Novel Oral Anticoagulants in Patients With Acute Coronary Syndrome

Editorial

Novel oral anticoagulants in patients with acute coronary syndrome - R. Ferrari, K. Fox 239

Lead Article

Novel oral anticoagulants after an acute coronary syndrome - K. A. A. Fox 241

Expert Answers to Three Key Questions

How do we manage a patient with atrial fibrillation who develops an acute coronary syndrome? - P. G. Steg 259

What are the recommendations for adding novel oral anticoagulants to P2Y12-receptor inhibitors, with or without aspirin? - G. Campo, S. Biscaglia, L. Fileti, R. Parvasini 266

Is it recommended to switch from novel oral anticoagulants to warfarin after an acute coronary syndrome? - G. Montalescot 275

Fascinomina Cardiologica

Trails of Discovery: The discovery of first-generation antithrombotic drugs - J. D. Fitzgerald 285

Summaries of Ten Seminal Papers - N. V. Joshi 289

Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial
L. Wallentin and others

Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial - J. H. Alexander and others

Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomized, double-blind, phase II trial - J. L. Mega and others

Apixaban with antiplatelet therapy after acute coronary syndrome - J. H. Alexander and others

RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome - P. G. Steg and others

Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial - J. Oldgren and others

Rivaroxaban in patients with a recent acute coronary syndrome - J. L. Mega and others

Rivaroxaban in patients stabilized after a ST-segment elevation myocardial infarction - J. L. Mega and others

New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis - J. Oldgren and others

Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS-ACS 2 TIMI 51 - C. M. Gibson and others

Bibliography of One Hundred Key Papers 301
MEDICINE IS UNDERGOING CONSTANT CHANGE, WITH CARDIOLOGY BEING ARGUABLY THE FASTEST-CHANGING FIELD OF ALL. THE EVOLUTION—OR SHOULD WE SAY, REVOLUTION—OF ANTIMOBILANT THERAPY IS A CASE IN POINT. WE HAVE CERTAINLY COME A LONG WAY SINCE THE EARLY DAYS OF HEPARIN AND WARFARIN (THE LATTER HAVING A RATHER UNSAVORY ASSOCIATION WITH RAT POISON). THIS INCIDENTAL ASSOCIATION ASIDE, WARFARIN, WITH ITS UNDISPUTED EFFICACY, HAS BEEN A HUGE BOON TO ANTIMOBILANT THERAPY, DESPITE LIMITATIONS RELATED TO THE RISK OF OVERDOSE, SIDE EFFECTS, AND INTERACTIONS WITH OTHER MEDICATIONS, DIET, AND CLINICAL CONDITIONS. TODAY, THE NOVEL ORAL ANTIMOBILANTS (NOACS), WHICH HAVE LESS SEVERE SIDE EFFECTS AND AN EFFICACY PROFILE AS GOOD AS OR BETTER THAN THAT OF COUMARINS LIKE WARFARIN, PROMISE A BRIGHT FUTURE AND ARE IN INCREASINGLY WIDESPREA USE.

NOT ONLY IS THIS REVOLUTION IN ANTIMOBILANT THERAPY SCIENTIFIC, BUT ALSO PSYCHOLOGICAL AND EVEN LOGISTICAL. PSYCHOLOGICAL BECAUSE PATIENTS NO LONGER HAVE TO HAVE REGULAR INR TESTS AND THEREFORE NO MORE REGULAR VISITS TO HOSPITALS OR COAGULATION CENTERS, WHICH HAS TRANSFORMED ANTIMOBILANT INTO AN “ORDINARY” THERAPY, WHILE SIMULTANEOUSLY MAKING IT LESS OF A LIFE-DISRUPTING BURDEN. DESPITE THE INITIAL RESERVATIONS OF DOCTORS, WHO WERE INSECURE ABOUT THE LACK OF A REFERENCE THERAPEUTIC MARKER FOR NOACS AND, EVEN WORSE, ANTIDOTES, NOACS HAVE BECOME AN ESTABLISHED PART OF ANTIMOBILANT THERAPY. TODAY, THESE RESERVATIONS HAVE BEEN ALLAYED AS THERE ARE, OR SOON WILL BE, A CHOICE OF ANTIDOTES, AND THE EARLY PESSIMISM AND RELUCTANCE OF DOCTORS HAS BEEN OVERCOME BY THE OVERWHELMING SCIENTIFIC RESULTS SHOWING THE CLEAR ADVANTAGES OF NOACS IN THE TREATMENT OF NONVALVULAR ATRIAL FIBRILLATION, IN TERMS OF BOTH IMPROVED OUTCOME AND LESS BLEEDING.

THE REVOLUTION IN ANTIMOBILANT THERAPY IS ALSO LOGISTICAL IN NATURE BECAUSE, WITH THE INCREASING POPULARITY OF NOACS AND INR SELF-MONITORING, THE DEMAND FOR TRADITIONAL ANTIMOBILANT SERVICES WILL WANNE AND THE HEALTH PERSONNEL PROVIDING THESE SERVICES WILL NEED TO BE REALLOCATED. HOWEVER, CHANGE ALSO COMES WITH NEW ADVANTAGES; FOR EXAMPLE, THE NEW INDICATIONS OF NOACS, SUCH AS THE ACUTE CORONARY SYNDROMES (ACS), WHICH IS THE TOPIC OF THIS ISSUE OF DIALOGUES IN CARDIOVASCULAR MEDICINE.
When we consider thrombosis, we think of two different types of thrombus that originate via different pathways of the coagulation cascade: the red thrombus, occurring in the low-pressure venous system with the coincidence of blood flow stasis, vessel wall injury, and blood hypercoagulability (Virchow’s triad); and the white thrombus, occurring in the high-pressure atrial system due to endothelial damage with subsequent platelet aggregation. This is why antiplatelet agents are normally the gatekeeper that protects against thrombus formation in ACS. However, despite a great deal of progress in antiplatelet therapy, recent studies—such as TRITON–TIMI 38 DAPT (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitors with prasugrel Thrombolysis In Myocardial Infarction–38 Dual AntiPlatelet Therapy) with prasugrel and PLATO DAPT (PLAtelet inhibition and patient Outcomes–Dual AntiPlatelet Therapy) with ticagrelor—clearly and unanimously suggest a substantial number of ischemic recurrences due to acute thrombosis.

Part of the reason for this is that, in real life, a thrombus in the coronary arteries is not only composed of platelets, but also of red blood cells and other hematological components, such as fibrin, leukocytes, neutrophils, etc. Thus, logically, there is also room for anticoagulants in the treatment of ACS. In fact, anticoagulants are already successfully used in the acute setting, but not in the chronic one (when tried in WARIS [Warfarin–Aspirin ReInfarction Study], warfarin caused more damage [bleeding] than benefit). So what can we expect from the NOACs in ACS? Bleeding problems are less of an issue, compared with warfarin. Furthermore, a therapeutic strategy based on prescribing a NOAC and antiplatelet agents together would antagonize thrombus formation via a “double” pathway blockade of the coagulation cascade rather than by only blocking the formation of white thrombus with “double” antiplatelet therapy. The results of ongoing clinical trials in ACS will tell us which of these therapies “doubled”—two antiplatelet agents or two different drug types (antiplatelet plus anticoagulant)—is the right choice.

In this issue of Dialogues, our expert lead author, Keith Fox, has highlighted the importance of short treatment duration and low dose in maximizing the benefit, while minimizing the harm, of anticoagulant therapy in ACS. With their insight and expertise, our three expert respondents have shed light on where we are now with NOACs in ACS and what the future may hold. Ph. Gabriel Steg describes how a patient with atrial fibrillation who develops ACS should be managed, with special reference to the European Society of Cardiology consensus document and its four-step approach based on the assessment of thrombotic risk, bleeding risk, clinical setting, and optimal antithrombotic therapy. Gianluca Campo, Simone Biscaglia, Luca Fileti, and Rita PAVASINI investigate whether, in ACS, the addition of NOACs to new P2Y12-receptor inhibitors, with or without aspirin, is associated with efficacy and safety benefits. Gilles Montalescot finishes by examining whether or not an atrial fibrillation patient on a NOAC who subsequently develops ACS and/or undergoes coronary stenting should be switched to warfarin.
Novel oral anticoagulants after an acute coronary syndrome

Keith A. A. Fox, BSc (Hons), MBChB, FRCP, FESC, FMedSci, FACC
Centre for Cardiovascular Science - Edinburgh - UK

Despite modern secondary prevention therapy, important risks of coronary events remain after acute coronary syndromes (ACS). The options for reducing the rate of these events include more prolonged and more potent dual antiplatelet therapy (aspirin plus ticagrelor, prasugrel, or vorapaxar). For stroke prevention in atrial fibrillation, novel oral anticoagulants (NOACs) are effective. After ACS, antiplatelet therapy is also necessary, and the challenge for NOACs is to provide sufficient anticoagulation to improve outcomes, without increasing major and fatal bleeding. Full-dose anticoagulation combined with dual antiplatelet therapy has been tested for warfarin and apixaban, but both combinations resulted in higher rates of major bleeding. In the apixaban secondary prevention trial, this bleeding hazard was not accompanied by improved outcomes. Current guidelines indicate that the duration of triple therapy must be kept as short as possible to reduce bleeding when using warfarin plus dual antiplatelet combinations. For rivaroxaban, one-half or one-quarter of the full anticoagulant dose was tested in conjunction with antiplatelet therapy after ACS. The optimal balance between benefit and risk was achieved with the lowest dose of rivaroxaban and the numbers needed to treat to achieve a benefit, while minimizing harm, are comparable, or better, than those using potent antiplatelet combinations for secondary prevention.

Keywords: acute coronary syndrome; anticoagulant; antiplatelet; hemorrhage; thrombosis

Address for correspondence:
Keith A. A. Fox, Centre for Cardiovascular Science, Chancellor’s Building, 49 Little France Crescent, Edinburgh EH16 4SB, UK
(e-mail: k.a.a.fox@ed.ac.uk)

Copyright © 2015, MICH - Servier Research Group. All rights reserved

Copyright © 2015, MICH - Servier Research Group. All rights reserved

PHYSIOLOGICAL BACKGROUND

Acute coronary syndrome (ACS) is not a single disease entity, rather it describes the clinical manifestations of a heterogeneous spectrum of conditions that share key pathophysiological features. The central features include disruption or erosion of coronary atheromatous plaques, changes in vascular tone, and thrombus formation. The clinical presentations comprise ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). The clinical presentation is determined by the extent of coronary obstruction, the volume of ischemic myocardium, and the temporal pattern of the atherothrombotic disease process (Figure 1). Thus, complete coronary occlusion typically underlies STEMI, whereas incomplete coronary occlusion is associated with NSTEMI and UA. Importantly, ACS occurs in patients with underlying symptomatic or occult coronary artery disease and flow-limiting or non-flow-limiting atheromatous plaques in the coronary arterial wall. Such patients are at risk of recurrent and de novo plaque rupture and thrombotic events.

Figure 1. Thrombus extending into the lumen of a coronary artery after acute plaque rupture associated with a myocardial infarction. Postmortem specimen. Reproduced with the permission of Michael Davies.
In ACS, the pattern and severity of clinical manifestations depend on the degree of obstruction to perfusion, the presence or absence of collateral perfusion, the extent and distribution of fragmented microthrombi, and myocardial oxygen demand in the perfused territory. Thus, the clinical consequences of plaque rupture can include the following range of events: (i) an entirely silent episode; (ii) unstable symptoms of ischemia without measurable markers of myocardial infarction; (iii) profound ischemia complicated by a progressive myocardial infarction, or (iv) heart failure and sudden death. Thrombus formation and micro-embolization are key pathophysiological components across the spectrum of ACS.

### The role of anticoagulation and platelet inhibition in ACS

The early management of ACS aims to relieve ischemia by reducing myocardial oxygen demand, inhibiting thrombotic occlusion, and reducing coronary obstruction. The goal is to prevent the formation of additional thrombi and prevent or manage complications. Modern management strategies involve pharmacological therapies and percutaneous coronary interventions (PCI). Both platelet inhibition and anticoagulation are critically important to reduce early thrombotic complications of ACS and reduce thrombotic complications that would otherwise be associated with PCI and stent implantation.

Prior to modern interventional therapy, the combination of intravenous heparin and low-dose aspirin was first tested 25 years ago by Wallentin et al in the RISC trial (Relationship between Insulin Sensitivity and Cardiovascular disease risk). A total of 796 men with unstable coronary artery disease (UA or NSTEMI) were randomized to a double-blind, placebo-controlled treatment of oral aspirin 75 mg/day and/or 5 days of intermittent intravenously administered unfractionated heparin. With aspirin, the risk of myocardial infarction and death was reduced by more than half (risk ratio [RR] at day 5, 0.43 [95% CI, 0.21-0.91]; RR at 1 month, 0.31 [95% CI, 0.18-0.53]; RR at 3 months, 0.36 [95% CI, 0.23-0.57]). Aspirin reduced the rate of NSTEMI and UA events, independent of electrocardiographic abnormalities or concurrent drug therapy. The group treated with aspirin and heparin had the lowest number of events during the initial 5 days. Following the RISC trial, aspirin and some form of anticoagulation have formed part of the acute treatment of ACS.

Although aspirin is effective in ACS, multiple pathways of platelet stimulation are active in patients with ACS. In the CURE trial (Clopidogrel in Unstable angina to prevent Recurrent Events), the adenosine diphosphate antagonist clopidogrel was tested with aspirin, which proved to be more effective than aspirin alone. Internationally, the combination of low-dose aspirin and clopidogrel has been widely adopted. Clopidogrel requires metabolism for activation and some patients exhibit reduced responsiveness to clopidogrel. In recent trials, ticagrelor and prasugrel have been shown to be more effective than clopidogrel, and consequently ticagrelor and prasugrel are preferred to clopidogrel in the European Society of Cardiology (ESC) guidelines for ACS. The glycoprotein IIb/IIIa complex continues to have a role for receptor antagonists in some patients with thrombotic complications during PCI.

Continuous intravenously administered unfractionated heparin required monitoring and dose adjustment, and the treatment was associated with bleeding complications and a small risk of heparin-induced thrombocytopenia. This regimen proved logistically complex in clinical practice; therefore, more clinically applicable anticoagulation strategies were developed. These included low-molecular-weight heparin and the factor Xa inhibitor fondaparinux. Low-molecular-weight heparin was simpler to administer (subcutaneous injection) and did not require monitoring. Several trials were conducted using a more prolonged administration of low-molecular-weight heparin, which was continued on an outpatient basis after ACS. The low-molecular-weight heparin (dalteparin) was tested against placebo in aspirin-treated patients (n=1506) after hospitalization for ACS. During the 6-week treatment phase major bleeding events were uncommon and there was a sig-

### SELECTED ABBREVIATIONS AND ACRONYMS

| ACS | acute coronary syndrome |
| IVUS | intravascular ultrasound |
| Lp-PLA₂ | lipoprotein-associated phospholipase A₂ |
| NOAC | novel oral anticoagulant |
| NSTEMI | non-ST-segment elevation myocardial infarction |
| PAR-1 | protease-activated receptor-1 |
| PCI | percutaneous coronary intervention |
| STEMI | ST-segment elevation myocardial infarction |
| TIMI | Thrombolysis In Myocardial Infarction |
| UA | unstable angina |
| VKA | vitamin K antagonist |
significant reduction in the rate of the composite of death or myocardial infarction ($P=0.04$). However, the treatment effect was not sustained with a longer-term follow-up and the subcutaneous administration limited the practicality of longer treatment durations.

Low-molecular-weight heparin was also shown to be more effective than unfractionated heparin in STEMI. Consequently, low-molecular-weight heparin was widely adopted in the acute management of ACS. Following ACS, two major challenges remained: (i) reducing the risk of bleeding; and (ii) the impracticality of long-term subcutaneous injections.

Direct factor Xa inhibitors (low-molecular-weight heparins act indirectly and have a partial antifactor Xa activity) were first used in the treatment and prevention of venous thrombosis. Fondaparinux was the first factor Xa inhibitor to be tested against low-molecular-weight heparin (enoxaparin) in ACS and proved to be as effective in the acute phase (first 9 days), but was associated with significantly less bleeding and lower rates of late mortality. In the context of PCI and stent implantation, there was a small, but potentially important, risk of thrombus formation with guidewires, hence, for PCI procedures, fondaparinux use requires additional heparin. Both platelet inhibition and anticoagulation regimens have been extensively tested in the acute phase of ACS and their combination forms part of the standard of care in patients with ACS.

**UNDER-RECOGNIZED AND UNDERESTIMATED CARDIOVASCULAR EVENTS FOLLOWING ACS**

The early management of ACS has been transformed after implementation of evidence-based strategies to provide prompt reperfusion in STEMI and reduce ischemia in non–ST-segment elevation ACS. However, prior to the development of comprehensive registry programs in ACS, the late consequences of ACS were under-recognized and underestimated and few trials focused on reducing cardiovascular events following ACS. Guidelines recommend lifestyle modifications,
smoking cessation, rehabilitation after myocardial infarction, and secondary prevention medications (statins, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and dual antiplatelet therapy). Most patients are discharged from the hospital with 6 to 10 medications to take each day, but are these secondary prevention measures sufficient to reduce the late consequences of ACS?

The large-scale, multinational, observational GRACE registry (Global Registry of Acute Coronary Events; 1999-2009) was established to provide reliable and precisely defined data on the treatment, practice patterns, and outcomes of more than 70,000 patients with ACS from 14 countries. As part of the program, the GRACE risk score was developed and validated for patients with ACS to guide the triage and early management of ACS and to provide a robust method for measuring the risk of subsequent cardiovascular events.

The key findings of this trial demonstrate that the long-term hazards are greatest after NSTEMI (presenting with ST-segment depression, Panel B). These event rates continue to rise over time. Abbreviations: ACS, acute coronary syndrome; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

The category of ACS (STEMI, NSTEMI, or UA) influenced the distribution of subsequent deaths; however, by 5 years, there were remarkably similar rates of total mortality (20% to 22%) for those surviving the initial ACS event. When considering all deaths from the initial ACS admission to 5 years after admission, 86% of the NSTEMI deaths and 68% of the post–STEMI deaths occurred during the postdischarge follow-up. The trial also revealed a large morbidity and resource burden of recurrent cardiovascular events and admissions for suspected ACS (≈1.6 admissions per patient) (Figure 3). These events occurred despite implementation of guideline-based secondary prevention therapies.

