevalence and seriousness of this complica-
tion, all patients diagnosed with thrombocytopenia or a
thrombotic complication within 4 to 14 days after starting
heparin therapy should have heparin discontinued immedi-
ately and screening tests performed.\textsuperscript{52}

Autoimmune reactions are another cause of thrombocyto-
penia. True thrombocytopenia (platelet count $<50,000/\text{mm}^3$)
develops in $\approx 2\%$ of patients treated with abciximab.\textsuperscript{53} Severe
thrombocytopenia (platelet count $<20,000/\text{mm}^3$) develops
with abciximab in 0.7\% of patients with the first exposure but
in 12.2\% on reexposure. This complication increases the risk
of bleeding and mortality at 1 year and requires immediate
discontinuation of heparin and abciximab.\textsuperscript{54} Thrombocyto-
penia is less common ($<1\%$) in those treated with a small-
molecule glycoprotein IIb/IIIa inhibitor. It is thought to be
mediated via antibody recognition of the ligand-platelet
receptor complex, with resulting activation and destruction of
the circulating platelets.\textsuperscript{55}

**Drug-, Patient-, and Provider-Associated Risk**
The safety profile of antithrombotic therapy is determined by
drug-, patient-, and provider-associated factors. These factors
are interdependent, yet the right combination is often required
to trigger an adverse event (Figure 1). The field of safety
science has likened this to a “Swiss cheese” model of
causation. According to this model, events must happen in a
particular sequence for an adverse consequence to occur,
much like lining up the holes in slices of Swiss cheese.\textsuperscript{56} As
such, the “average risks” quoted for a particular antithrom-
botic therapy may inaccurately define the actual risk facing a
specific patient and care setting. For example, enoxaparin,
a renally cleared anticoagulant, may not pose much risk when
used in young persons with normal kidney function; however,
if enoxaparin is given to an elderly patient with impaired
renal clearance and the dose is not adjusted, the likelihood for
bleeding quickly escalates. The positive implication of com-
plex causation is that there may be multiple means of
mitigating an individual’s risks and avoiding a potential
event.

**Drug Factors**
Drug-specific factors in antithrombotic safety include the
degree of inhibition related to a specific dose, bioavailability,
metabolism, immune response, and therapeutic window. One
of the first challenges facing the development of a new
antithrombotic agent is selecting the right dose. For most
agents, pharmacological studies in humans help define a
dose-dependent effect of the agent on thrombosis. Yet, these
dose-finding studies are typically limited in total size, and
thus, it is often difficult to select the right dose that reduces
ischemia without increasing bleeding to an unpalatable level.
In addition, the drug dose ultimately selected and tested may
not be ideal when used in heterogeneous populations seen in
clinical practice and when applied in combination with other
antithrombotic therapies.

As a result, several drugs have had their recommended
dose adjusted late in development or after market approval.
An example of this is aspirin. Despite its use for more than
100 years, there remains considerable uncertainty relative to
the “right dose” of aspirin, both acutely and long-term in
various clinical scenarios. In the United States, the majority
of ACS patients receive 325 mg of aspirin, whereas in
Europe, dosing is considerably less. The CURRENT-OASIS
7 (Clopidogrel optimal loading dose Usage to Reduce Recur-
rent EveNTs/Optimal Antiplatelet Strategy for InterventionS)
trial has provided further insight.\textsuperscript{57} In this aspirin- and
clopidogrel-dosing trial among patients with ST-elevation
myocardial infarction or non–ST-segment elevation ACS,
acute ischemic and bleeding events were similar with either
low- or high-dose aspirin; however, there was a significant
interaction between aspirin dose and clopidogrel dose. In the
higher-dose aspirin arm, higher-dose clopidogrel was associ-
ated with less ischemia and less bleeding. Yet, treatment with
high-dose aspirin was not associated with a difference in the
composite end point of cardiovascular death, myocardial
infarction, or stroke at 30 days overall compared with
low-dose aspirin. Likewise, a double dose of clopidogrel was
not associated with a reduction in the primary end point
compared with standard-dose clopidogrel. Recent guidelines
have further modified recommendations for aspirin dose after
coronary stent implantation.\textsuperscript{58}
Beyond the level of anticoagulation associated with dose, each agent also has unique properties that influence its half-life, distribution, activation, and clearance (Table 1). These characteristics contribute to the patient-to-patient variability of each drug. For example, drugs with a short half-life and those with a ready antidote (eg, protamine for UFH) are often associated with a lower risk of bleeding and with bleeding events that are less severe when they do occur. Conversely, drugs with a narrow therapeutic window may be associated with greater risk of bleeding. Antigenicity of a drug or off-target effects may further complicate drug safety (eg, HIT from UFH).

