Abstract—After an acute coronary syndrome, patients continue to be at risk of adverse cardiovascular events despite treatment with the current standard of antithrombotic therapy. The risk may be in part secondary to thrombin, which remains elevated after an acute coronary syndrome event. Several studies have investigated the utility of adding oral anticoagulation to post-acute coronary syndrome medical regimens, with the most promising results coming from the addition of low-dose oral direct anticoagulants. Focusing on optimal dosing strategies and applying therapies to the appropriate populations provide the ability to maximize benefit and minimize risk. (Arterioscler Thromb Vasc Biol. 2015;35:520-524. DOI: 10.1161/ATVBAHA.114.303401.)

Key Words: acute coronary syndrome ▪ anticoagulation ▪ non-vitamin K dependent oral anticoagulants

Acute coronary syndrome (ACS) continues to be associated with significant morbidity and mortality. While adverse cardiovascular events occur at the highest rates during the initial hospitalization and first 30 days after an ACS, there is a persistently elevated risk of recurrent cardiovascular events beyond this early time period. The current standard antithrombotic medical regimen for the long-term care of ACS focuses primarily on antiplatelet therapy. The risk may be in part secondary to thrombin, which plays a major role in thrombus formation and platelet activation in ACS. During acute ACS management, anticoagulants which target thrombin and other factors in the coagulation system are standard of care. Nonetheless, thrombin remains elevated in patients after the initial ACS event, which has prompted investigation into the utility of adding anticoagulation to post-ACS medical regimens. Studies have shown mixed results, with the most promising data coming from the addition of low-dose oral direct anticoagulants to standard post-ACS therapy. Importantly, utilizing optimal dosing strategies and applying therapies to the appropriate populations provide the ability to maximize benefit and minimize risk.

Pathophysiology of ACS

In ACS, platelets adhere to exposed collagen and von Willebrand factor on a ruptured atherosclerotic plaque. Tissue factor released by the subendothelium triggers coagulation, and coagulation factors assemble to create factor Xa, which is responsible for converting prothrombin into thrombin. Approximately 95% of thrombin generation occurs after the initial thrombus formation, which triggers its own expansion. Thrombin also activates protease-activated receptors which lead to further platelet activation. The current standard of care for in-hospital treatment of ACS includes both antiplatelet and anticoagulant medications to inhibit multiple components of the thrombotic process, while long-term care for patients with stabilized ACS focuses primarily on antiplatelet therapy. Despite treatment with dual-antiplatelet therapy, patients with stabilized ACS have an ≈9% to 11% risk of suffering a recurrent adverse cardiovascular event within 1 year. Studies have shown that thrombin levels stay elevated for months after an ACS event. Given the pathobiological evidence to suggest that these patients have persistently elevated thrombin levels and the clinical data to show a persistently elevated risk of adverse events despite antiplatelet therapy, it is appealing to consider adding anticoagulation to the long-term care of patients with stabilized ACS to lower thrombin levels and improve outcomes.

History of Oral Anticoagulants in ACS

The use of anticoagulants to treat myocardial infarction (MI) dates back to the 1930s, when intravenous heparin was found to be effective at preventing thrombus formation in dogs. Further studies in the 1940s showed a benefit of oral anticoagulants in humans with MI. More recently, numerous studies have demonstrated that warfarin, when added to aspirin for long-term therapy after ACS, reduced recurrent MI when the international normalized ratio was kept in a therapeutic range, at the cost of increased bleeding. Warfarin has multiple limitations, including drug and food interactions, genetic variability in metabolism, delayed onset and offset, and the need for frequent monitoring and dose adjustments. As such, non-vitamin K dependent oral anticoagulants, also known as novel oral anticoagulants (NOACs), that
avoid many of these issues have been considered and studied in the management of stabilized ACS.