Are the rates of late events in recent, well-treated trial populations similar to those reported from the comprehensive GRACE registry? The results from the SOLID–TIMI 52 trial (Stabilization Of plaques using Darapladib–Thrombolysis In Myocardial Infarction 52), showed no evidence for a reduction in events when using the lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor, as there was a 15% rate of cardiovascular death, myocardial infarction, or stroke in the 36 months following ACS admission. Thus, both registry trials in ACS and recent trials with excellent implementation of secondary prevention therapy showed rates of late cardiovascular events that cumulatively far exceed those of the in-hospital phase of ACS. A key question is whether the late cardiovascular events after ACS are due to de novo ACS events or whether they
are related to the original culprit lesion. Studies using angioscopy, intravascular ultrasound (IVUS), and optical coherence tomography have all revealed multiple plaques, showing evidence of disruption and intraplaque hemorrhage at the time of ACS presentation. Thus, plaque disruption is not a singular event confined to a single “vulnerable plaque,” rather there is evidence of simultaneous plaque rupture events in the coronary tree and elsewhere. For example, in Japan, carefully conducted angioscopy trials on multiple non-occlusive plaques showed evidence of intraplaque hemorrhage in addition to the culprit lesion. These trials compliment the earlier investigations of upregulated systemic inflammation at the time of ACS presentation.

In the PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), IVUS analysis revealed that approximately half of the events occurring within 3 years after ACS were related to the culprit lesion and about half were related to de novo plaque rupture events (Figure 4, page 246). Recent trials have used combined positron emission tomography (PET) and computerized tomography (CT) to detect vulnerable plaques after ACS presentation and in patients with stable coronary artery disease. This novel approach detects microcalcification triggered by plaque inflammation using a 18F-fluorine PET tracer. Thus, plaque vulnerability is not a singular event, nor is it confined to the site of the culprit lesion in ACS. Therefore, systemic approaches are needed to mitigate the impact of multiple plaque ruptures in patients who are at the highest risk for these events.

A second question is whether the late cardiovascular events are potentially preventable with antithrombotic and anticoagulant strategies. Based on the GRACE registry, 12.7% of patients discharged after an ACS admission will have an additional myocardial infarction in the following 5 years and 56% will have another admission for ACS. More than half of the late deaths were due to cardiovascular reasons and, among the cardiovascular deaths, some occurred soon after an additional myocardial infarction. Thus, the recurrent myocardial infarctions and further ACS presentations will have involved coronary thrombosis and a proportion of these are preventable. The CURE, PLATO (PLATelet inhibition and patient Outcomes), and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in patients with prior heart attack using ticagrelor tablets compared to placebo on a background of aspirin–Thrombolysis In Myocardial Infarction 54) trials all had a late divergence of the curves in favor of the more potent antiplatelet strategy, showing that the adjunctive antiplatelet therapy reduced later events. In analogous trials on anticoagulation or platelet-thrombin inhibition, both the ATLAS ACS 2 trial (Anti-Xa Therapy to Lower cardiovascular events in Subjects with Acute Coronary Syndrome) on rivaroxaban and the TRACER trial (Thrombin Receptor Antagonist for Clinical Event Reduction in acute coronary syndrome) on vorapaxar, a platelet thrombin receptor antagonist, showed that late events could be reduced with antithrombin strategies (discussed below).

**PRIOR TO THE DEVELOPMENT OF THE CURRENT NOACs, WAS THERE EVIDENCE FOR USING ANTICOAGULATION AFTER ACS?**

The concept of anticoagulation after myocardial infarction or ACS is not new and trials on the anticoagulant warfarin predate modern ACS management. The combination of warfarin plus aspirin, in a variety of
intensity regimens, was tested against aspirin alone (RR, 0.89; 95% CI, 0.84-0.94), but this was accompanied by a significant increase in major and minor bleeding. For example, a trial that compared warfarin (international normalized ratio [INR], 1.8) plus 81 mg aspirin vs 162 mg of aspirin alone in approximately 5000 patients with a recent myocardial infarction, major bleeding was more common with warfarin plus aspirin than with aspirin alone (1.28 vs 0.72 events per 100 person-years; \( P=0.001 \)).

In 16 randomized controlled trials using high-intensity anticoagulation with warfarin (INR >2.8), total mortality was reduced by 22% (95% CI, 13%-31%), reinfarction by 42% (95% CI, 34%-48%), and stroke by 48% (95% CI, 33%-60%), but with a significant increase in major bleeding. Randomized controlled trials using moderate-intensity anticoagulation therapy with warfarin (INR, 2 to 3) reduced reinfarction by 52% (95% CI, 37% to 64%), but this was still associated with increased bleeding.

Despite evidence of benefit with anticoagulation using vitamin K antagonists (VKA), the balance between efficacy and major bleeding was not sufficiently favorable. VKA anticoagulation after myocardial infarction was never adopted in the international guidelines for secondary prevention after ACS.

**Role of direct thrombin inhibitors following ACS?**

Fibrin-bound thrombin is enzymatically active and resistant to heparin-induced inactivation. Through a positive feedback loop (via the coagulation factors V and VIII), fibrin-bound thrombin releases fibrinopeptide A, which promotes further thrombus formation. Fibrin-bound thrombin also activates platelets through thromboxane A2–independent mechanisms that cannot be blocked by aspirin. The pathways of thrombin activation and platelet aggregation are interconnected. Thrombin is a potent activator of platelets and platelet aggregation stimulates the generation of thrombin. In
addition, feedback amplification loops exist in both the pathways of coagulation and platelet activation. In a meta-analysis of published trials, direct thrombin inhibitors (hirudin, bivalirudin, agatrobain, efgatran) were associated with a lower risk of death or myocardial infarction at the end of treatment (4.3% vs 5.1%, odds ratio [OR], 0.85; 95% CI, 0.77-0.94; \( P < 0.001 \)) and at 30 days posttreatment (7.4% vs 8.2%; OR, 0.91; 95% CI, 0.84-0.99; \( P = 0.02 \)). This was primarily due to a reduction in myocardial infarction (2.8% vs 3.5%; OR, 0.80; 95% CI, 0.84-0.99; \( P < 0.001 \)), but with no effect on death (1.9% vs 2.0%; OR, 0.97; 95% CI, 0.83-1.13; \( P = 0.69 \)). Compared with heparin, there was an increase in major bleeding with hirudin, but a reduction with bivalirudin.

These findings suggest that a more effective and consistent anticoagulation than can be achieved with heparin is associated with reduced rates of cardiovascular events (especially myocardial infarction). In summary, older trials with VKAs, low-molecular-weight heparins, and direct thrombin antagonists have all shown evidence of benefit in reducing the rate of cardiovascular events after ACS. The “Achilles’ heel” of these approaches is the increased risk of major bleeding, offsetting the potential benefits. Hence, the search for a more favorable risk-benefit ratio with novel agents is rational and based on substantial trial evidence.

**Role of platelet inhibition following ACS**

The trials of oral antiplatelet therapy, beyond aspirin, initiated dual antiplatelet treatment after the presenting diagnosis of ACS (CURE trial and PLATO trials) or in the catheterization laboratory after angiography (TRITON–TIMI 38 trial) TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel–Thrombolysis In Myocardial Infarction 38) and they were continued for 9 or 12 months after ACS. Landmark analyses have demonstrated a long-term treatment effect. For example, the CURE and PLATO trials demonstrated that antiplatelet therapy effectively inhibits the impact of new atherothrombotic events.

The TRILOGY trial (TaRgeted platelet Inhibition to cLarify the Optimal straGeY to medically manage acute coronary syndromes) tested prasugrel against clopidogrel for more than 30 months post–ACS in patients unsuitable for revascularization. Although prasugrel was markedly and persistently more effective than clopidogrel at inhibiting upregulated platelets (measured with platelet reactivity assays), this did not translate into improved outcomes for the trial as a whole. Previously, prasugrel had been shown to be more effective than clopidogrel in ACS patients undergoing PCI, but this more potent platelet inhibition failed to reduce the frequency of later cardiovascular events in conservatively managed patients after ACS. Vorapaxar inhibits the protease-activated receptor-1 (PAR-1) on platelets. Phase 2 trials suggest that this approach may have a lower risk of bleeding than was observed with prior trials. In the TRA 2P–TIMI 50 trial (Thrombin Receptor Antagonist in secondary Prevention of atherothrombotic ischemic events–Thrombolysis In Myocardial Infarction 50), stable patients (2 weeks to 12 months after a myocardial infarction, an ischemic stroke, or in patients with peripheral arterial disease) were randomized to vorapaxar plus aspirin or aspirin alone for secondary prevention. Cardiovascular death, myocardial infarction, or stroke was reduced with vorapaxar (hazard ratio [HR], 0.87; 95% CI, 0.80-0.94; \( P < 0.001 \)). However, moderate or severe bleeding occurred in 4.2% of patients who received vorapaxar plus aspirin vs 2.5% with aspirin alone (HR, 1.66; 95% CI, 1.43-1.93; \( P < 0.001 \)). There was an increase in the rate of intracranial hemorrhage with vorapaxar plus aspirin (1.0% vs 0.5% with aspirin alone, \( P < 0.001 \)). The benefits were mainly seen in patients with a prior myocardial infarction, and conversely, bleeding complications and intracerebral bleeding were the most common in patients with a prior stroke.

The challenge is to devise an optimal antithrombotic strategy that involves platelet inhibition and anticoagulation, and the optimal balance between potency in reducing cardiovascular events and the risk of bleeding, ie, the “sweet spot” between efficacy and safety.

**FOR SECONDARY PROTECTION AFTER ACS, CAN NOACs PLUS ANTIPLATELET THERAPY ACHIEVE THE OPTIMAL BALANCE BETWEEN EFFICACY AND SAFETY?**

This challenge is complex. A combination of platelet inhibition and anticoagulation that is too potent will result in an excess bleeding hazard, as demonstrated in the earlier trials of high-intensity warfarin plus aspirin and several of the more recent trials of drug combinations (see above). Conversely, in addition to current secondary prevention measures, a combination that is too weak will not achieve a clinically worthwhile treatment effect. Therefore, after ACS, which antiplatelet/antithrombin regimens are the closest to the “sweet spot” in the balance between efficacy and safety?
The oral direct thrombin inhibitor ximelagatran was tested in a dose-ranging trial using four doses of xime-
lagatran vs placebo after ACS. The ESTEM trial (Efficacy and Safety of the oral direct Thrombin inhibitor ximElagatran in patiEnts with recent Myocardial dam-
age) compared a 6-month treatment of ximelagatran plus aspirin with aspirin alone to determine the effects-
tiveness in preventing ischemic events (ie, all-cause mortality, nonfatal myocardial infarction, and severe recurrent ischemia) in 1883 patients randomized within 14 days after a myocardial infarction. Oral ximelagat-
tran plus aspirin reduced the risk for the primary end point compared with aspirin alone from 16.3% to 12.7% (HR, 0.76; 95% CI, 0.59-0.98; *p*=0.036). There was also a significant reduction in the composite rate of death, nonfatal myocardial infarction, or nonfatal stroke compared with aspirin alone (7% vs 11%; OR, 0.66; 95% CI, 0.48-0.90 for all doses combined), which was associated with a small increase in bleeding (2% vs 1%). However, ximelagatran had to be withdrawn from the market due to hepatotoxicity. Nevertheless, the trial raised the possibility that thrombin inhibition, with a nontoxic agent, may favorably impact cardiovascular outcomes after ACS.

**APPRAISE-2 trial**

Apixaban, a factor Xa inhibitor, has been successfully developed for the management of venous thrombosis and the prevention of stroke in patients with atrial fibrillation. In the stroke prevention trials, a dosage of 5 mg twice daily was used. In parallel with the rivaroxaban trials in ACS, a program was developed to test apixaban after ACS. The APPRAISE-2 trial (APixaban for PeRevention of Acute Ischemic Events 2) recruited 7392 patients and deliberately targeted high-risk pa-
tients, including patients with a prior stroke or tran-
sient ischemic attack. Further, the trial tested the full atrial fibrillation dose of apixaban (5 mg twice daily), in addition to platelet inhibition. The trial was terminated early due to an increase in major bleeding events with apixaban in the absence of a significant reduct-
ion in recurrent ischemic events.

At a median follow-up of 241 days, the primary outcome of cardiovascular death, myocardial infarction, or ischemic stroke occurred in 7.5% of the patients randomized to apixaban and 7.9% of the patients randomized to placebo (HR with apixaban, 0.95; 95% CI, 0.80-1.11; *p*=0.51). The primary safety outcome of major bleeding (TIMI criteria) occurred in 1.3% of pa-
tients who received apixaban (2.4 events per 100 pa-
tient-years) and in 0.5% of those who received placebo (0.9 events per 100 patient-years) (HR with apixaban, 2.59; 95% CI, 1.50-4.46; *p*=0.001). A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo. At the time of random-
ization, nearly all patients (97%) were taking aspirin. The majority of patients (81%) were receiving aspirin plus a P2Y12-receptor antagonist, predominantly clopidogrel.

The APPRAISE-2 trial enrolled a high-risk patient pop-
ulation, where a large proportion of the patients had diabetes (48%), heart failure (28%), renal insufficiency (29%), or cerebrovascular disease (10%). The combination of a population at a high risk of bleeding and using a full anticoagulant dose plus a dual antiplatelet regimen missed the “sweet spot,” achieving similar ef-
icacy, but significantly more bleeding. Nonetheless, it is worth noting that the apixaban group had num-
erically fewer myocardial infarctions and cardiovas-
dicular deaths: myocardial infarction (4% with apixaban vs 5.3% with placebo; HR, 0.93; 95% CI, 0.76-1.14) and cardiovascular deaths (2.8% with apixaban vs 3.0% with placebo; HR, 0.96; 95% CI, 0.73-1.25).

The APPRAISE-2 trial investigators examined the risk factors for bleeding within the trial. The proportion of patients that experienced TIMI major or minor bleed-
ing, International Society on Thrombosis and Hemo-
stasis (ISTH) major or clinically relevant nonmajor bleeding, or any bleeding was 1.5%, 2.2%, and 13.3%, respectively. The incidence of bleeding was highest in the immediate post–ACS period, but more than 60% of major bleeding events occurred >30 days after the end of the index hospitalization. Gastrointestinal bleeding was the most common cause of major bleed-
ing. Independent predictors of bleeding events includ-
ed older age, renal dysfunction, dual oral antiplatelet therapy, smoking history, increased white blood cell count, and coronary revascularization. However, ad-
tional factors influencing the overall rate of bleeding were the enrichment of the trial population and use of the anticoagulation dose of apixaban used for stroke prevention in addition to dual antiplatelet therapy.

The APPRAISE-2 trial chose to include a population of patients with an increased risk of bleeding and the trial used a full anticoagulant dose of apixaban in addition to dual antiplatelet therapy. As a result, the trial was unable to find the optimal balance between efficacy and safety.
ATLAS ACS trials (TIMI 46, TIMI 51)

The ATLAS ACS trials comprised a multidose phase 2 trial of rivaroxaban (TIMI 46) and a large outcome trial testing two doses of rivaroxaban vs placebo in addition to antiplatelet therapy after ACS.21,35

ATLAS ACS–TIMI 46 trial

The ATLAS ACS–TIMI 46 phase 2 trial was a double-blind, dose-escalation trial that randomized 3491 patients who had been stabilized after ACS.35 They were stratified into one of two groups, based on the investigator’s decision to use aspirin only (stratum 1; n=761) or aspirin plus a thienopyridine (stratum 2; n=2730). Participants were randomized within each stratum to receive either placebo or rivaroxaban (at doses ranging from 5 to 20 mg), which was given once daily or the same total daily dose given twice daily.35 The primary safety end point was clinically significant bleeding, the primary efficacy end point was the time to the first episode of death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularization during the 6 months following randomization, and the secondary efficacy end point was death, myocardial infarction, or stroke.

Rivaroxaban treatment was associated with a trend toward a reduction in the primary efficacy end point (7.0% vs 5.6%; P=0.10) and a significant reduction in the secondary efficacy end point (5.5% vs 3.9%; P=0.03) (Figure 5).35 There was a dose-dependent increase in bleeding events and a consistent trend for benefit in both stratum. In those treated with aspirin alone, rivaroxaban reduced the risk of death, myocardial infarction, or stroke from 11.9% to 6.6% (HR, 0.54; 95% CI, 0.27-1.08; P=0.08) and among patients treated with both aspirin plus clopidogrel, rivaroxaban showed a similar trend (reduced risk of death, myocardial infarction, or stroke from 3.8% to 2.0% [HR, 0.55; 95% CI, 0.27-1.11; P=0.09]) vs placebo.35 The lowest hazard ratios were seen at the lowest twice-daily doses, whereas there was a dose-dependent increase in bleeding events as the dosage of rivaroxaban increased.35 For these reasons, the two lowest doses of rivaroxaban (2.5 and 5.0 mg given orally twice daily) were chosen for the phase 3 trial—ATLAS ACS 2–TIMI 51 trial (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction).

ATLAS ACS 2–TIMI 51 trial

In the phase 3 trial ATLAS ACS 2–TIMI 51,21 15,526 patients with a recent ACS event were randomized to receive either 2.5 mg or 5 mg of rivaroxaban or placebo twice daily, for an average of 13 months. The index ACS events included STEMI, NSTEMI, and UA, which occurred in 50.3%, 25.6%, and 24.0% of patients, respectively, with a median time from the index event to randomization of 4.7 days; therefore, this was a secondary prevention trial.21

The primary efficacy end point was the composite of death from cardiovascular causes, myocardial infarction, or stroke. The decision as to whether the patient received single antiplatelet therapy (aspirin; stratum 1)
or dual antiplatelet therapy (aspirin plus a thienopyridine; stratum 2) was determined by the physician managing the patient, and unsurprisingly, most patients received dual antiplatelet therapy (93%).

The primary efficacy end point was significantly reduced with rivaroxaban treatment vs placebo. According to the statistical analysis plan, both groups of rivaroxaban (combined) were analyzed first. If the results were significant, then the individual doses would be analyzed (HR for rivaroxaban (combined), 0.84; 95% CI, 0.74-0.96; P=0.008). There was significant improvement in both the twice-daily 2.5-mg dose of rivaroxaban (9.1% vs 10.7%, P=0.02) and the twice-daily 5-mg dose (8.8% vs 10.7%, P=0.03) (Figure 6). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs 4.1%, relative risk reduction (RRR), 34%; P=0.002) and from any cause (2.9% vs 4.5%, RRR, 32%; P=0.002). The survival benefit was not observed with the twice-daily 5-mg dose. Rivaroxaban reduced the risk of stent thrombosis (definite, probable, or possible) vs placebo (2.3% vs 2.9%; HR, 0.69; 95% CI, 0.51-0.93; P=0.02) (Figure 7).