### Patient Factors

Patient-specific factors in antithrombotic safety include body composition, comorbidity, genetics, and lifestyle factors. Weight-based dosing algorithms (eg, heparin) provide dose adjustment based on weight as an estimate for volume of distribution. Yet, weight may not be an accurate surrogate when the proportion of lean body mass to fat is altered, such as in the very old or overweight. Formulas to calculate adjusted body weight are useful in these settings. Body habitus may also alter the effective dose of agents in cases in which the dose is not typically weight-adjusted. For example, weight influences the activity of clopidogrel and has led some to call for higher doses in obese patients.

Medical comorbidity increases the risk for bleeding with antithrombotic therapy. Key risk factors associated with bleeding risk include impaired renal function, older age, female sex, anemia, prior bleeding, and heart failure (Table 2). This list demonstrates the high degree of overlap between risk factors for ischemic events that are also risk factors for bleeding. For example, age increases the risk for death and also increases the risk for bleeding with antithrombotic therapy. Occasionally, however, there are exceptions. A young diabetic patient with ACS without any other comorbidity has a high ischemic risk but a low risk for bleeding. In such patients, the net clinical benefit of intensive antithrombotic therapy is likely. At the other end of the spectrum may be an older patient with poor renal function and ACS in the setting of an acute tachyarrhythmia that causes demand ischemia. In this patient, the benefit of antithrombotic agents for prevention of ischemic events is lower, and the bleeding risk is substantially higher.

Composite scores have been developed based on these factors to assess an individual’s bleeding risk. Although existing scores are helpful to generally risk-stratify patients, they lack information such as genetics, nutrition, frailty, vasculopathy, or bleeding diatheses, which also contribute to hemostasis. Prior bleeding, gastrointestinal ulcerations, or treatment with antiinflammatory agents may also increase bleeding risk with antithrombotic therapy. Some scores include process-of-care factors such as whether the patient underwent an invasive procedure or received antithrombotic therapies, which are known to increase risk of bleeding. This demonstrates that patient factors and drug factors are distinct but additive in determining bleeding risk (Figure 2).

### Provider Factors

Provider-specific factors in antithrombotic safety include drug dosing, use of concurrent drugs or procedures, prevention, patient education, and complication manage-
ment. The most obvious factor, however, is the decision to use antithrombotic therapy in the first place. Personalization of the decision to use 1 or more antithrombotic therapies must be made in light of the balance between bleeding and ischemic risk as noted above (Table 2). Furthermore, switching from 1 agent to another can result in higher ischemic risk by exposing a patient to fluctuating levels of anticoagulation or lower bleeding risk by opting for an agent with less associated bleeding. In the SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein inhibitors) trial, switching heparins at the time of randomization had a likely influence on the observed outcomes. Consistent therapy with enoxaparin was superior for ischemic events but was associated with a minor increase in bleeding.78

Proper dosing is needed to optimize efficacy and safety. In a study of 30 136 ACS patients, 42% of those given heparin or a glycoprotein IIb/IIIa inhibitor received an initial dose that was too high. Older adults, women, and those with renal dysfunction were at particular risk for excessive dosing and also had higher baseline risks for bleeding. These risks were multiplied if an excess dose of 2 or more antithrombotic agents was received. These avoidable dosing errors are estimated to account for up to 15% of major bleeding episodes among patients with ACS.79

Prescribing drugs in combination alters antithrombotic risks. For example, use of amiodarone or antibiotics with warfarin can potentiate its effect, whereas use of some proton pump inhibitors with clopidogrel can lessen its effect.80,81 Recently, the simultaneous use of omeprazole and clopidogrel has been associated with an increased risk of death and recurrent hospitalization for ischemic events.82 Use of antithrombotic agents with warfarin in patients with an ACS event increases risks of bleeding.83 Clinicians must decide whether the benefits of “triple therapy” (ie, warfarin, aspirin, and clopidogrel) are worth the risks, and if so, take steps to ensure careful dosing and prevention (ie, gastrointestinal prophylaxis) in this setting.84