**Novel Oral Anticoagulants in ACS**

The largest studies of NOACs in ACS patients have tested apixaban and rivaroxaban, both direct factor Xa inhibitors. In the phase 2 dose-ranging APPRAISE-1 trial (n=1715), apixaban was tested versus placebo in patients with recent ACS the majority of whom were also treated with aspirin and clopidogrel. Apixaban showed a dose-dependent increase in bleeding and reduction in ischemic events.\(^\text{17}\) In the phase 3 APPRAISE-2 trial (n=7392), when tested at a dose of 5 mg twice daily, equivalent to the full anticoagulant dose tested for stroke prevention in patients with atrial fibrillation (AF), there was an increase in TIMI major bleeding as compared with placebo (1.3% versus 0.5%; HR 2.59; 95% CI, 1.50–4.46; \(P=0.001\)) without a significant reduction in ischemic events (7.5% versus 7.9%; HR 0.95; 95% CI, 0.80–1.11; \(P=0.51\)).\(^\text{18,19}\) The trial was terminated prematurely because of the increase in major bleeding without an adequate corresponding reduction in ischemic events. Notably, the study population was of relatively high risk and included patients with prior strokes or transient ischemic attacks. If patients with prior strokes or transient ischemic attacks were excluded, the HR for apixaban versus placebo for cardiovascular death, MI, or ischemic stroke was 0.89 (95% CI, 0.74–1.06). Additionally, despite being stopped early, apixaban was associated with a nonsignificant reduction in stent thrombosis compared with placebo (1.6% versus 2.2%; HR 0.73; 95% CI, 0.47–1.12; \(P=0.15\)).\(^\text{18,19}\)

Rivaroxaban is another oral factor Xa inhibitor that was studied versus placebo in patients with recent ACS, the majority of whom were also treated with aspirin and clopidogrel. In the phase 2 dose-ranging ATLAS ACS-TIMI 46 trial (n=3491), rivaroxaban was associated with a dose-dependent increase in clinically significant bleeding and an overall significant reduction in cardiovascular death, MI, or stroke with the numerically lowest HRs seen with the lowest twice-daily doses.\(^\text{1}\) In the phase 3 ATLAS ACS 2-TIMI 51 trial (n=15526), doses of rivaroxaban 2.5 and 5 mg twice daily, which are approximately one-quarter and one-half, respectively, of the total daily doses tested for stroke prevention in patients with AF, were compared with placebo.\(^\text{20,21}\) Patients were followed for a mean of 13 months and up to 31 months. Of note, patients with prior stroke or transient ischemic attacks were excluded from this trial if they were to be treated with background aspirin and clopidogrel. Rivaroxaban reduced the primary end point of cardiovascular death, MI, or stroke (8.9% versus 10.7%; HR, 0.84; 95% CI, 0.74–0.96; \(P=0.008\)) as well as stent thrombosis (2.3% versus 2.9%; HR 0.69; 95% CI 0.51–0.93; \(P=0.02\)).\(^\text{19}\) In terms of the individual doses, both the 2.5 and 5 mg twice-daily doses reduced the primary end point and stent thrombosis as compared with placebo.

The 2.5 mg twice-daily dose versus placebo demonstrated a significant reduction in cardiovascular mortality (2.7% versus 4.1%; HR 0.66; 95% CI 0.51–0.86; \(P=0.002\)) and all-cause mortality (2.9% versus 4.5%; HR 0.68; 95% CI 0.53–0.87; \(P=0.002\)), which was not seen with the 5 mg twice-daily dose.

There was an overall increase in non-CABG TIMI major bleeding (2.1% versus 0.6%; HR, 3.96; 95% CI, 2.46–6.38; \(P<0.001\)) and TIMI bleeding requiring medical attention (14.5% versus 7.5%; HR 2.09; 95% CI 1.83–2.38; \(P<0.001\)) but without a significant increase in fatal bleeding (0.3% versus 0.2%; HR 1.19; 95% CI 0.54–2.59; \(P=0.66\)).\(^\text{20}\) When directly comparing the two active treatment doses, the 2.5 versus 5 mg twice-daily dose resulted in significantly less TIMI bleeding requiring medical attention (12.9% versus 16.2%; \(P=0.001\)) and fatal bleeding (0.1% versus 0.4%, \(P=0.04\)) (Figure 2).\(^\text{22}\) In aggregate, the results suggested that the 2.5 mg twice-daily dose offered the better balance of efficacy and safety, and the 2.5 mg twice-daily dose has been approved by the European Medicines Agency, for example, for patients with recent ACS with elevated markers of cardiac necrosis.