**Figure 6. Results of the ATLAS ACS 2–TIMI 51 phase 3 trial.**

Significant benefits were seen for the 2.5-mg twice-daily dose of rivaroxaban vs placebo. The primary end point of cardiovascular death, myocardial infarction, or stroke, cardiovascular death alone, and all-cause death had absolute benefits of 1.6%, 1.4%, and 1.6%, respectively.

**Figure 7. Rates of stent thrombosis in the ATLAS ACS 2–TIMI 51 phase 3 trial.**

Significant benefits were seen for the 2.5-mg twice-daily dose of rivaroxaban vs placebo (absolute benefit, 0.6%).

Abbreviations: CV, cardiovascular; HR, hazard ratio; ITT, intention to treat; MI, myocardial infarction; mITT, modified intention to treat; NNT, number needed to treat.


cacy end point with rivaroxaban was consistent among the subgroups except for patients with a history of stroke or transient ischemic attack. The benefits of rivaroxaban were similar in each category of ACS (STEMI, NSTEMI, and UA) with hazard ratios of 0.85, 0.85, and 0.82, respectively. Rivaroxaban increased the rates of major bleeding not related to coronary artery bypass grafting (2.1% vs 0.6%; \( P < 0.001 \)) or intracranial hemorrhage (0.6% vs 0.2%; \( P = 0.009 \)), without a significant increase in fatal bleeding (0.3% vs 0.2%; \( P = 0.66 \)) or other adverse events.21 The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs 0.4%; \( P = 0.04 \)).

An increase in bleeding events has been seen with each of the trials testing an antithrombotic agent plus antiplatelet therapy after ACS. These phase 2 trials evaluated rivaroxaban, apixaban, dabigatran, and darexaban, and they all showed dose-dependent increases in bleeding. In the ATLAS ACS–TIMI 46 and APPRAISE-1 (NCT00313300)37 trials, rivaroxaban and apixaban also showed trends toward a reduction in cardiovascular events.

In summary, both the 2.5-mg and 5.0-mg doses of rivaroxaban significantly reduced the primary efficacy end point, with the twice-daily 2.5-mg dose also reducing mortality. In terms of safety, the two doses of rivaroxaban increased the rates of major bleeding and intracranial hemorrhage vs placebo, without a significant increase in fatal bleeding. The lower dose of rivaroxaban resulted in less bleeding than the higher dose.

**KEY ISSUES TO CONSIDER WHEN INTERPRETING THE RESULTS OF THE ATLAS ACS 2 AND APPRAISE-2 TRIALS**

The findings of the different trials and different dose regimens raise a number of issues that need to be addressed when interpreting the results and the potential clinical applications of NOACs for secondary prevention after ACS.

**Why did the ATLAS ACS 2 trial with rivaroxaban, but not the APPRAISE-2 trial with apixaban, provide beneficial outcomes after ACS?**

Both rivaroxaban and apixaban have been shown to be effective agents for stroke prevention in atrial fibrillation, but the dosages used to inhibit factor Xa after ACS were very different (one-half to one-quarter of the full atrial fibrillation dose for rivaroxaban vs the full atrial fibrillation dose for apixaban). In addition, the patient population in the APPRAISE-2 trial was “enriched” with high-risk patients, including patients with prior cerebral events. Thus, despite the encouraging findings in the prior dose-finding trial with apixaban in ACS, there was excess bleeding in the main ACS trial, where patients were also treated with dual antiplatelet therapy. The potential benefits were obscured by the excess bleeding hazard.

**Why was rivaroxaban administered twice daily in the ACS program, but only once daily in the atrial fibrillation program?**

In both the atrial fibrillation and venous thrombosis programs, the biological half-life of the antifactor Xa agent is longer than the biochemical half-life in the circulation, so a once-daily regimen was sufficient and demonstrated a similar area under the curve for efficacy as a twice-daily regimen. In the arterial circulation, there was concern that the trough levels may not have been sufficiently high using very low doses to inhibit arterial thrombosis; hence, rivaroxaban was administered twice daily.

**Why was there no dose-related increase in efficacy in the ATLAS ACS 2 trial?**

Although a dose-related response was observed for bleeding in the ATLAS ACS–TIMI 46 and ATLAS ACS 2–TIMI 51 trials (number needed to harm [NNH] for the 5-mg dose was 53 and the NNH for the 2.5-mg dose was 63), it is likely that the bleeding events with the higher dose of rivaroxaban offset the benefits.21,35 Prior trials after ACS have demonstrated that major bleeding resulted in worse cardiovascular outcomes, eg, in the trials with either bivalirudin or fondaparinux. Interestingly, in the OASIS-5 trial (fifth Organization to Assess Strategies in acute Ischemic Syndromes), the prior dose-ranging trial with fondaparinux, there was also a dose-related response for bleeding, but not for benefit; therefore, the choice was made to use the lowest effective dose in each trial to minimize bleeding.8

**Why were more benefits observed for all-cause mortality and cardiovascular mortality rather than myocardial infarction?**

This was an interesting and unexpected finding. Careful examination of the findings shows a clear trend for a dose-related effect on the prevention of myocardial infarction: 6.6% with placebo, 6.1% with the 2.5-mg dose
of rivaroxaban, and 4.9% with the 5-mg dose of rivaroxaban. In addition, it has been postulated that larger myocardial infarctions may have presented as sudden deaths, which was more commonly seen with placebo. The higher rates of bleeding with the 5-mg dose will have also masked some of the potential benefits on myocardial infarction, as prior trials have shown that major bleeding is associated with late increases in myocardial infarction and death.

**Were benefits influenced by the group of patients treated with only rivaroxaban and single antiplatelet therapy in the ATLAS ACS 2 trial?**

In order to test whether the impact of the antifactor Xa therapy was influenced by the patients on single antiplatelet therapy (7% of the trial population), a secondary analysis was performed for those only taking dual antiplatelet therapy and the benefits remained unchanged (HR for dual antiplatelet therapy [2.5-mg dose], 0.85; HR for all patients, 0.84).

**WHAT IS THE OPTIMAL COMBINATION OF ANTICOAGULANT AND ANTIPLATELET THERAPY FOR STENT IMPLANTATION?**

Please also see the response to the question: “How do we manage a patient with atrial fibrillation who develops an acute coronary syndrome (page XXX)?”

Depending on the stent choice, guidelines currently recommend using VKA anticoagulants plus a dual antiplatelet therapy for the shortest time possible. To minimize bleeding, the guidelines recommend using radial rather than femoral access for coronary interventional procedures. Nevertheless, large national registries reveal that this triple combination carries a high risk of bleeding (14.2% fatal and nonfatal bleeding per year). The WOEST trial (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StentTing) was modest in size (573 patients) and it tested VKA anticoagulation plus dual antiplatelet therapy (aspirin, clopidogrel) vs VKA plus clopidogrel only. The VKA/clopidogrel combination caused the lowest amounts of bleeding (mainly reducing minor bleeding) and did not appear to have an increased risk of coronary events. However, larger trials are needed to test these findings, especially with NOACs. The PIONEER AF-PCI trial [exPloration of two treatment strategies of Rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with Atrial Fibrillation who undergo Percutaneous Coronary Intervention, NCT01830543] tested the guideline’s recommended VKA/antiplatelet combination against both a “WOEST trial-like” combination of 15 mg rivaroxaban (75% of the full anticoagulant dose) with clopidogrel and an “ATLAS trial-like” combination of 2.5 mg rivaroxaban and dual antiplatelet therapy. This trial has entered the follow-up phase and the results should be presented in 2016. From the APPRAISE-2 trial, we know that the full dose of a NOAC plus dual antiplatelet therapy significantly increases bleeding, so it is likely that the optimal risk-benefit ratio will require a reduced dose of NOAC and single antiplatelet therapy or perhaps the combination used in the ATLAS ACS 2–TIMI 51 trial—one-quarter dose of NOAC and dual antiplatelet therapy.

**Which patients should be selected for secondary prevention treatment with a NOAC after an ACS event?**

From the evidence presented above, there is a need for additional antithrombotic therapies to reduce the risk of cardiovascular events after an ACS event, in addition to current secondary prevention measures. The options include: (i) an antiplatelet combination using aspirin plus a platelet antagonist that is more potent than clopidogrel; (ii) a novel anticoagulant plus single or dual antiplatelet therapy; or (iii) a VKA anticoagulant plus dual or single antiplatelet therapy.

Currently, more potent antiplatelet therapy options include aspirin plus ticagrelor, prasugrel, or vorapaxar. Table 1 provides calculations from the respective secondary prevention trials for the number needed to treat (NNT) to prevent a primary outcome event and the NNH to produce an adverse event. It must be noted that the trial populations differed in baseline characteristics, the active or placebo comparator, the time after an ACS event when therapy was started, and the treatment duration. As discussed above, an optimal antithrombotic therapy is one that achieves benefit, with the least amount of risk of inducing bleeding, thus the balance needs to be carefully considered. The treatment options that encompassed the acute phase of ACS (CURE, PLATO, and TRITON–TIMI 38) were excluded from this analysis because these trials included both the acute treatment effect and the secondary prevention effect.

Table 1 clearly shows that between 48 and 100 individuals need to be treated to prevent a patient experiencing cardiovascular death, myocardial infarction, or stroke.
However, the duration of the trials differ, with the longest being over 3 years in the PEGASUS–TIMI 54 trial (ticagrelor plus aspirin) and the shortest being 13 months in the ATLAS ACS 2–TIMI 51 trial. Therefore, the benefit calculated for an average of 12 months has the lowest NNT value for rivaroxaban (68 for the 2.5-mg dose and 57 for the 5-mg dose). Conversely, the benefits in the PEGASUS–TIMI 54 trial were over 3 years and so approximately 237 patients would need to be treated for one year to prevent the same number of outcome events. However, caution must be exercised with these extrapolations as they assume a linear treatment effect over time. Nevertheless, it is apparent from Table 1 that the secondary prevention option with rivaroxaban 2.5 mg twice daily is attractive and it has one of the lowest NNT values for benefit, no excess in fatal bleeding, and one of the largest NNH values for major bleeding events over the shortest duration compared with other secondary prevention trials.

The clinical practicalities will also influence the treatment choices. If a patient has dual antplatelet therapy with aspirin and clopidogrel in the acute phase, then addition of rivaroxaban after an ACS event is a practical option. If patients were started in the acute phase with prasugrel or ticagrelor, then this would require...
discontinuation of the more potent antiplatelet agent to commence the triple therapy of aspirin, clopidogrel, and rivaroxaban, which may be a less attractive option. Strong candidates for the antiplatelet-NOAC combination may include patients with large infarcts, patients at risk of developing an intraventricular thrombus or atrial fibrillation, or patients with an extensive intracoronary thrombus. Similarly, patients experiencing a side effect, such as dyspnea on ticagrelor, may be suitable for switching to the triple therapy (aspirin, clopidogrel, and rivaroxaban).

Internationally, the cost of long-term therapy and drug reimbursement options are important considerations in many settings. In many parts of the world, the combination of aspirin and clopidogrel remains the standard of care. Thus, the decision needs to consider the patient’s particular risks of thrombosis and bleeding, the likely benefits and hazards of treatment (NNT and NNH estimations), and the available treatment options.

REFERENCES


Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial.  

2014 ESC/EACTS Guidelines on myocardial revascularization.  

Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study.  

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial.  

An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI).  

42. Mauri L, Kereiakes DJ, Yeh RW, et al; DAPT Study Investigators.  
Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents.  
Novel Oral Anticoagulants in Patients With Acute Coronary Syndrome

Expert Answers to Three Key Questions

1) How do we manage a patient with atrial fibrillation who develops an acute coronary syndrome?

  P. G. Steg

2) What are the recommendations for adding novel oral anticoagulants to P2Y12-receptor inhibitors, with or without aspirin?

  G. Campo, S. Biscaglia, L. Fileti, R. Pavanini

3) Is it recommended to switch from novel oral anticoagulants to warfarin after an acute coronary syndrome?

  G. Montalescot
The combination of atrial fibrillation and an acute coronary syndrome (ACS) is a common clinical conundrum. The ESC consensus document details a four-step approach to determine the appropriate treatment involving an assessment of the thrombotic risk, bleeding risk, and clinical setting, as well as providing guidance on the best way to shorten and simplify combination antithrombotic therapy. For patients with ACS, the duration of triple therapy should be 4 weeks or 6 months when the risk of bleeding is high or low, respectively: followed by oral anticoagulation plus a single antiplatelet agent; and beyond 12 months, oral anticoagulation should be continued alone. In patients with a high risk of bleeding, additional consideration can be given to discontinuing aspirin earlier. These recommendations provide a useful framework, but ultimately, the decision should remain individualized.

**Keywords:** acute coronary syndrome; anticoagulation; aspirin; atrial fibrillation; clopidogrel; direct oral anticoagulant; stent; warfarin

**Address for correspondence:**
Ph. Gabriel Steg, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris (e-mail: gabriel.steg@bch.aphp.fr)

*Dialogues Cardiovasc Med.* 2015;20:259-265
telet therapy (ie, a P2Y12-receptor blocker and aspirin) with oral anticoagulation to prevent thrombotic events and the desire to minimize the risk of bleeding associated with the “stacking” of antithrombotic agents. A myriad of factors are involved in determining the optimal duration, intensity, and nature of the possible combinations.

WHAT IS THE EVIDENCE?

There are solid data to document the increased risk of bleeding related to combining dual antiplatelet therapy with oral anticoagulation and the desire to minimize the risk of bleeding associated with the “stacking” of antithrombotic agents. A myriad of factors are involved in determining the optimal duration, intensity, and nature of the possible combinations.

Indeed, data suggest that P2Y12-receptor inhibition may be the most important target to prevent stent thrombosis, rather than inhibiting the cyclooxygenase pathway with aspirin. In the early bare-metal stent era, it was not until ticlopidine was added to aspirin that rates of stent thrombosis were low enough to incorporate first-generation stents into routine practice. The pioneering WOEST trial (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and Stenting) showed that removing aspirin from the antithrombotic regimen soon after bare-metal stent or drug-eluting stent placement was associated with a marked reduction in major bleeding rates without any excess in acute thrombotic events or stent thrombosis rates and, in fact, lower rates of thrombotic events. In addition, all-cause mortality was actually lower with the combination of aspirin and clopidogrel after stenting than with the “conventional” triple therapy combining oral anticoagulation, aspirin, and clopidogrel (2.6 vs 6.4%, \( P = 0.027 \)). This modest-sized trial was not powered for either mortality or cardiovascular events and this may represent a chance finding. However, over two-thirds of the patients enrolled in the WOEST trial were non–ACS patients and the combination of aspirin and oral P2Y12-receptor inhibition remains the standard of care for such patients.10-14

Figure 1. Antithrombotic therapy in patients with coronary artery disease and atrial fibrillation with increasing CHA2DS2-VASc score.

Abbreviations: AP, antiplatelet; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex Category [score]; OAC, oral anticoagulation.

apy in patients on oral anticoagulation after drug eluting stent implantation), compared the net clinical outcome (combined ischemic and bleeding events) with 6 weeks vs 6 months of clopidogrel treatment as part of a triple therapy (combining dual antiplatelet therapy and oral anticoagulation). There was no reduction in the net clinical outcome with 6 weeks vs 6 months of clopidogrel treatment, although there was an increase in more sensitive measures of bleeding with the longer duration of triple therapy. These findings are consistent with the observation that the greatest risk of stent thrombosis occurs in the first days and weeks following stent placement and rapidly decreases to a steady, but low, rate of event accrual, suggesting that minimizing the period of combined triple therapy to 4 to 6 weeks is probably not only safe, but wise. Conversely, there is accumulating evidence demonstrating that the risk of late stent thrombosis with the newer generations of drug-eluting stents is now lower than with bare-metal stents and the required duration of antiplatelet therapy is lower than previously thought.

Given the difficulty in determining an optimal strategy, there have been many attempts to propose recommendations to help clinicians, which have been recently reviewed and synthesized in a joint consensus document.

**Consensus document**

The consensus indicates a number of principles. In general, the duration of triple therapy should be as short as possible, followed by the combination of oral anticoagulation and single antiplatelet therapy (preferably clopidogrel 75 mg/day or, as an alternative, aspirin 75 to 100 mg/day). The duration of triple therapy depends on the conditions for the stenting procedure (ACS vs stable CAD), the risk of bleeding (eg, as assessed by the HAS-BLED score [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly]), and the type of stent (with emphasis on using new-generation drug-eluting stents or bare-metal stents, which have a lower risk of stent thrombosis). In terms of oral anticoagulation for nonvalvular AF, the anticoagulant can be either a well-controlled, adjusted-dose vitamin K antagonist (VKA) (with a time in the therapeutic range >70%) or a direct oral anticoagulant.

The consensus starts with a number of general recommendations, which involves assessing the risk of thrombosis and bleeding in all patients using both the CHA2DS2-VASc...
How do we manage a patient with atrial fibrillation who develops an acute coronary syndrome? - Steg

and HAS-BLED scores. Whenever an adjusted-dose VKA is used, a good-quality anticoagulant should be used to achieve a time in the target range exceeding 70%. Whenever a VKA is combined with antiplatelet therapy, the intensity of anticoagulation should be carefully regulated, with a target international normalized ratio (INR) of 2.0 to 2.5. Likewise, when a non–VKA oral anticoagulant (NOAC) is used in combination with antiplatelet therapy, the lower doses tested for stroke prevention should be used (eg, dabigatran 110 mg twice daily, rivaroxaban 15 mg four times daily, apixaban 2.5 mg twice daily, and edoxaban 30 mg). Patients with AF and stable vascular disease may be treated with anticoagulation alone, without obligatory antiplatelet ther-

apy. Whenever PCI is considered, a radial approach should be preferred and bare-metal stents should be selected over drug-eluting stents. Finally, pending the availability of trial results, there is currently no role for the novel P2Y12-receptor inhibitors ticagrelor or prasugrel in this setting. Compared with clopi-
dogrel, clinical trials and observational studies concur in showing an increased risk of bleeding with these “novel” P2Y12-receptor antagonists. Therefore, clopidogrel should be preferred over P2Y12-receptor antagonists when used as part of a triple antithrombotic therapy to minimize the risk of bleeding, at least until the optimal regimens of novel antiplatelets and anticoagu-
lants have been clarified from ongoing, prospective, randomized trials, such as REDUAL (Randomized Evaluation of DUAL therapy with dabigatran vs triple therapy with warfarin in patients with AF that undergo a PCI with stenting. NCT02164864) and PIONEER AF-PCI.19

The consensus then describes a four-step approach to help deter-
mine the antithrombotic regimen to use in patients with AF and ACS or PCI (Figure 2). The first step is to assess the risk of stroke, the second step is to assess the risk of bleeding, the third step is to deter-
mine the clinical setting (stable CAD or ACS), and the fourth step is to determine the appropriate anti-
thrombotic therapy. Therapy always starts with a triple therapy consist-
ing of aspirin, clopidogrel, and oral anticoagulation. One of the oral an-

![Figure 2. Antithrombotic therapy in patients with coronary artery disease and atrial fibrillation, as suggested by the European Society of Cardiology consensus document.](image)

**Abbreviations:** ACS, acute coronary syndrome; CAD, coronary artery disease; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex Category [score]; DAPT, dual antiplatelet therapy; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly [score]; PCI, percutaneous coronary intervention.

tiplatelet agents (either aspirin or clopidogrel) is discontinued between 4 weeks (when the risk of bleeding is high, e.g., a HAS-BLED score of 0 to 2) and 6 months (when the risk of bleeding is low). In patients with a high risk of bleeding, additional consideration can be given to discontinuing aspirin earlier. Subsequently, patients receive a combination of oral anticoagulation and a single antiplatelet agent (aspirin or clopidogrel). Beyond 12 months, oral anticoagulation is continued alone, without antiplatelet therapy.