Procedural techniques and other aspects of care modify the risks of bleeding with an invasive strategy. For example, the incidence of groin-site complications is lessened by use of fluoroscopy or ultrasound during femoral access, smaller guide-catheter diameters, and prompt femoral sheath removal.30,31,85–88 Alternatively, compared with femoral access, radial access reduces bleeding by 50% and access-site complications by 80%.89,90 One study also found that radial access reduced 30-day and 1-year mortality compared with femoral access.91 This may be particularly important for patients at risk for access-site complications, such as women and the elderly.88,92

Finally, vigilance for complications may enable timely efforts to interrupt a downward spiral (eg, discontinuation of antithrombotics and supportive care). A shorter duration of bleeding may eliminate the need for transfusions, which themselves have been associated with harm.93 The European Society of Cardiology clinical practice guidelines for unstable angina/non–ST-elevation myocardial infarction now recommend that transfusions be withheld in hemodynamically stable patients with a hematocrit level >25% or a hemoglobin level >8 g/L.94 Continuation of antithrombotic therapy in the setting of a minor contained bleeding event may be advisable. When antithrombotic therapy is stopped for more substantial bleeding events, providers should consider restarting it when it is deemed safe to do so. Patients with bleeding during an ACS are 50% less likely to be discharged on aspirin or clopidogrel and remain off these antithrombotic agents at 6 months, which may be longer than ideal in terms of ischemic protection.88

Future Directions

Development of Safer Agents

The ideal antithrombotic agent has yet to be found; however, anticoagulant and antiplatelet formulations that have predict-

Figure 2. Major bleeding with antithrombotic therapy (from Subherwal et al42). The rate of major bleeding is shown across the 5 groups of baseline bleeding risk by the CRUSADE bleeding score (very low to very high) in patients who then received ≥2 antithrombotics vs <2 antithrombotics. Two or more antithrombotics: antiplatelet (aspirin or clopidogrel), antithrombin agents, or glycoprotein IIb/IIIa; n=50 969; c-index 0.72. Less than 2 antithrombotics: antiplatelet, antithrombin agents, or glycoprotein IIb/IIIa; n=5931; c-index 0.73.
able pharmacokinetics, specific targets, or reversibility come close to achieving this goal. Examples of “safer” agents include those with specific and targeted mechanisms of action, such as the thrombin receptor antagonists. Thrombin receptor antagonists specifically target the protease-activated receptor (PAR-1) on the surface of the platelet, which inhibits thrombin-mediated activation. In theory, their specific action inhibits prothrombotic activity while leaving intact hemostatic properties of platelets, thereby resulting in less bleeding.99 The first thrombin receptor antagonist tested in trials, SCH 530348, supports this hypothesis, because it demonstrated a benefit on reducing ischemic events without increasing bleeding beyond rates seen in the placebo arm.96–98 Whether this class of agents will continue to demonstrate reduced ischemic risks without appreciably increasing bleeding remains to be seen in ongoing phase III trials.

“Safer” agents may also be those that have hit on the ideal inhibitory dose. For example, ticagrelor, an oral ADP-mediated platelet inhibitor, is a more potent and consistent platelet inhibitor than clopidogrel, but perhaps not more so than prasugrel. As studied in the recently released PLATO (PLATElet inhibition and patient Outcomes) trial, the level of inhibition with ticagrelor was associated with a 15% reduction in clinical events relative to clopidogrel, with minimal increases in major bleeding. As a result, ticagrelor had a favorable impact on downstream mortality.24

A third mechanism for “safer” agents is to develop agents with less need for monitoring and a predictable patient-to-patient response. The RE-LY (Randomized Evaluation of Long-term anticoagulation therAPY) trial found that dabigatran, an oral direct thrombin inhibitor, when given in a dose of 110 mg twice daily, had similar efficacy on stroke or systemic embolism with less bleeding than with the standard strategy of warfarin.99 In part, this is likely due to the variable effect across the therapeutic range with warfarin. In addition, dabigatran, unlike warfarin, is specific for thrombin and preserves other hemostatic mechanisms in the coagulation system, thereby preventing bleeding.