**Higher Degrees of Antithrombotic Therapy**

For years, most patients after an ACS were treated with aspirin and the adenosine diphosphate receptor blocker clopidogrel. However, higher degrees of antithrombotic therapy, such as increased platelet inhibition with prasugrel or ticagrelor, have proven effective in the post-ACS setting. In TRITON-TIMI 38, prasugrel versus clopidogrel in patients with ACS with planned percutaneous coronary intervention reduced the primary end point of cardiovascular death, MI, or stroke (9.9% versus 12.1%; HR, 0.81; 95% CI, 0.73–0.90; \(P<0.001\)), as well as urgent revascularization and stent thrombosis, at the cost of an increased rate of non-CABG TIMI major bleeding.\(^\text{9}\) In PLATO, ticagrelor demonstrated a significant decrease in cardiovascular death, MI, or stroke as compared with clopidogrel (9.8% versus 11.7%; HR, 0.84; 95% CI, 0.77–0.92; \(P<0.001\)) without an increase in overall major bleeding but with an increase in the rate of nonprocedure-related bleeding. Additionally, ticagrelor reduced all-cause mortality compared with clopidogrel (4.5% versus 5.9%; HR 0.78; 95% CI, 0.69–0.89; \(P<0.001\)).\(^\text{15}\) More recently, the protease-activated receptor 1 antagonist vorapaxar was studied versus placebo.
and specifically in patients with a recent MI, vorapaxar was found to significantly reduce the risk of cardiovascular death or ischemic events (8.1% versus 9.7%; HR, 0.80; 95% CI, 0.72–0.89; \( P < 0.0001 \)) at the cost of increases in GUSTO moderate or severe bleeding (3.4% versus 2.1%; HR, 1.61; 95% CI, 1.31–1.97; \( P < 0.001 \)).

These studies, in addition to the ATLAS ACS 2-TIMI 51, further support the concept that intensifying antithrombotic therapy for ACS patients beyond that provided by aspirin and clopidogrel can provide further reduction in adverse cardiovascular events. Generally, the bleeding rates increase as well with this intensification of therapy, but there still remains net benefit in the appropriate patient populations. Intensifying antiplatelet therapy by substituting clopidogrel with either prasugrel or ticagrelor, or adding vorapaxar, is a way to enhance antithrombotic therapy. Likewise, adding low-dose twice-daily rivaroxaban to aspirin and clopidogrel is another strategy to reduce cardiovascular events in patients with a recent ACS.

**Discussion**

When considered in aggregate, the studies examining the addition of oral anticoagulants to aspirin and clopidogrel post-ACS suggest that there is a reduction in adverse cardiovascular events at the expense of an increase in bleeding. There seems to be a level of anticoagulation at which the overall risk-versus-benefit ratio is optimized and the reduction in cardiovascular and all-cause mortality is maximized. For rivaroxaban, a low dose at \( \approx \) one-fourth of the therapeutic dose for stroke prevention in AF demonstrated the most promising results. At full dose, the addition of anticoagulants to dual-antiplatelet therapy after ACS, as was seen with apixaban in APPRAISE-2, resulted in increased bleeding without further efficacy.

Importantly, different populations and disease states influence the response to the addition of anticoagulation to dual-antiplatelet therapy for stabilized ACS. Specifically, patients with prior stroke or transient ischemic attacks do not benefit in the same way from the addition of anticoagulation to dual-antiplatelet therapy after ACS. When excluding these subjects from the APPRAISE 2 trial, there was a trend toward a reduction in the primary efficacy end point of cardiovascular death, MI, or stroke, although further conclusions are limited because the trial was terminated early. Likewise, among the group of patients who underwent percutaneous coronary intervention, rivaroxaban reduced stent thrombosis as compared with placebo, with directionally similar findings with apixaban.

After ACS, the first few months seem to be the period of highest risk for recurrent ischemic events, and studies suggest that elevated thrombin levels and increased coagulation activity also persist during this period of time. Potentially, higher degrees of antithrombotic therapy would be most beneficial in this setting. Further investigation is needed to assess whether a shorter duration, of either the addition of a low-dose anticoagulant or higher degrees of antiplatelet therapy, would indeed be optimal for balancing efficacy and safety.