While preventing stent thrombosis using oral antiplatelet agents is an important consideration, the frequency and lethality of this condition have decreased because more attention has been given to optimal sizing and deployment of stents and, most importantly, because newer generations of drug-eluting stents have become widely adopted, which provide superior results and lower rates of stent thrombosis. In contrast, a stroke incurs a major risk of death or permanent disability, therefore, stroke prevention should be the first imperative in these patients. Oral anticoagulation remains the “foundation therapy” to which oral antiplatelet therapy needs to be added for as short as possible.

The data from both randomized trials and observational series show that “novel” oral anticoagulants are associated with a lower risk of an intracranial hemorrhage than VKAs, and generally, with a similar or lower risk of major bleeding, although there does appear to be a signal of greater risk for gastrointestinal hemorrhage. Therefore, whenever possible, “novel” anticoagulants should be preferred over VKAs. Of course, this recommendation does not apply to patients with advanced chronic kidney disease, in whom VKAs remain the preferred anticoagulation option due to a greater history of use. There is no evidence that using moderate-to-high doses of aspirin is associated with improved efficacy. In fact, evidence from the CURRENT-OASIS 7 trial (Clopidogrel optimal loading dose Usage to Reduce Recurrent EvenNTs–Optimal Antiplatelet Strategy for InterventionS) shows that a dose of aspirin ≤100 mg is as effective as doses >200 mg, but the lower dose is associated with a reduced risk of gastrointestinal bleeding.

**CONCLUSIONS**

Due to the complexity of current recommendations for optimal antithrombotic regimens for AF patients requiring oral anticoagulation who underwent a PCI, there are concerns regarding adoption, implementation, and adherence to these consensus recommendations, particularly as there are many nonspecialists involved in the care of these patients. Therefore, to simplify management, we have suggested a three-stage regimen, which is summarized below, to prevent stroke and stent thrombosis in AF patients receiving stents (Table 1, Figure 3).

**Table 1. A proposed simplified antithrombotic regimen for bare-metal and second-generation drug-eluting stents placed in patients requiring anticoagulation for nonvalvular atrial fibrillation.**

Abbreviations: NOAC, non–vitamin K antagonist oral anticoagulant; PPI, proton pump inhibitor.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low-dose aspirin ≤100 mg + clopidogrel</td>
<td>Up to 1 month after PCI</td>
</tr>
<tr>
<td>II</td>
<td>Clopidogrel + NOAC</td>
<td>6 months (3-12 months)*</td>
</tr>
<tr>
<td>III</td>
<td>NOAC monotherapy</td>
<td>Indefinite duration</td>
</tr>
</tbody>
</table>

*The duration of stage II can be modulated from 3 to 12 months depending on the patient and procedural characteristics.

Figure 3. Schematic representation of a proposed simplified algorithm for the antithrombotic regimen.

Abbreviations: NOAC, non–vitamin K antagonist oral anticoagulant; PPI, proton pump inhibitor.

**Stage I:** At the time of the PCI and up to 1 month later, a combination of aspirin, clopidogrel, and a NOAC should be used. This ensures that the procedural risk of thrombosis is reduced to a minimum, even if the patient is undergoing PCI in the context of an ACS. If the oral anticoagulant chosen has a lower dose range approved for clinical use (e.g., dabigatran 110 mg twice daily or edoxaban 30 mg), then the lower range should be used. Given the risk of gastrointestinal bleeding in patients receiving triple therapy, treatment with a proton pump inhibitor should be used.

**Stage II:** From 1 month to 6 months after a PCI, the combination of clopidogrel and a NOAC should be used.

**Stage III:** Clopidogrel should be stopped at 6 months and NOAC therapy maintained alone for an indefinite
duration because there is lingering uncertainty regarding the benefits and risks of adding an antiplatelet agent for chronic therapy in patients with AF receiving oral anticoagulation. The addition of an antiplatelet agent is certain to increase the risk of bleeding and its benefits on the prevention of ischemic events are unproven. These recommendations and proposals provide a useful framework to navigate the difficult decision-making process for these patients, but ultimately, the decision should remain individualized and it should also involve patient values and preferences regarding efficacy vs safety, the risk of bleeding vs stroke, and the risk of a myocardial infarction.

There are obvious and important limitations to this proposal. First, it is no more evidence based than the many existing consensus documents and it does not claim to be a guideline or represent anything else than the opinion of its authors. Second, it does not apply to patients requiring oral anticoagulation with VKAs because of prosthetic heart valves or other indications outside of nonvalvular AF and it is not applicable to patients who have had a stent placed and subsequently developed an indication for anti- coagulation. Third, with clopidogrel being used as a single antiplatelet agent after a PCI, there may be a concern that poor responders to clopidogrel may be insufficiently protected against stent thrombosis. However, there is often a disconnection between high persistent platelet reactivity on clopidogrel and actual clinical events. Finally, this proposal has not been tested formally, which is unlikely to occur given the enrollment difficulties of testing various anti-thrombotic strategies in this setting. However, we believe that, pending the availability of hard evidence from large ongoing trials (such as REDUAL and PIONEER AF-PCI), which are unlikely to be released for several years, it provides a framework, which has the merit of simplicity and safety for helping clinicians in this complex setting. It provides a single algorithm that is easy to remember and is applicable to a broad range of patients (stable or unstable) and stent types (both bare-metal stents and drug-eluting stents).

REFERENCES


What are the recommendations for adding novel oral anticoagulants to P2Y₁₂-receptor inhibitors, with or without aspirin?

Gianluca Campo, MD; Simone Biscaglia, MD; Luca Fileti, MD; Rita Pavasini, MD

Department of Cardiology and Laboratorio per le Tecnologie delle Terapie Avanzate (LTTA) center - University Hospital of Ferrara and Maria Cecilia Hospital - GVM Care & Research - Ettore Sansavini Health Science Foundation - Cotignola - ITALY

The clotting cascade and platelets interplay in thrombus formation during acute coronary syndromes. Accordingly, the combination of anticoagulants and antiplatelets could be an interesting approach to minimize ischemic complications in the acute and chronic phases of acute coronary syndromes. Currently, there are no data supporting the combination of new P2Y₁₂-receptor inhibitors (ticagrelor and prasugrel) and non–vitamin K antagonist oral anticoagulants in the long-term treatment after an acute coronary syndrome. An intriguing option could be the association of ticagrelor and non–vitamin K antagonist oral anticoagulants, without aspirin, but future studies are clearly required.

Until the late 2000s, aspirin and clopidogrel represented the standard therapeutic regimen for the majority of patients admitted to the hospital with acute coronary syndromes (ACS).¹⁻⁴ Meanwhile, the approach to revascularization has changed, mainly through a net increase in the proportion of patients treated with percutaneous coronary intervention (PCI). Consequently, one of the most feared complications of PCI is stent thrombosis, an infrequent, but severe, event with mortality rates up to 45%.⁵ Therefore, more powerful antiplatelet agents, such as ticagrelor and prasugrel, have been introduced in recent years to reduce this complication, especially in the setting of coronary interventions.²⁻³ The introduction of newer P2Y₁₂-receptor inhibitors, as an adjunctive treatment to long-term aspirin treatment, resulted in a further improvement in patient outcomes after PCI.²⁻³

STUDY ACRONYMS

<table>
<thead>
<tr>
<th>Study Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPRAISE-2</td>
<td>APixaban for Prevention of Acute Ischemic Events 2 [trial]</td>
</tr>
<tr>
<td>ATLANTIC</td>
<td>Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST-segment elevaTion myocardial Infarction to open the Coronary artery [trial]</td>
</tr>
<tr>
<td>ATLAS ACS 2</td>
<td>Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2 [trial]</td>
</tr>
<tr>
<td>GEMINI ACS</td>
<td>Global phasE 2 trial coMparing the safety of rivaroxaban vs acetylsalicylic acid in additioN to either clopidogrel or ticagrelor therapy in participants with Acute Coronary Syndrome</td>
</tr>
<tr>
<td>GLOBAL LEADERS</td>
<td>ticagrelor pLus aspirin fOllowed By ticAgreLor monotherapy vs a current-day intensive dual. antiplatElet therApy in pa-tients unDergoing pErcutaneous coRonary intervention with bivalirudin and biomatrix family drug-eluting Stents [trial]</td>
</tr>
<tr>
<td>PLATO</td>
<td>PLATelet inhibition and patient Outcomes [trial]</td>
</tr>
<tr>
<td>RT-AF</td>
<td>Rivaroxaban in paTients with Atrial Fibrillation and coronary artery disease undergoing percutaneous coronary intervention [trial]</td>
</tr>
<tr>
<td>TRITON–TIMI 38</td>
<td>TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel–Thrombolysis In Myocardial Infarction 38</td>
</tr>
</tbody>
</table>

Keywords: anticoagulants; acute coronary syndrome; antiplatelet agents; non–vitamin K antagonist oral anticoagulant

Address for correspondence:
Gianluca Campo, U.O. di Cardiologia, Azienda Ospedaliera Universitaria S.Anna, via Aldo Moro 8, Cona (FE), 44124, Italy (e-mail: cm pglc@unife.it)

Dialogues Cardiovasc Med. 2015;20:266-274
ACS. Nevertheless, there is a non-negligible rate of death, myocardial infarction, and stroke at 1 year (range, 9% to 12%).\(^1\)\(^-\)\(^3\) while in real-life registries, this rate is even higher.\(^4\) A more aggressive antplatelet regimen might lower the rate of ischemic complications, but at an increased rate of bleeding.\(^1\)\(^-\)\(^3\) Unfortunately, the impact of bleeding complications on clinical outcomes is as relevant as the risk of a myocardial infarction recurrence.\(^4\) These findings show that further optimization of antithrombotic regimens, especially during the follow-up and chronic phases, is needed. The available approaches involve using one of the following: (i) the platelet reactivity value as an indicator of a higher risk of adverse events and as a guide for choosing the antplatelet agent; (ii) prolonged treatment (beyond the currently recommended 12 months post–ACS) with dual antplatelet therapy (combination of aspirin plus a P2Y\(_{12}\)-receptor inhibitor); and (iii) medical strategies that combine newer available antplatelet and anticoagulant agents.

The first approach appeared very promising, but failed in the main randomized clinical trials on clinical end points. Thus, there are no data to support tailored therapy as a regular clinical approach.\(^6\)\(^,\)\(^7\) The second approach has been investigated in several studies (Table I).\(^8\)\(^-\)\(^17\) The DAPT trial (Dual AntiPlatelet Therapy) is the biggest trial on this topic.

### Table 1. Randomized clinical trials investigating different duration of dual antplatelet therapy.

*compared with prolonged dual antplatelet therapy vs shorter therapy; definit and probable stent thrombosis, with the exception of the ZEST-LATE/REAL-LATE, DES-LATE, ISAR-SAFE trials, where definite stent thrombosis alone was considered.

**Abbreviations:** EES, bioresorbable vascular scaffold; DAPT, dual antplatelet therapy; DES-LATE, optimal duration of clopidogrel therapy after Drug-Eluting Stent implantation to reduce Late coronary Arterial Thrombotic Events; EES, everolimus-eluting stent; EXCELLENCE, Efficacy of Xience/Promus vs Cypher to REdge Late Loss after stEnting; ISAR-SAFE, Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6-month dual antplatelet therapy after drug-eluting stenting; ITALIC, Is There A Life for drug-eluting stents after discontinuation of Clopidogrel; no; OPTIMIZE, OPTIMIZEd duration of clopidogrel therapy following treatment with the zotarolimus-eluting stent in real-world clinical practice; PES, paclitaxel-eluting stent; PRODIGY, Prolonging Dual antplatelet treatment In patients with coronary artery disease after Graded stent-induced intimal Hyperplasia; REAL-LATE, correlation of clopidogrel therapy discontinuation in REAL-world patients treated with drug-eluting stent implantation and Late coronary Arterial Thrombotic Events; RESET, REAL Safety and Efficacy of 3-month dual antplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SECURITY, SECond-generation drug-eluting sTents implantation followed by 6 vs 12-month dual antplatelet therapy; SES, sirolimus-eluting stent; Y, yes; ZES, zotarolimus-eluting stent; ZEST-LATE, evaluation of the long-term safety after Zotarolimus-Eluting Stent, sirolimus-eluting stent, or paclitaxel-eluting stent for coronary lesions–Late coronary Arterial Thrombotic Events.

### SELECTED ABBREVIATIONS AND ACRONYMS

- **ACS**: acute coronary syndrome
- **CABG**: coronary artery bypass graft
- **NOAC**: non–vitamin K antagonist oral anticoagulant
- **NSTEACS**: non–ST-segment elevation acute coronary syndrome
- **PCI**: percutaneous coronary intervention
- **STEMI**: ST-segment elevation myocardial infarction
- **TF**: tissue factor
- **TIMI**: Thrombolysis In Myocardial Infarction
- **VKA**: vitamin K antagonist

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Stent type</th>
<th>Length of DAPT (mo)</th>
<th>Timing of end point</th>
<th>Superiority for death</th>
<th>Superiority for cardiac death</th>
<th>Superiority for MI</th>
<th>Superiority for stent thrombosis*†</th>
<th>Increase in bleeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESET(^8)</td>
<td>2117</td>
<td>EES, ZES</td>
<td>3 vs 12</td>
<td>1 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>OPTIMIZE(^9)</td>
<td>3119</td>
<td>ZES</td>
<td>3 vs 12</td>
<td>1 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>EXCELLENT(^10)</td>
<td>1443</td>
<td>SES, EES</td>
<td>6 vs 12</td>
<td>1 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ISAR-SAFE(^11)</td>
<td>4005</td>
<td>SES, PES, EES, ZES, BVS</td>
<td>6 vs 12</td>
<td>1 y</td>
<td>N</td>
<td>-</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>SECURITY(^12)</td>
<td>1399</td>
<td>EES, ZES, BVS</td>
<td>6 vs 12</td>
<td>1 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>PRODIGY(^13)</td>
<td>2013</td>
<td>BMS, PES, EES, ZES</td>
<td>6 vs 24</td>
<td>2 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ITALIC(^14)</td>
<td>1822</td>
<td>EES</td>
<td>6 vs 24</td>
<td>2 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ZEST-LATE/REAL-LATE(^15)</td>
<td>2701</td>
<td>SES, PES, ZES</td>
<td>12 vs 24</td>
<td>2 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>DES-LATE(^16)</td>
<td>5045</td>
<td>SES, PES, ZES, EES</td>
<td>12 vs 24</td>
<td>2 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>DAPT(^17)</td>
<td>9961</td>
<td>SES, PES, ZES, EES</td>
<td>12 vs 30, 30 mo</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
</tbody>
</table>
to date. A prolonged dual antiplatelet therapy, beyond 1 year after the placement of a drug-eluting stent, was compared with aspirin alone and showed a significant reduction in stent thrombosis and major adverse cardiovascular and cerebrovascular events. This reduction in the ischemic end points was counterbalanced by an increased risk of bleeding. The increase in bleeding complications was present in a population where 64% of patients were treated with clopidogrel. Nevertheless, in a recent systematic review and meta-analysis, extended duration of dual antiplatelet therapy was not associated with a significant difference in the risk of all-cause, cardiovascular, or noncardiovascular death compared with aspirin alone or short-term dual antiplatelet therapy. The third approach is emerging as an attractive option after the introduction of second-generation drug-eluting stents that enable a shorter duration of dual antiplatelet therapy without increasing stent thrombosis. In this scenario, non–vitamin K antagonist oral anticoagulants (NOACs) may be a relevant therapeutic option.

**PATHOPHYSIOLOGICAL RATIONALE**

The activation of both circulating platelets and the coagulation cascade are the main factors responsible for arterial thrombus formation. The acute phase of ACS is characterized by thrombosis of a coronary artery, resulting in subtotal (non–ST-segment elevation ACS

---

**Figure 1. Interplay between the coagulation cascade and platelet activation in thrombus formation and principal antithrombotic agents.**

**Abbreviations:** a, activated; ADP, adenosine diphosphate; LMWH, low-molecular-weight heparin; P2Y<sub>12</sub>, G protein-coupled receptor for ADP on platelets; PAR-1, protease-activated receptor-1; PLT, platelet; RBC, red blood cell; TXA<sub>2</sub>, thromboxane A<sub>2</sub>; TF, tissue factor; UFH, unfractionated heparin; VKA, vitamin K antagonist; WBC, white blood cell.
NOACs and newer P2Y12-receptor inhibitors after ACS - Campo and others

The precipitating pathophysiological event is often plaque rupture, which exposes the subendothelial matrix. In response, platelets adhere to the damaged vessel wall (adhesion) and secrete chemoattractants, which are involved in both platelet aggregation and activation of the coagulation cascade (Figure 1). The key players in the process of coagulation include the factor VIIa complex, factor Xa, factor IIa, and tissue factor (TF). Thrombin (factor IIa) promotes the formation of a fibrin-rich blood clot, but it is also a potent activator of platelet aggregation (Figure 1).