“Safer” agents may also include those with the capacity to be reversed rapidly in the event of bleeding. Aprotinin/antidote combinations, which enable rapid onset and offset of anticoagulant action, are an example. Aprotinins (single-stranded oligonucleotides that fit a specific protein) are appealing because of their high-affinity binding to the target protein, short half-lives, and lack of immunogenicity. They also have predictable pharmacokinetics and no need for monitoring.100 Aprotinins are well suited for antidotes, which can regulate or turn off the anticoagulant action when desired.101 Preclinical work with aptamers has been directed at factor VIIa–tissue factor complex, factor IXa, factor Xa, and thrombin, with further clinical studies under way.102

There remains considerable work to be done in determining the “ideal” combination of anticoagulant and antiplatelet therapies in acute and chronic settings. Unfortunately, the risk-benefit ratios of various combinations of antithrombotic drugs cannot be predicted easily from their pharmacology. Thus, there is an ongoing need for randomized trials to delineate the optimal strategies for combination use in common clinical scenarios.

Pharmacogenetics
Personalized medicine is one of the more exciting developments in modern medicine. Selection of patients at high risk for ischemic events on the basis of clinical factors is the first step in deciding to prescribe a multidrug regimen or to select a potent agent from among available options. Pharmacogenomics may then help to identify the “right dose” of an agent on the basis of an individual’s genetic profile. Genetic variations are most relevant for drugs with high interpatient variability in their pharmacokinetics, such as warfarin and clopidogrel.103 Genetic variants related to the metabolism (CYP2C9) and mechanism of action (VKORC1) of warfarin are known to affect steady-state levels.69,70 For example, genetic information may supplement clinical information in bleeding-risk–prediction tools, as has been done for warfarin in atrial fibrillation.66 The application of genetic variation to antiplatelet agents is more complex owing to the variety of receptors that play key roles in platelet activity.104 Genetic variations that affect clopidogrel absorption (ABCB1), conversion to its active form (CYP 3A5 and CYP 2C19), and biological activity (P2Y12 and ITGB3) have been tested for their association with outcomes.105 Despite several plausible targets, only 1 variation (CYP 2C19) was associated with risk of ischemic events.73,106–108 Importantly, this genetic variation does not affect response to prasugrel.109 It might be possible to select antiplatelet therapy on the basis of genetics, but prospective trials are needed before pharmacogenetics can be incorporated into widespread practice.

Better Monitoring
Effective monitoring is a complementary avenue for improving antithrombotic safety. Several studies have demonstrated that 10% to 20% of patients treated with aspirin or clopidogrel demonstrate “resistance,” or a lower degree of inhibition, than the norm. Similarly, there are equal numbers of patients who are “supraresponsive” and demonstrate higher degrees of platelet inhibition than normal. Knowing the variations in the therapeutic effect of antiplatelet therapy in a timely fashion could enable individualized therapy, regardless of the root cause (eg, genetics, metabolic factors, drug interactions, or comorbidity). Commercial assays of platelet function are available, but their utility in the clinical arena remains under investigation.108 Only a few are accessible at the point of care or are capable of monitoring platelet activity across the variety of agents. In the future, better platelet function assays are needed, and their use needs to be better defined.

Process Improvement
In addition to optimization of drug characteristics, optimization of the system that uses the drugs can improve safety. Clinical process improvements in antithrombotic use and dosing are ways to take the dangerous variability (and risks) out of the care process. Over time, trends demonstrate lower rates of major bleeding among ACS patients with the available antithrombotic strategies, perhaps owing to greater provider experience in their incorporation into processes of care.110 Decision support tools, such as computer order entry and dosing guidelines, can also standardize safe antithrombotic
care. The most recent American College of Cardiology/ American Heart Association performance measures have added test measures for antithrombotic dosing accuracy, as well as a measure to encourage centers to put a dosing errors reporting system in place.111 Decision tools to identify risk and benefit on the basis of patient comorbidity can aid in the selection of appropriate treatments among available anti-thrombotic options. When bleeding does occur, decision support tools for use of transfusion have been shown to lessen provider use of transfusion among borderline cases. This may further limit adverse outcomes from unnecessary exposure to blood products.112

Conclusions
Meeting the challenge of optimizing the benefits and minimizing the risks of antithrombotic therapy requires consideration of the pharmacological effects of the drug, relevant individual patient factors, and the context of clinical care. Each of these factors individually or together alters the risk-benefit ratio of therapy. In the future, the genetic, pharmacological, and mechanistic determinants of treatment response will assist in optimizing care and reducing complications. Characteristics of newer antithrombotic agents, improvement in clinical processes, and more targeted drug selection and monitoring of effect may further optimize the care process.

Sources of Funding
This project was supported by cooperative agreement No. U18HS016964 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Disclosures
Dr Peterson receives modest research support from BMS/Sanofi from AstraZeneca and serves as a consultant for Eli Lilly. Dr Alexander reports no conflicts.

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