Likewise, the optimal treatment for patients with both ACS and an indication for full-dose anticoagulation, such as AF, continue to be explored. There are no completed, large-scale, randomized studies evaluating the role of NOACs in these patients. Given that the aggregate data from clinical trials for stroke prevention in AF suggest that NOACs as compared with warfarin are at least as efficacious, reduce mortality, and reduce intracranial bleeding by \( \approx 50\% \), their use may be favorable in patients requiring triple therapy. Ongoing trials, such as PIONEER and RE-DUAL, will hopefully provide further insight into this issue.

There are likely other particular patient characteristics associated with unique responses to anticoagulation for stabilized ACS that have yet to be identified. The use of cardiac biomarkers (ie, troponin, creatine kinase) is one current method to identify patients likely to benefit from enhanced antithrombotic therapy after ACS. Patients with elevated cardiac biomarkers seem to experience a particular benefit from oral anticoagulation after stabilized ACS, consistent with the findings that these patients have significantly elevated morbidity and mortality rates after ACS when compared with those without positive biomarkers. Further studies will
hopefully identify other populations and disease states that are more or less likely to benefit from oral anticoagulation after an ACS.

Regarding options, in patients who present with an ACS, treatment with aspirin and an adenosine diphosphate receptor blocker (such as clopidogrel, prasugrel, or ticagrelor) is usually initiated. In terms of the choice of adenosine diphosphate receptor blocker, increased platelet inhibition with prasugrel or ticagrelor has proven effective in the post-ACS setting with some nuances based on the management approach, bleeding risk, and decisions around preloading. In patients already stabilized on clopidogrel, who have tolerated dual-antiplatelet therapy and in whom a more potent strategy is desired, the addition of low-dose rivaroxaban is one possible option. Notably, low-dose rivaroxaban has not been tested in addition to prasugrel or ticagrelor. Moving forward, as the underlying pathobiology of ACS continues to be explored, it may become evident that some patients benefit most from maximizing the antiplatelet agents and others from combining an antiplatelet with an anticoagulant.

Conclusions

Patients with stabilized ACS have an appreciable risk of recurrent adverse cardiovascular events despite current interventional and medical therapies. Thrombin plays a major role in clot formation and platelet activation, and thrombin levels are persistently elevated after ACS. Parenteral anticoagulants are commonly used to address activated coagulation in the acute management of ACS, but oral antiplatelet therapy is the focus of antithrombotic regimens after hospital discharge. Given the persistently elevated thrombin levels and risk of recurrent adverse cardiovascular events, oral anticoagulants are a potential option for the long-term management of ACS.

Nonetheless, studies of anticoagulants in post-ACS patients have demonstrated mixed results, likely related to dosing and patient characteristics. When low doses of the factor Xa inhibitor rivaroxaban were tested in patients after an ACS, the anticoagulant reduced ischemic cardiac events as compared with placebo. This beneficial effect was accompanied by increased rates of bleeding. However, there was no excess of fatal bleeding events, and rivaroxaban 2.5 mg twice daily demonstrated an overall mortality benefit. Thus, the addition of low-dose rivaroxaban may offer a useful treatment strategy in patients with a recent ACS. Moving forward, it will be important to continue to study the use of oral anticoagulants in patients with ACS, with and without conditions such as AF where full-dose anticoagulation is recommended.

Disclosures

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References


Despite optimal medical management with dual-antiplatelet therapy after acute coronary syndrome, there is a persistent risk of recurrent cardiovascular events. Thrombin levels remain elevated in patients after ACS, prompting investigation into the utility of adding anticoagulation to post-ACS medical regimens. The results have been mixed, with the most promising data coming from the addition of low-dose oral direct anticoagulants to aspirin and clopidogrel post-ACS. Importantly, utilizing optimal dosing strategies and applying therapies to the appropriate populations provide the ability to maximize benefit and minimize risk.
Role of Oral Anticoagulants in Patients After an Acute Coronary Syndrome
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