The strong relationship between platelet aggregation and the coagulation cascade represents the rationale for the “dual-pathway” approach (simultaneous administration of antiplatelet and anticoagulant agents) to reduce the risk of subsequent adverse cardiovascular events. Additionally, ongoing thrombin generation in patients with ACS results in persistent hypercoagulability, which provides further support for targeting both pathways simultaneously. Indeed, the “dual-pathway” approach is already being employed in the acute hospitalization phase following an ACS event. However, this approach is not pursued in an outpatient setting. In the following section, we will try to explain the main reasons to avoid using anticoagulants in the chronic phase and the potential future research directions.

### ANTIPLATELET AGENTS AND WARFARIN AFTER ACS

Most of the clinical experience and randomized clinical trials on the impact of prolonged anticoagulation therapy in addition to aspirin after discharge for ACS concern vitamin K antagonists (VKA, eg, warfarin). There are robust data demonstrating that the long-term combination of anticoagulation and antiplatelet therapy results in better clinical outcomes than aspirin alone, but at the cost of an increased rate of bleeding (Table II). Data from a meta-analysis clearly showed that, in patients hospitalized for ACS, a combined strategy of aspirin plus warfarin (international normalized ratio [INR], 2-3) doubles the risk of major bleeding, but this is still superior to aspirin alone in preventing all-cause death, nonfatal myocardial infarction, and nonfatal thromboembolic stroke. This especially holds true for patients after ACS who are not undergoing coronary revascularization and stent implantation.

Currently, PCI and stent implantation are the preferred reperfusion strategies, the management of NSTEACS has become more aggressive, and the combination of aspirin and new P2Y12-receptor inhibitors has become the gold-standard antithrombotic treatment. Whether the combination of anticoagulant and antiplatelet agents is superior to dual antiplatelet therapy or to newer evolving treatments is unclear and warrants further investigation. Currently, the only available data are indirect comparisons between aspirin plus clopidogrel vs aspirin plus a VKA. No significant

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Type of ACS</th>
<th>Length of follow-up</th>
<th>Reduction in ischemic end point*</th>
<th>Increase in any bleeding</th>
<th>Increase in extracranial bleeding</th>
<th>Increase in intracranial bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATACS pilot study20</td>
<td>69</td>
<td>NSTEMI</td>
<td>3 mo</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ATACS21</td>
<td>214</td>
<td>NSTEMI</td>
<td>3 mo</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Williams22</td>
<td>57</td>
<td>AMI</td>
<td>2.5 mo</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>OASIS pilot study23</td>
<td>506</td>
<td>NSTEMI</td>
<td>6 mo</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Huynh24</td>
<td>90</td>
<td>NSTEMI</td>
<td>1 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>OASIS-225</td>
<td>3712</td>
<td>UA</td>
<td>5 mo</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ASPECT-226</td>
<td>669</td>
<td>AMI</td>
<td>1 y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>APRICOT-227</td>
<td>274</td>
<td>STEMI</td>
<td>3 mo</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>WARIS II28</td>
<td>2414</td>
<td>AMI</td>
<td>4 y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Zibaeenezhad29</td>
<td>140</td>
<td>AMI</td>
<td>1 y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Table II. Randomized clinical trials investigating the effectiveness and safety of the combination of warfarin (INR range, 2-3) and aspirin.

*ischemic end point was all-cause death, nonfatal myocardial infarction, and nonfatal thromboembolic stroke.

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; APRICOT, Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; ASPECT, Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis; ATACS, Antithrombotic Therapy in Acute Coronary Syndromes; N, no; NSTEMI, non–ST-segment elevation ACS; OASIS, Organization to Assess Strategies in acute Ischemic Syndromes; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; WARIS, Warfarin-Aspirin ReInfarction Study; Y, yes.
difference was found for aspirin plus warfarin vs aspirin plus clopidogrel for the risk of death and/or myocardial infarction. However, aspirin plus warfarin was associated with a significantly lower risk of thromboembolic stroke (odds ratio [OR], 0.53; 95% CI, 0.31-0.88) and all types of stroke (OR, 0.58; 95% CI, 0.35-0.94; P=0.038), but with an increased risk of major bleeding events (OR, 1.9; 95% CI, 1.2-2.8; number needed

Table III. Randomized clinical trials on prolonged treatment with novel oral anticoagulants after an acute coronary syndrome.

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Drugs</th>
<th>Antiplatelet regimen</th>
<th>Length of treatment</th>
<th>Reduction in composite ischemic end points*</th>
<th>Reduction in stent thrombosis</th>
<th>Increase in TIMI major bleeding</th>
<th>Increase in any bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESTEEM33</td>
<td>1883</td>
<td>Ximelagatran</td>
<td>Aspirin</td>
<td>6 mo</td>
<td>Y</td>
<td>-</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>APPRAISE34</td>
<td>1715</td>
<td>Apixaban</td>
<td>DAPT</td>
<td>6 mo</td>
<td>N</td>
<td>-</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>ATLAS ACS–TIMI 4635</td>
<td>761</td>
<td>Rivaroxaban</td>
<td>Aspirin</td>
<td>6 mo</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>ATLAS ACS–TIMI 4635</td>
<td>2730</td>
<td>Rivaroxaban</td>
<td>DAPT</td>
<td>6 mo</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>APPRAISE236</td>
<td>7392</td>
<td>Apixaban</td>
<td>DAPT</td>
<td>15 mo</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>RUBY 137</td>
<td>1279</td>
<td>Dabigatran</td>
<td>DAPT</td>
<td>6 mo</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>REDEEM38</td>
<td>1861</td>
<td>Dabigatran</td>
<td>DAPT</td>
<td>6 mo</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>ATLAS ACS–TIMI 523940</td>
<td>15526</td>
<td>Rivaroxaban</td>
<td>DAPT</td>
<td>31 mo</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

to harm, 300). At the same time, aspirin plus a P2Y12-receptor inhibitor (either with or without aspirin) significantly reduced the risk of stent thrombosis when compared with anticoagulants. The actual preference of dual antiplatelet therapy over anticoagulants after ACS is largely based on these findings.

**ANTIPLATELET AGENTS AND NOACS AFTER ACS**

It is well known that NOacs (ie, apixaban, dabigatran, and rivaroxaban) are effective and safer than VKAs in reducing stroke and other thromboembolic events in patients with atrial fibrillation. However, their use in ACS in phase 2 and 3 trials showed conflicting results (Table III). Findings from a recent meta-analysis reported that the use of NOacs in patients receiving antiplatelet therapy after ACS was associated with a dramatic increase in major bleeding events (OR, 3.03; 95% CI, 2.2-4.16). Significantly, but moderate, reductions in the risk of stent thrombosis or composite ischemic events were observed in patients with a recent ACS event (within the previous 7 days). The trial was prematurely terminated after recruitment of 7392 patients due to an increase in major bleeding events (ie, a greater number of intracranial and fatal bleeding events) in patients treated with apixaban vs placebo. Additionally, apixaban administration did not reduce recurrent ischemic events.36

| Abbreviations: APPRAISE, APixaban for PRevention of Acute Ischemic Events; ACS, acute coronary syndromes; ATLAS ACS–TIMI, Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/witout thienopyridine therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction; DAPT, dual antiplatelet therapy; ESTEEM, Efficacy and Safety of the oral direct Thrombin inhibitor ximElagatran in patiEnts with recent Myocardial infarction; N, no; RUBY, evaluation of the safety, tolerability and efficacy of YM150 in Subjects with acute coronary Y syndromes; RE–DEEM, RandomizEd Dabigatran E teflexalE dose-finding study in patients with acute coronary syndromes after an index event with additional risk factors for cardiovascular complications who are also receiving aspirin and clopidogrel; TIMI, Thrombolyis In Myocardial Infarction; Y, yes.
aspirin with or without a thienopyridine (clopidogrel or ticlopidine). Dual antiplatelet therapy was the intended therapy for most of the patients (93%). Compared with placebo, rivaroxaban 2.5 mg twice daily significantly reduced the composite end point (cardiovascular death, myocardial infarction, or stroke) by 16% and cardiovascular death alone by 34%. A similar reduction was present for the composite end point with the 5-mg twice-daily dose, but not for cardiovascular death alone. Rivaroxaban 2.5 mg twice daily reduced the risk of stent thrombosis by 35% vs placebo.40 In terms of safety, although rivaroxaban was associated with an increased rate of Thrombolysis In Myocardial Infarction (TIMI) major bleeding events not associated with coronary artery bypass grafting (CABG; 2.1% vs 0.6%; P<0.001), there were no significant differences in the rate of fatal bleeding events (including fatal intracranial hemorrhage) compared with placebo (0.3% vs 0.2%; P=0.6).40

Despite these results, the clinical use of a triple approach, including aspirin, rivaroxaban, and clopidogrel, for the secondary prevention of ischemic events in patients with ACS remains difficult. Several clinically relevant questions remain to be addressed. First, the current gold-standard therapy for ACS patients is represented by aspirin and new P2Y12-receptor inhibitors; therefore, are the results of the comparison with aspirin and clopidogrel outdated? Second, which patients should be considered for this approach? The coadministration of dual antiplatelet therapy and NOACs should undoubtedly be targeted toward specific patients with a low risk of bleeding, but how can these patients be identified? Third, what is the optimal time to introduce rivaroxaban? In the ATLAS ACS 2–TIMI 51 trial, the median time from index event to randomization was 4.7 days (interquartile range, 3.2 to 6.0 days), whereas the median time was 6 days (interquartile range, 4 to 7 days) in the APPRAISE-2 trial.36,39,40 Finally, practical issues regarding follow-up should be addressed, such as frequency of visits and how to optimize the follow-up to reduce the occurrence of bleeding (ie, hemoglobin controls). Moreover, the combination of rivaroxaban with the newer antiplatelet agents prasugrel or ticagrelor plus aspirin in ACS patients has never been studied.

NOVEL P2Y12-RECEPTOR INHIBITORS AND NOACs AFTER ACS VS UPTITRATED MONOTHERAPY

Clinical studies on novel P2Y12-receptor inhibitors (ie, ticagrelor and prasugrel) have shown promising results.2,3 In the PLATO trial (PLAtelet inhibition and patient Outcomes), ticagrelor was associated with a significantly reduced incidence of major adverse cardiovascular events when compared with clopidogrel in patients with ACS.3 Ticagrelor also reduced all-cause mortality, although statistical significance was not confirmed after hierarchical testing.3 Benefit with ticagrelor was seen both in invasively and noninvasively managed patients.3 Ticagrelor was generally well tolerated and not associated with an increased risk of major bleeding relative to clopidogrel.3 However, the incidence of non–CABG-related bleeding, major or minor bleeding, and some nonhemorrhagic adverse events, including dyspnea (usually of mild or moderate severity) and ventricular pauses (largely asymptomatic), were higher with ticagrelor.3

In addition, the ATLANTIC study (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST-segment elevaTion myocardial infarction to open the Coronary artery) showed that prehospital administration of ticagrelor did not improve pre–PCI coronary reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) compared with in-hospital administration.42 Ticagrelor was safe in both instances, with no significant between-group differences in non–CABG-related major and minor bleeding events. The rate of definite stent thrombosis was lower in the prehospital group than in the in-hospital group (0% vs 0.8% in the first 24 hours; 0.2% vs 1.2% at 30 days).42 Prasugrel is a third-generation thienopyridine that is associated with greater platelet inhibition than clopidogrel. The superior pharmacodynamic and pharmacokinetic profile of prasugrel translated into clinical benefit compared with clopidogrel.2

The TRITON–TIMI 38 trial (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet iNhibition with prasugrel–Thrombolysis In Myocardial Infarction 38) evaluated 13 608 patients with a moderate-to-high risk of ACS, including 10 074 patients with NSTEACS and 3534 patients with STEMI, who were to undergo PCI.2 Patients were randomized to receive a 60-mg loading dose of prasugrel followed by 10 mg/day or a 300-mg loading dose of clopidogrel followed by 75 mg/day.2 For STEMI patients, the study drug was given as soon as possible, meaning that prasugrel could be given without knowledge of the coronary anatomy, for NSTEACS patients, the study drug was given after the coronary angiogram.2

Prasugrel was associated with a 19% reduction in the risk of the primary composite end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) com-
pared with clopidogrel and fewer ischemic events (number needed to treat =46). This ischemic benefit was counterbalanced by an increased risk of bleeding. Among patients treated with prasugrel, 146 (2.4%) had at least 1 non–CABG-related TIMI major bleeding event compared with 111 (1.8%) patients treated with clopidogrel. The ischemic benefit was mainly driven by a reduction in myocardial infarction and stent thrombosis. No difference was observed in mortality. Thus, according to these studies, both prasugrel and ticagrelor are suggested as class I agents in the current European guidelines. Nevertheless, both ticagrelor and prasugrel increased bleeding complications in ACS patients when compared with clopidogrel. As reported above, the addition of NOACs to dual antiplatelet therapy was an independent and strong predictor of bleeding complications.

In the ATLAS ACS 2–TIMI 51 trial, the dual antiplatelet therapy approach was to use aspirin plus a P2Y12-receptor inhibitor (either clopidogrel or ticlopidine). Both clopidogrel and ticlopidine are older and considered less potent than ticagrelor or prasugrel. Nevertheless, the combination of clopidogrel or ticlopidine with rivaroxaban was associated with a higher risk of bleeding. Therefore, the coadministration of dual antiplatelet therapy with aspirin plus ticagrelor or prasugrel and NOACs is probably not feasible due to the lack of safety. Although no clinical trials are available to support this hypothesis, it is highly plausible that the association between aspirin, new P2Y12-receptor inhibitors, and NOACs will result in a heightened risk of bleeding. Accordingly, several studies are trying to determine if there is a better medication strategy to limit thrombotic complications and, at the same time, minimize adverse bleeding events by testing strategies without aspirin.

In the GLOBAL LEADERS trial (ticagrelor plus aspirin followed by ticAgrelor monotherapy vs a current-day intensive dual antiplatElet therApy in patients unDergoing pErCutaneous coRonal intervention with bivalirudin and biomatrix family drug-eluting Stents, NCT01813435), patients undergoing PCI and stent implantation will be randomized to gold-standard treatment (aspirin plus a P2Y12-receptor inhibitor for 1 year) vs aspirin plus ticagrelor for only 30 days and ticagrelor alone for 2 years. The primary end point is the 2-year cumulative occurrence of the composite end point of all-cause mortality or nonfatal new O-wave myocardial infarction. A similar approach will be tested for NOACs.

The GEMINI ACS trial (Global phasE 2 trial coMparing the safety of rivaroxaban vs acetylsalicylic acid in additioN to either clopido- grel or ticagrelor therapy in partici- pants with Acute Coronary Syn- drome) is an ongoing, prospective, randomized, double-blind, active-controlled, parallel-group, multicenter study that will enroll approxi- mately 3000 patients with a recent ACS event (NCT02933995). All the eligible participants receiving background treatment of aspirin plus clopidogrel or aspirin plus ticagrelor will be randomly assigned to receive either aspirin or rivaroxaban on a background of a P2Y12-receptor inhibitor treatment. The primary end point is the 1-year occurrence of clinically significant TIMI bleeding events.

An equivalent strategy will be evaluated in the KT-AF trial (Rivaroxaban in paTients with Atrial Fibrillation and coronary artery disease undergoing percutaneous coronary intervention; NCT02334254). The RT-AF study is an open-label, randomized, active-controlled, multicenter, clinical trial with up to 420 subjects to be enrolled in 5 centers. Eligible patients, who have either a history or a new onset of paroxysmal, per- sistent, or permanent nonvalvular atrial fibrillation and who have been referred to the study centers with indications for PCI, will be randomly assigned to receive triple therapy (including warfarin, clopidogrel, and aspirin) or dual therapy (rivaroxaban and ticagrelor). The primary end point is major or clinically relevant nonmajor bleeding events at 12 months. The major secondary end point is the composite efficacy outcome of death, myocardial infarction, stent thrombosis, and ischemic stroke.

CONCLUSIONS

At present, no data supporting the combination of novel P2Y12-recepto- tor inhibitors (ticagrelor and pras- sugrel) and NOACs in the long-term treatment of ACS patients have been provided. Specifically, there are no data suggesting a potential benefit from the association of aspirin, ticagrelor, or prasugrel with NOACs. This association entails a higher risk of bleeding complications, overcoming the potential ischemic benefit (eg, myocardial infarction and stent thrombosis reduc- tion). On the contrary, an emerging option could be the association of new P2Y12-receptor inhibitors (eg, ticagrelor) and NOACs, without as- pirin. Several studies are ongoing to demonstrate the effectiveness and safety of this medical strategy.

Acknowledgments: This work was supported by a grant from the Fondazione Anna Maria Stechi per il Cuore (FASC), Italy. The funders had no role in the study design, data collection, data analysis, decision to publish, or the preparation of the manuscript.
REFERENCES


Is it recommended to switch from novel oral anticoagulants to warfarin after an acute coronary syndrome?

Gilles Montalescot, MD, PhD
Université Paris 06 - ACTION Study Group - INSERM-UMRS 1166 - Institute de Cardiologie - Pitié-Salpêtrière University Hospital (AP-HP)
Paris - FRANCE

Warfarin is an oral anticoagulant that has been used for many years in atrial fibrillation, in particular for atypical or complex clinical situations, such as patients with severe renal failure or patients with multiple conditions (eg, acute coronary syndrome and atrial fibrillation). While the use of non–vitamin K antagonist oral anticoagulants is prioritized over warfarin in the European atrial fibrillation guidelines, the data are limited when these patients also develop an acute coronary syndrome. Several trials have been designed to address the risks and benefits of new strategies combining anticoagulation and antiplatelet therapy in patients with atrial fibrillation and either acute coronary syndrome or coronary stenting. While waiting for these results, strategies should be adapted to the decision for and the type of revascularization, which will be discussed in this article.

Approximately one-third of atrial fibrillation patients have coronary artery disease, where half of them will undergo stent implantation. In atrial fibrillation with long-standing stable coronary artery disease, oral anticoagulation with either vitamin K antagonists (VKA) or non–VKA oral anticoagulants (NOAC) may be sufficient; however, in atrial fibrillation patients with acute coronary syndrome (ACS) and/or coronary stenting, a combination of oral anticoagulation and antiplatelet therapy is needed to protect from stroke and particularly stent thrombosis—two rare, but serious, complications with high mortality rates. This paper will examine different situations to determine whether an atrial fibrillation patient on NOACs, who has developed an ACS, should be switched to a VKA knowing that the patient must then also receive antiplatelet therapy.

WHAT IS KNOWN ABOUT THE COMBINATION OF NOACS AND ANTIPLATELET AGENTS?

The information is limited since patients receiving dual antiplatelet therapy after an ACS were excluded from the atrial fibrillation trials and patients with atrial fibrillation were excluded from the ACS trials. Two doses of rivaroxaban (2.5 mg twice daily and 5 mg twice daily), in addition to standard antiplatelet therapy, were studied in the ATLAS ACS 2–

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex Category [score]</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (&gt;65 years), Drugs/alcohol concomitantly [score]</td>
</tr>
<tr>
<td>NOAC</td>
<td>non–VKA oral anticoagulant</td>
</tr>
<tr>
<td>NSTEACS</td>
<td>non–ST-segment elevation ACS</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>VKA</td>
<td>vitamin K antagonist</td>
</tr>
</tbody>
</table>

Copyright © 2015, AICHI - Servier Research Group. All rights reserved
TIMI 51 trial (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 51). These doses had the best efficacy/safety profile in the phase 2 ATLAS ACS–TIMI 46 trial (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 46). Rivaroxaban significantly reduced the primary efficacy end point of cardiovascular death, myocardial infarction, or stroke when added to standard dual antiplatelet therapy vs placebo, irrespective of the dose. The 2.5-mg dose of rivaroxaban was associated with a reduction in mortality and an increase in major bleeding complications.

In the APPRAISE-2 trial (APixaban for PRevention of Acute ISchemic Events 2), apixaban 5 mg twice daily, in addition to standard antiplatelet therapy, provided no reduction in recurrent ischemic events, but significantly increased the rate of bleeding events, including fatal bleeding events. Similarly, in the phase 2 RE-DEEM trial (Randomised dabigatran Eteixilate Dose finding study in patiEnts with ACS after the index Event with additional risk factors for cardiovascular coMpli9cations also receiving aspirin and clopidogrel), dabigatran treatment resulted in a dose-dependent increase in bleeding events in patients after a myocardial infarction, but there was no significant reduction in ischemic events.

Interpretation remains difficult for several reasons: (i) the NOAC doses were different from those used in atrial fibrillation trials; (ii) atrial fibrillation patients were excluded, meaning that data from ACS trials cannot be directly extrapolated to atrial fibrillation patients who develop ACS and/or undergo stenting; (iii) the risk of bleeding was always higher with the concomitant use of antiplatelet and anticoagulant therapy compared with antiplatelet therapy alone; and (iv) the results on efficacy were not consistent across studies and drugs. An increased risk of bleeding was also observed in atrial fibrillation trials when there was concomitant use of antiplatelet and anticoagulant therapies compared with anticoagulant therapy alone, but, in terms of efficacy and safety, the NOAC vs VKA effect was not affected by using antiplatelet therapy (Figure 1).

A meta-analysis also evaluated the efficacy and safety of adding NOACs to single or dual antiplatelet therapy. NOACs plus single antiplatelet therapy reduced major adverse cardiac events by 90%, but increased bleeding events by 79%, whereas NOACs plus dual antiplatelet therapy reduced major adverse cardiac events by 13%, but increased bleed-
Is it recommended to switch from NOACs to warfarin after an ACS? - Montalescot

After an ACS, the optimal risk-benefit ratio was obtained by combining NOACs and single antiplatelet therapy. This outcome results in a dilemma because current guidelines recommend using dual antiplatelet therapy for 1 year in ACS patients.

Warfarin, when added to antiplatelet therapy after an ACS, does not appear to perform better than NOACs in the same situation. In a meta-analysis, warfarin plus aspirin vs aspirin monotherapy after an ACS resulted in a lower risk of myocardial infarction, ischemic stroke, and revascularization. However, there was no benefit on mortality and a significant increase in major bleeding. Other studies evaluating anticoagulation in ACS failed to show a significant benefit for the combination of VKAs and aspirin compared with aspirin alone, showing instead a consistent increase in bleeding events. In addition, there is limited evidence to support the combination of warfarin with dual antiplatelet therapy and/or with the new P2Y12-receptor antagonists, considering the excessive risk of bleeding observed in the registries.

Globally, VKAs and NOACs have been associated with antiplatelet therapy for the prevention of ischemic or stent-related events. A significant and gradual increase in the risk of bleeding has been observed according to the potency and the number of antiplatelet agents. While VKAs were always used to reach an effective international normalized ratio (INR) for controlled anticoagulation, various NOAC regimens have also been used. The risk of bleeding also seems dependent on the dose regimens used with NOACs.

MANAGING ATRIAL FIBRILLATION PATIENTS ON NOACS WHO ARE BEING MEDICALLY TREATED FOR AN ACS

Current international guidelines recommend managing ACS with a dual antiplatelet therapy that consists of aspirin and a P2Y12-receptor antagonist, preferably ticagrelor or prasugrel. However, these drugs are currently contraindicated in patients on warfarin. Similarly, the trials evaluating NOACs in combination with dual antiplatelet therapy used the P2Y12-receptor antagonist clopidogrel. Therefore, no evidence can support the combination of oral anticoagulation, either prasugrel or ticagrelor, and aspirin, and studies have reported that this combination increases the risk of bleeding. One possibility is to use the triple therapy of aspirin, clopidogrel,
and warfarin. According to a Danish registry, this triple antithrombotic treatment is associated with a large increase in bleeding. In addition, this registry showed that oral anticoagulation plus single antiplatelet therapy was the safest strategy and did not result in too many coronary or cerebrovascular events.12

Shortening the duration of dual antiplatelet therapy may be an option in these medically managed patients. In both the CURE study (Clopidogrel in Unstable angina to prevent Recurrent Events) and the Chinese COMMIT study (Clopidogrel and Metoprolol in Myocardial Infarction Trial), most of the benefit was achieved in the first 3 months, suggesting that withdrawal after 3 months of clopidogrel treatment may be possible.13,14

Another option in patients considered to be low-risk ACS patients or in those who did not undergo a coronary angiogram, often for reasons of frailty or comorbidities, would be to select single antiplatelet therapy, rather than dual antiplatelet therapy, in combination with oral anticoagulation. If these atrial fibrillation patients were on NOACs before the ACS event, continuation of this treatment would be fully acceptable for the prevention of stroke and peripheral embolism after the acute ACS phase.

Thus, both options (shortening the duration of dual antiplatelet therapy or removal of one antiplatelet agent) deserve further investigation with adequate randomized controlled trials to clarify the strategy to achieve an optimal risk-benefit ratio for the medically managed atrial fibrillation patient after an ACS event. While waiting for such trials, these conservatively managed patients represent, in general, a population that has a high risk of bleeding. In this context, continuing NOAC treatment with single antiplatelet therapy (immediately or soon after an ACS) seems to be a reasonable option.

Figure 2. Main results of the WOEST study.

Abbreviations: MI, myocardial infarction; ST, stent thrombosis; TIMI, Thrombosis In Myocardial Infarction; TVR, target-vessel revascularization.

The choice and duration of combination treatment does not depend strongly on the type of stent. Previously, bare-metal stents were recommended to reduce the duration of triple therapy compared with the first-generation drug-eluting stents. New-generation drug-eluting stents do not have any particular disadvantage vs bare-metal stents with respect to thrombotic events. Dual antiplatelet therapy confers protection by suppressing platelet reactivity and their ability to aggregate.

The pathophysiology of stent thrombosis includes patient-related, stent-related, and procedure-related factors. Patient-related factors include presentation with ACS (in which ST-segment elevation myocardial infarction [STEMI] carries the highest thrombotic risk), diabetes mel-
Is it recommended to switch from NOACs to warfarin after an ACS?

No. Clinical surrogate, such as multivessel coronary artery disease, previous myocardial infarction, left ventricular dysfunction, and high platelet reactivity. Procedure-related factors include stent underexpansion or undersizing, incomplete stent apposition, residual edge dissection, number of stents implanted, final stent length, and lesion complexity. Finally, stent-related factors include polymer hypersensitivity with incomplete endothelialization, stent design, and strut thrombogenicity. A substantial improvement in stent endothelialization and strut thrombogenicity has been achieved with second-generation drug-eluting stents vs their predecessors. Moreover, biodegradable polymer drug-eluting stents have the potential advantage of eliminating polymer-related triggers for late and very late stent thrombosis after the elution of the antirestenotic drug.

A cohort of patients with bare-metal stents were included in the DAPT trial (Dual Antiplatelet Therapy). Among the 1,026 propensity-matched patients, the results of the DAPT trial (Dual Antiplatelet Therapy) were published in 2015. The trial compared dual antiplatelet therapy (aspirin plus clopidogrel) with triple therapy (warfarin, clopidogrel, and aspirin) for 12 months after percutaneous coronary intervention. The results showed a significantly lower risk of bleeding than the dual-therapy group (warfarin and clopidogrel). In this trial, dual therapy did not carry a high risk of coronary events and was associated with a significantly lower risk of bleeding than triple therapy (Figure 2). Although the data from the DAPT study were clear, there are limitations in applying these results to the care of all patients with atrial fibrillation and coronary artery disease. The indication for anticoagulation in patients with atrial fibrillation is based on the results of the WOEST study to the management of patients with atrial fibrillation and coronary artery disease.

The data from registries and a single randomized study, although limited, suggest that aspirin could be removed from the treatment of these patients. These findings apply to clopidogrel and not to the newer and more potent P2Y12 receptor antagonists, which must be avoided in patients on oral anticoagulants. Studies testing similar strategies with NOACs are ongoing (Figure 3, page 280). The PIONEER AF-PCI trial (exPloration of tWO treatment strategies in patients with atrial fibrillation who undergo a Percutaneous Coronary Intervention) is specifically exploring the use of rivaroxaban vs warfarin in atrial fibrillation with various combinations of dual antiplatelet therapy. The RENDEZVOUS trial (Randomized Evaluation of DUAL therapy with dabigatran vs triple therapy with warfarin in patients with atrial fibrillation that undergo a percutaneous coronary intervention with stenting) is comparing dual therapy with dabigatran plus clopidogrel or ticagrelor with a triple antithrombotic therapy combination of warfarin plus clopidogrel or ticagrelor plus aspirin in patients undergoing a percutaneous coronary intervention.

If one approach is to remove aspirin, as in the WOEST study, another approach is to shorten the exposure time to triple therapy after a percutaneous coronary intervention. The recommended 12-month period of dual antiplatelet therapy comes from the CURE trial, in which aspirin-treated patients with non-ST-segment elevation ACS (NSTEMI) were randomized to clopidogrel.
treatment (300 mg loading dose followed by 75 mg/day) or placebo for 3 to 12 months with an average duration of only 9 months. Only 20% of patients underwent a percutaneous coronary intervention in the CURE trial and only bare-metal stents were available. Obviously, the results of the CURE trial cannot be applied to atrial fibrillation patients requiring oral anticoagulation, as they were excluded, and all the data suggest an excess risk of bleeding by adding anticoagulation to dual antiplatelet therapy. No randomized trial has formally evaluated the duration of oral dual antiplatelet therapy shorter than 12 months (eg, 6 vs 12 months) in ACS patients. Some indirect evidence is provided from recent trials that evaluated the duration of treatment in stented patients, where the majority of enrolled patients were ACS patients. The PRODIGY (PRoLonging Dual antiplatelet treatment in patients with coronary artery disease after Graded stent-induced intimal hyperplasia), RESET (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation), and EXCELLENT (the Efficacy of Xience/Promus versus Cypher to rEduce Late Loss after stENTing) studies enrolled more than 5000 patients and had 75%, 55%, and 51% of patients, respectively, with ACS. There was no significant interaction between the duration of antiplatelet therapy (short vs long) and clinical presentation (ACS vs no ACS) for the primary end points of all three studies. In these studies, there was no substantial difference on ischemic end points between short- and long-duration dual antiplatelet therapies, but there was a tendency to have more bleeding with long-duration treatment. The shortest duration of dual antiplatelet therapy tested was 3 months in RESET and 6 months in the EXCELLENT and PRODIGY studies. In these studies, clopidogrel (and not aspirin) was removed earlier. Observational studies have also suggested a low risk of major events after the first month of dual antiplatelet therapy with the new drug-eluting stents and a low risk with physician-supervised cessation.
Whether 1 month of triple therapy is enough, whether dual treatment (eg, clopidogrel plus VKA) is optimal, whether the same strategy can be applied to NOACs (eg, P2Y12-receptor antagonist plus NOAC), and whether clopidogrel rather than aspirin should be removed are unanswered questions. While waiting for the results of the ongoing trials, individualized decisions are recommended, weighing the risks of stroke (CHA2DS2-VASc score [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category]), stent thrombosis (STEMI, diabetes, stent size, number of stents, etc), ischemic risk (GRACE score [Global Registry of Acute Coronary Events]), and bleeding risk (HAS-BLED score [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly]). In many situations, if NOACs are prescribed and well tolerated before the ACS event, then NOACs would be viewed as a valid option compared with the classic VKA option.

MANAGING ATRIAL FIBRILLATION PATIENTS ON NOACS WHO UNDERWENT CABG REVASCULARIZATION AFTER AN ACS

Atrial fibrillation should be seen as an important parameter in the decision process when discussing percutaneous coronary intervention vs coronary artery bypass graft (CABG) revascularization. Indeed, atrial fibrillation patients tend to be older, have more frequent multivessel coronary artery disease, and have a higher risk for bleeding complications on antithrombotic therapy.

Secondary antithrombotic treatment may be minimized with CABG revascularization. Although we are lacking hard evidence from randomized clinical trials, these patients may be seen as stable (stabilized) coronary artery disease patients in whom anticoagulation for atrial fibrillation becomes the main goal after CABG. This is particularly true when multivessel CABG and total revascularization have been performed. Nevertheless, even in saphenous vein grafts, anticoagulation therapy probably provides results similar to...
antiplatelet therapy. Although the clinical situation has been poorly studied, it would make sense to limit antiplatelet therapy to a single agent in combination with anticoagulation in atrial fibrillation patients after CABG revascularization for ACS. It is unknown whether this single antiplatelet therapy should be removed or, if removed, when it should be done. International recommendations are silent on the subject. It is certainly wise to take decisions according to the individual risk of bleeding for each patient, particularly for the first year after the onset of ACS. Concerning the anticoagulant drug, atrial fibrillation has priority over completely revascularized coronary artery disease, and NOACs could be restarted after CABG revascularization.

In other words, long-term antithrombotic treatment for stroke prevention in atrial fibrillation patients who presented an ACS with subsequent CABG revascularization could follow the guidelines for antithrombotic treatment of atrial fibrillation occurring outside the setting of ACS and CABG. However, more information on these patients and more commitment from the guideline committees to provide clearer indications to the physicians are necessary.

**CONCLUSIONS**

Warfarin is an oral anticoagulant that can be used in multiple clinical settings, which were omitted in the clinical trials on NOACs, such as severe renal failure, patients unsuitable for anticoagulation with NOACs, or ACS in atrial fibrillation patients. While the use of NOACs is prioritized over warfarin according to the European atrial fibrillation guidelines, the data are limited when these patients have ACS or a myocardial infarction (Figure 4, page 281).

Oral anticoagulation must be continued after ACS in atrial fibrillation patients because it is indicated for stroke prevention in atrial fibrillation, which preceded the ACS event. In addition, there is no reason to change an already established anticoagulation regimen either with one of the NOACs or an adjusted VKA. Several trials have been designed to address the risk-benefit ratio of new strategies combining anticoagulation and antiplatelet therapy in patients with both atrial fibrillation and ACS. While waiting for these results, strategies should be adapted to the decision for and type of revascularization as discussed above. Removing one antiplatelet agent immediately or 1 to 3 months after the ACS event appears to be a solution to minimize the risk of bleeding, which is high in atrial fibrillation patients who need effective anticoagulation for stroke prevention.

**REFERENCES**


Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions. Eur Heart J. 2014;35:3155-3179.


New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. Eur Heart J. 2013;34:1670-1680.

9. Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR.

Is it recommended to switch from NOACs to warfarin after an ACS? - Montalescot

Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation.

Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention.

Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.

Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial.

Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment.

Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials.

Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: the dual antiplatelet therapy randomized clinical trial.
JAMA. 2015;313:1113-1121.

Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents.

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial.

20. Fox KA.
Dual or single antiplatelet therapy with anti-coagulation?

An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI).

22. clinicaltrial.gov.
Evaluation of dual therapy with dabigatran vs triple therapy with warfarin in patients with AF that undergo a PCI with stenting (REDUAL-PCI).

Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study.

Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial.

A new strategy for discontinuation of dual antiplatelet therapy: the RESET trial (Real Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation).

Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute zotarolimus-eluting stent implantation.

Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study.

2014 ESC/EACTS Guidelines on myocardial revascularization.
Despite the profound advances in molecular biology, systems biology, and medicinal chemistry, nature provides still unanticipated sources of novel improved drugs as is evidenced by the recently awarded Nobel Prize in 2015 to Tu Youyou for her work in the early 1970s on the discovery and development of the new Chinese antimalarial drug artemisinin.1 Similarly, in the field of cardiovascular treatments, the first effective antithrombotic agents were provided by either plant or animal tissues.

**WARFARIN**

The most widely prescribed oral anticoagulant is warfarin. Research to identify warfarin was triggered by a seeming epidemic of hemorrhage in cattle in Canada and the US in the early 1920s. This problem caught the eye of a young undergraduate called Frank Schofield who emigrated to Canada from the UK at the age of 16 in order to attend the Ontario Veterinary College in Toronto in 1907. After graduating in 1909, he conducted bacteriology research at the Ontario Health Center, studying bacterial infections in animals. Outbreaks of hemorrhagic disease in calves caught his attention since the episodes were incorrectly attributed to bacterial sepsis by the clinical veterinarians. Schofield visited the affected farms personally and noted that in the cold Canadian winter, cattle were fed silage from sweet clover (*Melilotus alba*) (Figure 1).

![Sweet Clover](http://example.com/sweet_clover.jpg)

Figure 1. *Melilotus officinalis*.

Despite this, he demonstrated that analogous symptoms in rabbits were expressed in response to moldy hay, similar to the ones in cattle. The mold *Aspergillus* (Figure 2, page 286) produced a toxic factor in either yellow or white *Melilotus officinalis* (the term mel referred to the fact that bees harvested honey from sweet clover) or *Melilotus albus*. Sweet clover can be used for hay or silage.

He believed that these problems were secondary to toxins originating in the moldy hay fed over the winter, which also contained sweet clover. In a masterly conducted experiment, he fed rabbits either clean stalks of sweet clover or moldy stalks of sweet clover. He demonstrated that analogous symptoms in rabbits were expressed in response to moldy hay, similar to the ones in cattle. The mold *Aspergillus* (Figure 2, page 286) produced a toxic factor in either yellow or white *Melilotus officinalis* (the term mel referred to the fact that bees harvested honey from sweet clover) or *Melilotus albus*. Sweet clover can be used for hay or silage. The key scientist involved in characterizing the mechanism of cattle-induced hemorrhage was Karl Link who was working at the University of Minnesota in the early 1930s with a scientific col-
They isolated and crystallized the hemorrhagic agent from damaged sweet clover. At the same time, Armand Quick’s group had developed a test for prothrombin time. By April 1940, the structure of 3,3′-methylene-bis-(4-hydroxycoumarin) had been identified and it was subsequently synthesized. The formation of dicoumarol in moldy sweet-clover vegetation required a combination of fungal activities to induce the oxidation of coumarin to 4-hydroxycoumarin, plus the addition of formaldehyde and another coumarin molecule. Subsequently, Link’s group synthesized and evaluated 100 analogues of dicoumarol for anticoagulant activity; patents were granted for several of these analogues. Link assigned the patents to the University of Wisconsin Alumni Research Foundation (WARF), an acronym forming the word warfarin.

Further evaluation of the analogues showed that compound 42 was more potent and effective than the parent dicoumarol. Compound 42 was also patented (3-phenyl acetyl ethyl 4-hydroxycoumarin) and given the name of warfarin based on the above acronym. Currently, warfarin is marketed in the US by DuPont, Abbott, and Lemmon. Many years later, the mode of action of warfarin was shown to be due to inhibition of vitamin K epoxide reductase, which caused a reduction in the generation of vitamin K–dependent clotting factors.

HEPARIN

A further example of nature’s contribution to anticoagulation is heparin. It was discovered by Jay McLean who worked in William Howell’s laboratory in 1915 (Figure 4). When approaching Howell, McLean stated that he wished to determine if he could solve a scientific problem by himself. Howell assigned him the task of determining the value of a thromboplastic substance in the body. In 1915, McLean started to study a procoagulant extract from brain, which they called cephalin, which was shown to be a mixture of phospholipids. McLean also studied extracts of dog heart and dog liver for their procoagulant properties. Scrutiny of the German chemical literature on phosphatides showed that there were articles by Erlandsen describing courin isolated from the canine heart and by Baskoff describing an hepatic phosphatide called heparphosphatid. This latter term gave rise to the name heparin. McLean’s superior, Howell, was unaware of these findings. Repeated extractions of the liver unexpectedly
revealed that once cephalin was removed from the extract, the batch of heparphosphatid prevented experimental blood clotting. Howell was convinced that this was a novel observation and subsequently reported on the chemical and physiological reactions of heparin. Subsequently, Charles Best and Arthur Charles, who were working in Toronto, showed that heparin could be found in many organs throughout the body. A highly purified form was isolated in 1933. Advances in chemical analysis subsequently showed that heparin comprised a sequence of trisulfated disaccharide L-iduronic acid-2-sulfated–glucosamine-N,6-disulfate. The disaccharide sequences were interrupted by either undersulfated or oversulfated sequences of D-glucuronic acid and N-acetylated D-glucosamine (Figure 5).

The purification of heparin isolated from different tissues was difficult. In the first human volunteer experiment with heparin, 100 mg or more was needed to cause anticoagulation that lasted a matter of hours, which was accompanied by unpleasant side effects. The pharmaceutical company Vitrum became interested in heparin as a parenteral anticoagulant and developed a large-scale purified preparation. The first clinical study of heparin, as an anticoagulant, was published by the Swedish surgeon Clarence Crafoord with the aim of reducing the incidence of postoperative pulmonary embolism. The usual incidence of this, at that time, was 3% to 4%, but patients receiving heparin did not develop emboli. Thus, it was 20 years from the initial identification of heparin to the proof of its clinical effectiveness in trials. Studies on the mode of action of heparin as an anticoagulant were carried out over 20 years starting in 1939. It was shown that the anticoagulant effects were mediated by binding to both antithrombin III and heparin cofactor II, which inhibited activation of thrombin production.

HIRUDIN

Hirudin is a natural anticoagulant, which was initially isolated from the leech Hirudo medicinalis (Figure 6). For centuries, it was known that bites in the skin by leeches bled long after the animal was detached. Haycroft identified a substance from the leech that had anticoagulant actions. Extracts obtained from leeches in the early 20th century were called hirudin, but both the chemical structure and the mode of action were unknown. Subsequent advances in chemistry technology led to the characterization of hirudin as a 65–amino acid polypeptide with a molecular weight of about...
7 kDa. Biological studies showed that hirudin bound specifically, irreversibly, and extremely potently to thrombin. It inhibited both fibrinogen clotting as well as the downstream factors V, VIII, and XIII. Due to the potent and specific binding of hirudin to thrombin, its potency has been expressed as antithrombin activity.

The gene for hirudin was cloned, which enabled the generation of recombinant hirudin (r-hirudin), in which the sulfate group on tyrosine 63 has been deleted. This recombinant protein has been shown to be as potent as natural hirudin. From the clinical point of view, r-hirudin is a competitor of heparin in the whole field of parenteral antithrombosis. In extensive clinical trials (GUSTO II [Global Use of Strategies To open Occluded coronary arteries II], TIMI-9A [Thrombolysis In Myocardial Infarction 9A], and HIT-III [Hirudin for the Improvement of Thrombolysis III]), there was an unexplained and unanticipated increase in the incidence of stroke, which led to the suspension of clinical trials. The comparative risk-benefit ratio of r-hirudin compared with heparin remains a source of controversy.

EPILOGUE

This essay has focused on the origin of classic anticoagulants. It shows that those seeking improved medicines should not discount nature as a source of novel interesting compounds. It illustrates again the critical contribution of serendipity to scientific progress.

REFERENCES

1. Tu YY.
The discovery of artemisinin (Gainghauose) and gifts from Chinese medicine.

2. Schofield FW.
Hemorrhagic sweet clover disease in cattle.

3. Campbell HA, Roberts WL, Smith WK, Link KP.
Studies of the hemorrhagic sweet clover disease: I. The preparation of hemorrhagic concentrates.

4. Huebner CF, Link KP.
Studies on the hemorrhagic sweet clover disease: VI. The synthesis of the δ-diketone derived from the hemorrhagic agent through alkaline degradation.
J Biol Chem. 1941;138:529-534.

5. Link KP.
The discovery of dicoumarol and its sequels.

Vitamin K-dependent modification of glutamic acid residues in prothrombin.

7. McLean J.
The thromboplastic action of cephalin.
Am J Physiol. 1916;41:250-257.

8. Powell WH.
Heparin, an anticoagulant.

9. Best CH.
Heparin and thrombosis.
Harvey Lectures. 1940;36:66-90.

10. Casu B.
Heparin structure.

11. Mason EC.
A note on the use of heparin in blood transfusion.

12. Crafoord C.
Preliminary report on post-operative treatment with heparin as a preventive of thrombosis.

13. Abildgaard U.
Highly purified antithrombin 3 with heparin cofactor activity prepared by disc electrophoresis.

14. Haycraft JH.
On the action of a secretion obtained from the medicinal leech on coagulation of the blood.

Nuclear magnetic resonance solution structure of hirudin(1-51) and comparison with corresponding three dimensional structures determined using the complete 65-residue hirudin polypeptide chain.

Adjunctive use of direct thrombin inhibitors in patients receiving fibrinolytic therapy for acute myocardial infarction.
 Novel Oral Anticoagulants in Patients With Acute Coronary Syndrome

Summaries of Ten Seminal Papers

Nikhil V. Joshi, MD, MRCP (UK), MRCPE, PgC Med Ed

Edinburgh Heart Centre and British Heart Foundation Centre for Cardiovascular Sciences - SU 305
Chancellors Building - Little France Crescent - Edinburgh - UK (e-mail: nikhil.joshi@ed.ac.uk)

Dialogues Cardiovasc Med. 2015;20:289-299

1. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial
   L. Wallentin and others. Lancet. 2003

2. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome...

3. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46)...
   J. L. Mega and others. Lancet. 2009

4. Apixaban with antiplatelet therapy after acute coronary syndrome

5. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban...
   P. G. Steg and others. Eur Heart J. 2011

6. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial
   J. Oldgren and others. Eur Heart J. 2011

7. Rivaroxaban in patients with a recent acute coronary syndrome

8. Rivaroxaban in patients stabilized after a ST-segment elevation myocardial infarction
   J. L. Mega and others. J Am Coll Cardiol. 2013

9. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis
   J. Oldgren and others. Eur Heart J. 2013

10. Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS-ACS 2 TIMI 51
    C. M. Gibson and others. J Am Coll Cardiol. 2013

Selection of seminal papers by Nikhil V. Joshi, MD, MRCP (UK), MRCPE, PgC Med Ed - Edinburgh Heart Centre and British Heart Foundation Centre for Cardiovascular Sciences - Edinburgh - UK

Highlights of the years by Sherri Smith, PhD
Publications office
Ever since heparin was shown to be effective in preventing thrombus formation in dogs in the 1930s, a great deal of interest has been given to treating patients with a myocardial infarction using anticoagulants. Anticoagulants, such as unfractionated heparins and low-molecular-weight heparins, have become the cornerstone in the immediate management of patients with acute coronary syndromes (ACS). The long-term benefits of anticoagulation were only tested ≈10 years ago, with several studies suggesting a benefit with vitamin K antagonists (VKA), such as warfarin.

Adding warfarin to aspirin reduced the rates of recurrent myocardial infarction, although at the cost of an increase in bleeding events. In parallel, the role of dual antiplatelet therapy with aspirin and thienopyridines was established in patients with ACS, as was the role of oral anticoagulants in patients with atrial fibrillation. The use of warfarin has several limitations, including frequent monitoring and dose adjustments, drug and food interactions, genetic variability in metabolism, and delayed onset and offset. With the advent of the so-called novel oral anticoagulants (NOACs) or the non–VKA oral anticoagulants, the interest in using these agents in ACS has been rejuvenated.

NOACs can be classified as direct thrombin inhibitors, such as dabigatran, or factor Xa inhibitors, such as rivaroxaban, apixaban, etc. The study of these agents in ACS has significant implications. First, these agents are clearly indicated in about 15% of patients with established and new onset atrial fibrillation with ACS. Second, several studies have shown promise when using NOACs in addition to dual antiplatelet therapy, with a reduced risk of recurrent myocardial infarction albeit with a higher risk of bleeding.

The first evidence for the utility of these drugs in patients with ACS was provided by the phase 2 ESTEEM trial (Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patients with recent Myocardial damage). Ximelagatran was the first available oral direct thrombin inhibitor to be introduced in the market. The ESTEEM investigators assessed the efficacy of ximelagatran and aspirin in preventing death, recurrent myocardial infarction, and ischemia in patients with ACS. In this placebo-controlled, double-blind, multidosing trial, 1883 patients with ACS were randomized to aspirin or ximelagatran plus aspirin within 14 days of the index event and followed up for 6 months. There was a significant reduction in the rate of the composite of death, nonfatal myocardial infarction, or nonfatal stroke at 6 months in the ximelagatran group vs placebo (7% vs 11%, odds ratio, 0.66, 95% CI, 0.48-0.90), with a small increase in the rate of bleeding (2% vs 1%). Ximelagatran appeared to reduce the efficacy end point by 24% compared with placebo in ACS patients without a significant increase in bleeding.

The results of the ESTEEM trial provided the first evidence for the concept of direct thrombin inhibitors as effective agents in the secondary prevention of ACS. Subsequent studies showed an increased incidence of liver toxicity with ximelagatran; therefore, the development was stopped and the drug was withdrawn from the market. Nonetheless, this important proof-of-principle study documents the rationale for combining antiplatelet and anticoagulant therapies and that, if the right therapeutic profile could be developed for the outpatient setting, this combination could potentially offer long-term benefits, such as good oral bioavailability, a reliable anticoagulant effect, and an acceptable safety profile.

---

Yang Liwei, China’s first astronaut, returns to earth safely aboard the spacecraft Shenzhou 5 after circling the planet 14 times in 21 hours; Andrew J. Barberi, the Staten Island ferry (New York, USA), crashes into the dock at full throttle; and an Ebola outbreak in the Congo kills 75 people.
Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial


Circulation. 2009;119:2877-2885

Apixaban is a potent, oral, direct, and highly selective active-site inhibitor of factor Xa. By inhibiting factor Xa, apixaban prevents thrombin generation and subsequent thrombus development. In adult patients with nonvalvular atrial fibrillation, the use of apixaban has been approved as 5 mg twice daily and 2.5 mg twice daily for the prevention of stroke and systemic thromboembolism, respectively.

The role of apixaban in patients with acute coronary syndrome was tested in the APPRAISE trial (APixaban for PRevention of Acute IShemic Events). APPRAISE was a phase 2, double-blind, placebo-controlled, dose-ranging study in patients with a recent ST-segment elevation acute coronary syndrome or non–ST-segment elevation acute coronary syndrome and one or more additional risk factors for recurring events (eg, age ≥ 65 years, elevated cardiac biomarkers, heart failure, diabetes, or prior myocardial infarction). A total of 1715 patients were randomized to 6 months of placebo or one of four doses of apixaban (2.5 mg twice daily, 10 mg once daily, 10 mg twice daily, and 20 mg once daily). Almost all of the patients were on aspirin and around three-quarters of the patients (76%) received clopidogrel. The primary outcome was major or clinically relevant nonmajor bleeding, while the secondary outcome measures were cardiovascular death, myocardial infarction, severe recurrent ischemia, or ischemic stroke. The 10-mg twice-daily and 20-mg once-daily treatment arms were discontinued due to an increase in total bleeding events and a dose-dependent increase in major or clinically relevant nonmajor bleeding compared with placebo.

A dose-dependent increase in bleeding with both the 2.5-mg twice-daily dose and 10-mg once-daily dose of apixaban was observed. There was a trend toward lower rates of ischemic events in patients receiving apixaban compared with placebo (hazard ratio [HR] for the 2.5-mg twice-daily dose, 0.73; 95% CI, 0.44-1.19; HR for the 10-mg once-daily dose, 0.61; 95% CI, 0.35-1.04; HR = 0.90). The increase in bleeding was more pronounced and the reduction in ischemic events was less evident in patients taking aspirin plus clopidogrel than those on aspirin alone.

This study provided one of the first experiences with an oral, direct, selective factor Xa inhibitor in patients with a recent ST-segment elevation acute coronary syndrome or non–ST-segment elevation acute coronary syndrome treated with contemporary antiplatelet therapy. The addition of apixaban to antiplatelet therapy resulted in a dose-dependent increase in bleeding and a trend toward a reduction in ischemic events. This study formed the basis for the subsequent APPRAISE-2 trial.

Barack Obama is awarded the Nobel Peace Prize for his “extraordinary efforts to strengthen international diplomacy and cooperation between peoples”; Carol Ann Duffy becomes the UK’s first female Poet Laureate; and Rio de Janeiro, Brazil wins the bid for the 2016 Olympics, becoming the first South American city to host the Games.
Rivaroxaban is an oral anticoagulant that directly and selectively inhibits factor Xa. Factor Xa initiates the final common pathway of the coagulation cascade and results in the formation of thrombin, which catalyzes additional coagulation-related reactions and promotes platelet activation. Rivaroxaban has been approved for the treatment of patients with nonvalvular atrial fibrillation for stroke prevention. Rivaroxaban has also been approved for the prevention and treatment of deep vein thrombosis.

The ATLAS ACS–TIMI 46 trial (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 46) was the first clinical study to test the use of rivaroxaban in patients with acute coronary syndromes. In this double-blind, dose-escalation, randomized phase 2 study, the investigators aimed to determine the optimal dosing for further assessment of rivaroxaban in larger clinical trials. Patients were randomly assigned to placebo or rivaroxaban at varying doses (5 mg, 10 mg, 15 mg, and 20 mg) for 6 months after an acute coronary syndrome. Randomization was stratified by the treating physician’s choice of antiplatelet therapy (aspirin alone vs aspirin plus thienopyridine).

The primary safety end point was clinically significant bleeding (Thrombolysis In Myocardial Infarction [TIMI] major, TIMI minor, or requiring medical attention) and the primary efficacy end point was death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularization in 6 months. There was an increase in the rates of bleeding as the dose increased, with the highest rates of bleeding occurring when the drug was used on a background of dual antiplatelet therapy. There was no difference in the incidence of the primary efficacy end point in the overall cohort (hazard ratio [HR], 0.79; 95% CI, 0.6-1.05; P=0.10), although there was a reduction in events in patients on aspirin alone (HR, 0.53; 95% CI, 0.33-0.84) and no benefit was observed in patients on dual antiplatelet therapy (HR, 0.99, 95% CI, 0.69-1.42). Although somewhat underrepresented, both elderly patients and patients with renal dysfunction had the highest rates of bleeding. Overall, rivaroxaban was associated with a 2- to 4-fold increase in bleeding. Nonetheless, the findings of this study showed a trend toward a reduction in the primary end point and this study formed the basis of the larger ATLAS ACS 2–TIMI 51 study.

2009

American politician Sarah Palin, current Governor of Alaska and 2008 Vice Presidential candidate, announces her resignation as Governor; Zac Sunderland, at the age of 17, becomes the youngest person to sail around the world alone; and the first giant panda conceived through artificial insemination using frozen sperm is born in China.
Apixaban with antiplatelet therapy after acute coronary syndrome


Building on the findings of the APPRAISE trial (APixaban for Prevention of Acute ISchemic Events), the investigators undertook the APPRAISE-2 trial, a randomized, double-blind, placebo-controlled, phase 3 clinical trial. In patients with a recent acute coronary syndrome and at least two additional risk factors for recurrent ischemic events, the study compared apixaban 5 mg twice daily with placebo, in addition to standard antiplatelet therapy. The aim of the study was to determine whether, in high-risk patients with an acute coronary syndrome, the benefit of apixaban in reducing ischemic events would outweigh the increased risk of bleeding.

The primary efficacy outcome was the composite of cardiovascular death, myocardial infarction, or ischemic stroke and the primary safety outcome was major bleeding according to the Thrombolysis In Myocardial Infarction (TIMI) definition. After recruiting 7392 patients, the trial was terminated prematurely due to an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. There was a 1.3% increase in TIMI major bleeding compared with the 0.5% increase with placebo (hazard ratio [HR], 2.59; 95% CI, 1.50-4.46; \( P = 0.001 \)), and no significant reduction in ischemic events was observed (7.5% vs 7.9%; HR, 0.95; 95% CI, 0.80-1.11; \( P = 0.51 \)).

These findings were consistent in all subgroups, including subgroups defined according to antiplatelet therapy (aspirin plus clopidogrel vs aspirin alone) and according to the management of the acute coronary syndrome (revascularization vs noninvasive management). The increase in bleeding with apixaban led to a more frequent discontinuation of apixaban and resulted in the premature termination of the study—limiting the certainty of the conclusions that can be drawn about efficacy. Notably, the study population was at a relatively high risk, including patients with prior strokes or transient ischemic attacks. If patients with prior strokes or transient ischemic attacks were excluded, the hazard ratio for apixaban vs placebo for cardiovascular death, myocardial infarction, 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% vs 2.2%; HR, 0.73; 95% CI, 0.47-1.12; \( P = 0.15 \)).

Nonetheless, due to premature termination of the trial, no conclusive evidence can be drawn from the trial apart from the increased risk of bleeding with apixaban.

Christian Dior fires fashion designer John Galliano;
John Higgins wins the World Snooker Championship for the fourth time;
and Johan Marius Nicolaas “Johannes” Heesters, a Dutch-born actor of stage, television, and film, dies at age 108
Patients have a high risk of recurrent cardiovascular events after an acute coronary syndrome. Despite treatment with dual antiplatelet therapy (ie, aspirin and clopidogrel), the recurrence of ischemic events after an acute coronary syndrome can be as high as 9.1% at 6 months. Therefore, adding antithrombotic therapy to antiplatelet therapy is an interesting option. The RUBY-1 trial (evaluation of the safety, tolerability, and efficacy of YM150 in subjects with acute coronary syndromes) was conducted to analyze darexaban, a direct oral thrombin factor Xa inhibitor, in patients with a recent acute coronary syndrome. The main aim of the study was to establish the safety and tolerability of different doses of darexaban for the secondary prevention of ischemic vascular events.

The RUBY-1 trial was a 26-week, multicenter, double-blind study that enrolled a total of 1279 patients within 7 days after either an ST-segment elevation myocardial infarction or a non-ST-segment elevation myocardial infarction. The patients were randomized to receive one of six different doses of darexaban (5 mg twice daily, 10 mg once daily, 15 mg twice daily, 30 mg once daily, 30 mg twice daily, or 60 mg once daily) or placebo, in addition to dual antiplatelet therapy. The primary outcome was the incidence of major or clinically relevant nonmajor bleeding events during the 6 months of the study, which was determined according to a modified version of the International Society on Thrombosis and Hemostasis definition. The main efficacy outcome was the composite of death, stroke, myocardial infarction, systemic thromboembolism, and severe recurrent ischemia.

As with other novel oral anticoagulants, there was a dose-dependent increase in the risk of bleeding as the dose of darexaban increased (P=0.009). The rate of bleeding was 2- to 4-fold higher with darexaban than with placebo (hazard ratios ranged from 1.8 to 3.8), and the cumulative incidence of bleeding was 6.2%, 6.5%, and 9.3% for the 10 mg, 30 mg, and 60 mg total daily doses of darexaban, respectively. There were no incidences of fatal bleeding or intracranial hemorrhage in any group. Despite the fact that this study was underpowered to determine the efficacy of darexaban, there was no reduction in the composite efficacy end point with darexaban vs placebo. In addition, there was an infrequent occurrence of the composite efficacy end point with the lower doses of darexaban.

Overall, darexaban was well tolerated with an expected increase in the rates of bleeding. A larger-scale, phase 3 trial will need to be conducted to determine the potential of adding low-dose darexaban to antiplatelet agents in patients with acute coronary syndromes.

Betty Ford, an American feminist, activist, philanthropist, and former First Lady, dies at age 93; the Mars Science Laboratory’s rover Curiosity, the most elaborate space exploration vehicle to date, is launched from the Kennedy Space Center; and the world’s first tissue-engineered urethras are successfully transplanted.
Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial


_Eur Heart J._ 2011;32:2781-2789

Dabigatran etexilate is an orally administered anticoagulant that directly inhibits the thrombin Xa enzyme. Dabigatran has been approved for patients with nonvalvular atrial fibrillation to prevent stroke and systemic embolism. The utility of this drug in patients with acute coronary syndrome was tested in the RE-DEEM study (Randomised dabigatran ETEXilate Dose-finding study in patients with acute coronary syndromes after the index Event with additional risk factors for cardiovascular complications also receiving aspirin and clopidogrel).

RE-DEEM was a multicenter, double-blind, placebo-controlled, dose-escalation trial that enrolled patients with acute ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation myocardial infarction (NSTEMI). The primary outcome of the study was to assess major or clinically relevant minor bleeding during the 6-month treatment period. The majority of the patients were established on dual antiplatelet therapy (99.2%). A total of 1861 patients were enrolled in the study after a mean of 7.5 days post–STEMI (60%) or post–NSTEMI (40%). The patients were randomized to one of four different doses of dabigatran (50 mg, 75 mg, 110 mg, and 150 mg) twice daily or placebo. The 6-month incidence of the primary end point—the composite of major or clinically relevant minor bleeding events—was 3.5%, 4.3%, 7.9%, and 7.8% with 50 mg, 75 mg, 110 mg, and 150 mg in the dabigatran groups, respectively, compared with 2.2% in the placebo group (P<0.001 for linear trend). Thus, a dose-dependent increase in bleeding was observed in patients taking dabigatran, although the absolute risk of bleeding was low. The risk of bleeding was higher in women and in patients >77 years of age. There was no meaningful reduction in ischemic clinical events in patients treated with dabigatran compared with placebo.

There were several differences between the RE-DEEM study and previous studies. First, RE-DEEM was the first study to evaluate an oral anticoagulant in patients with acute coronary syndrome in which all patients were required to be on antiplatelet treatment with both aspirin and clopidogrel. The previous studies with non–vitamin K antagonist oral anticoagulants (NOACs) had a varied use of dual antiplatelet therapy. For instance, in the ESTEEM trial (Efficacy and Safety of the oral direct Thrombin inhibitor ximElagatran in patients with recent Myocardial damage), the direct thrombin inhibitor ximelagatran was administered to patients receiving aspirin alone. Similarly, in the factor Xa inhibitor studies, in either the ATLAS ACS–TIMI 46 trial (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction) or a APPRAISE trial (Apixaban for PRevention of Acute ISchemic Events), treatment with rivaroxaban or apixaban, respectively, was combined with either single or dual antiplatelet therapy, 76% to 78% of the patients were on dual antiplatelet therapy at randomization.

Consistent with other studies, the RE-DEEM study concluded that dabigatran, in addition to dual antiplatelet treatment, resulted in a dose-related 2- to 4-fold increase in the risk of bleeding, which was accompanied by a significantly reduced coagulation activity in laboratory end points. There was no reduction observed in ischemic clinical events.

Bernd Eichinger, a German film producer, director, and screenwriter, dies at age 61 from a heart attack; since its discovery in 1846, the planet Neptune completes its first orbit; and a Cochrane Library review suggests that antioxidants may improve male fertility.
Rivaroxaban in patients with a recent acute coronary syndrome


Building on the observations of the ATLAS ACS–TIMI 46 trial (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 46), rivaroxaban was evaluated in a phase 3 prospective, double-blind, randomized placebo-controlled trial—ATLAS ACS 2–TIMI 51. The aim of the study was to determine an optimal clinically effective treatment dose in patients with a recent acute coronary syndrome.

A total of 15,526 patients who were hospitalized for an acute coronary syndrome were randomly assigned to receive one of two doses of rivaroxaban (2.5 mg or 5 mg twice daily) or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point—composite of death from cardiovascular causes, myocardial infarction, or stroke—was reduced in both groups receiving rivaroxaban compared with placebo (9.1% with the 2.5-mg dose and 8.8% with the 5-mg dose vs 10.7% [P=0.008] in the placebo group). There were also reductions in the rates of all-cause death and cardiovascular death for the 2.5-mg dose, but not the 5-mg dose. The rate of major bleeding (according to the Thrombolysis In Myocardial Infarction (TIMI) criteria) not related to coronary artery bypass grafting increased almost four times in patients receiving rivaroxaban vs those receiving placebo (2.1% vs 0.6%), although there was no significant increase in the rate of fatal bleeding (0.3% vs 0.2%, P=0.66) with rivaroxaban vs placebo.

Overall, the results of the study were extremely encouraging with a clear reduction in ischemic events without excess bleeding. There was a consistent treatment benefit across many important subgroups, but the proportion of patients who were at least 75 years of age (9.0%) or female (25%) were small, and more than 75% of the patients had normal renal function. Thus, the results may not be applicable to the higher-risk patients with acute coronary syndrome that are commonly treated in routine practice. The results of the study were an important development for patients with acute coronary syndrome who are otherwise young and healthy. However, the role of rivaroxaban in elderly patients with comorbidities needs to be evaluated better. In May 2012, the FDA rejected rivaroxaban in acute coronary syndrome patients because of concerns regarding missing data, an appeal was again rejected in March 2013. The FDA cited the following issues with the data on rivaroxaban: high incomplete follow-up (12%), vital status missing (9%); uncounted deaths; different rates of outcomes between the first and second halves of the trial, which is a concern for informative censoring; and generalizability of the data.

It is fair to say that, following this study, a new era began for secondary prevention after an acute coronary syndrome and it is now focused on finding the balance between ischemic risks and the risks of bleeding, as well as individualizing antiplatelet and anticoagulant therapies in patients with acute coronary syndrome.

A nest of dinosaur eggs is found in South Africa, which is 100 million years older than the oldest previously discovered site; Physicists at Germany’s Max Planck Institute unveil a microscope that can image brain cells inside a living animal; and Jean Henri Gaston Giraud, a French artist, cartoonist, and writer, dies at age 73
Rivaroxaban in patients stabilized after a ST-segment elevation myocardial infarction


J Am Coll Cardiol. 2013;61:1853-1859

The ATLAS ACS 2–TIMI 51 study (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 51) conclusively showed the benefit of adding rivaroxaban to the management of patients with acute coronary syndrome. The authors conducted a prespecified subgroup analysis from the ATLAS ACS 2–TIMI 51 study on patients with ST-segment elevation myocardial infarction (STEMI).

A total of 7817 patients with STEMI were randomized to rivaroxaban 2.5 mg, rivaroxaban 5 mg, or placebo after an initial period of stabilization. The majority of STEMI patients were treated with aspirin and a thienopyridine (predominantly clopidogrel) at baseline. Among the STEMI patients, rivaroxaban reduced the primary efficacy end point—cardiovascular death, myocardial infarction, or stroke—compared with placebo (hazard ratio [HR], 0.81; 95% CI, 0.67-0.97). The separation of events was evident within 30 days (P=0.042). With rivaroxaban 2.5 mg, there was a mortality benefit compared with placebo, which was not observed with the 5-mg dose (2.5% vs 4.2%, P=0.006).

The risk of major bleeding, as defined by Thrombolysis In Myocardial Infarction (TIMI) criteria (2.2% vs 0.6%, P<0.001) and intracranial bleeding (0.6% vs 0.1%, P=0.015), was significantly higher in patients receiving rivaroxaban, but there was no significant increase in fatal bleeding events (0.2% vs 0.1%, P=0.51).

The benefit of rivaroxaban was evident despite the use of antiplatelet therapies, which was confirmed by analyses that included patients continuing their background medications. Within the STEMI group, the survival benefit with the 2.5-mg twice-daily dose persisted and it was not seen with the higher dose of rivaroxaban. As a factor Xa inhibitor, rivaroxaban was associated with higher rates of bleeding than placebo, with the 2.5-mg twice-daily dose of rivaroxaban exhibiting a better safety profile than the 5-mg twice-daily dose. Thus, the addition of rivaroxaban 2.5 mg twice daily may offer an effective strategy to reduce thrombotic events in patients post–STEMI.

In this study, patients were not treated with one of the newer antiplatelet drugs, such as prasugrel or ticagrelor, and the use of rivaroxaban in addition to these agents has not been tested thoroughly. Nonetheless, in principle, the study supports the use of a low-dose antithrombotic agent in addition to standard antiplatelet therapy. Additional studies to determine the duration of the dose with newer antiplatelet agents will be interesting. Furthermore, the risk of bleeding will determine which patient subgroups are likely to benefit most from these novel agents.

2013

The first fossil of a mosquito with definitive evidence of blood is discovered; Ray Milton Dolby, the American inventor of the Dolby noise reduction system, dies at age 80 from leukemia; and the cargo ship Jolly Nero collides with the control tower in the port of Genoa, Italy, killing 11 people.
New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis


**Eur Heart J.** 2013;34:1670-1680

In this meta-analysis, Oldgren et al. studied all contemporary clinical trials with non–vitamin K antagonist oral anticoagulants (NOACs) in patients with acute coronary syndromes. The meta-analysis was comprised of data from seven published phase 2 and 3 studies, including the ESTEEM (Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patients with recent Myocardial damage), RE-DEEM (RandomizeEd Dabigatran EtxelixE dose-finding study in patients with acute coronary syndromes after the index event with additional risk factors for cardiovascular complications also receiving aspirin and clopidogrel), RUBY-1 (evaluation of the safety, toleRability and efficacy of YM150 in sUBjects with acute coronaY syndromes), APPRAISE-1 (Apixaban for Prevention of Acute IIschemic Events), APPRAISE-2, ATLAS ACS–TIMI 46 (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 46), and ATLAS ACS 2–TIMI 51 studies.

The efficacy and safety of NOACs in acute coronary syndromes were evaluated by assessing the addition of either a direct thrombin inhibitor (rivaroxaban) or a factor Xa inhibitor (any of the novel oral anticoagulants, i.e., apixaban, dabigatran, darexaban, rivaroxaban, and ximelagatran) to single (aspirin) or dual (aspirin and clopidogrel) antiplatelet therapy in patients with acute coronary syndromes. The efficacy outcome was any major adverse cardiovascular event (MACE), which was defined as all-cause mortality, myocardial infarction, or stroke, and the safety outcome was major bleeding events, which were defined by International Society on Thrombosis and Hemostasis (ISTH) and TIMI bleeding.

The majority of the patients (86.6%) were on dual antiplatelet therapy, while 13.4% were on a single antiplatelet agent. Patients were within 7 to 14 days after presenting with ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction. Addition of a NOAC to aspirin resulted in a reduction in the primary outcome of combined MACE compared with aspirin alone (hazard ratio [HR], 0.70, 95% CI, 0.59-0.84), but this was at the cost of an increased rate of bleeding (HR, 1.79; 95% CI, 1.54-2.09). Adding a NOAC to dual antiplatelet therapy modestly decreased the incidence of MACE (HR, 0.87, 95% CI, 0.80-0.95), but more than doubled the risk of bleeding (HR, 2.34; 95% CI, 2.06-2.66).

The most significant benefit of a NOAC seems to occur after adding a NOAC to a single antiplatelet agent, which reduces the combined MACE events by about 30%, although this increases the risk of bleeding by about 79%. In patients treated with dual antiplatelet therapy, the benefit obtained was lower (=13%), but at the cost of a higher risk of bleeding (134%). Now, the role of NOACs in various patient populations needs to be assessed to determine which patients will derive the most benefit from NOAC therapy in addition to antiplatelet agents.
Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS-ACS 2 TIMI 51


Percutaneous coronary intervention is the predominant revascularization strategy in patients with acute coronary syndromes. The advances in stent technology have substantially improved the success rates of the procedure and decreased the rates of stent failure. The most feared complication related to coronary stenting is stent thrombosis. Although stent thrombosis is relatively rare (0.5% to 1% patients within 12 months), most patients present with an acute myocardial infarction, and there is a high rate of mortality (about 25%) within 30 days. Furthermore, patients who have a stent thrombosis are more likely to have a reoccurrence rate of about 20% within 2 years.

The pathophysiology of stent thrombosis is complex, but dual antiplatelet therapy significantly reduces the risk of stent thrombosis. The ATLAS ACS 2-TIMI 52 trial investigators (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2-Thrombolysis In Myocardial Infarction 52) assessed the role of the factor Xa inhibitor rivaroxaban to determine whether rivaroxaban administration is associated with a reduction in stent thrombosis.

A subgroup analysis was undertaken in patients with acute coronary syndromes, who were undergoing a percutaneous coronary intervention and stent implantation. Patients were treated with rivaroxaban 2.5 mg, rivaroxaban 5 mg, or placebo, in addition to aspirin alone or dual antiplatelet therapy. A total of 9633 patients had coronary stenting before or at the time of their presentation. Rivaroxaban significantly reduced the risk of Academic Research Consortium definite and probable stent thrombosis (1.9% vs 1.5%, hazard ratio [HR], 0.65; P=0.017). The benefit was more pronounced in the 2.5-mg twice-daily treatment group (1.9% vs 1.5%; HR, 0.61; P=0.023), with a trend toward benefit with the 5-mg twice-daily dose. In patients receiving dual antiplatelet therapy, the addition of rivaroxaban reduced the risk of stent thrombosis, and indeed, mortality was lower with the 2.5-mg twice-daily dose (HR, 0.56, 95% CI, 0.35-0.89; P=0.014).

Rivaroxaban reduced the rate of stent thrombosis in patients who were actively treated with dual antiplatelet therapy and after cessation of thienopyridine therapy, which was an important and novel finding. Similarly, in the APPRAISE-2 trial (APixaban for Prevention of Acute Ischemic Events 2), a trend toward a significant reduction in stent thrombosis with apixaban was observed. However, this study had to be prematurely terminated due to an increased risk of bleeding. The results of this study highlight the potential benefit of inhibiting thrombin generation, in addition to treatment with dual antiplatelet therapy alone, in patients with acute coronary syndrome treated with stent implantation.

For the first time, Naegleria fowleri, a pathogenic amoeba, is found in a public water supply in the USA; Ariel Castro is sentenced to life in prison plus 1000 years for kidnapping 3 women and holding them hostage for a decade (Ohio, USA); and Benjamin Bethel Milstein, British surgeon and heart surgery pioneer, dies at age 94.
## Novel Oral Anticoagulants in Patients with Acute Coronary Syndrome

### Bibliography of One Hundred Key Papers

**selected by Keith A. A. Fox, BSc (Hons), MBChB, FRCP, FESC, FMedSci, FACC**

Centre for Cardiovascular Science - Edinburgh - UK
(e-mail: k.a.a.fox@ed.ac.uk)

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Reference</th>
</tr>
</thead>
</table>
### Bibliography of One Hundred Key Papers

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Title</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title and Journal References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Title</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>


