As of late 2013, novel oral anticoagulants (NOACs) have been approved in many countries for the prevention of venous thromboembolism after hip or knee arthroplasty (dabigatran, rivaroxaban, and apixaban), the treatment of deep vein thrombosis or pulmonary embolism (rivaroxaban), and for stroke prevention in non-valvular atrial fibrillation (dabigatran, rivaroxaban, and apixaban). NOACs have also been investigated for the management of patients with an acute coronary syndrome (ACS) as an addition to treatment with dual antiplatelet therapy (acetylsalicylic acid [ASA] and clopidogrel). The objective of this narrative review is two-fold: first, to summarize the randomized trials evaluating NOACs in patients with an ACS (dose finding and safety data from 6 phase-2 trials and efficacy data from 2 phase-3 trials) and consider the reasons why these agents, to date, have not been incorporated into routine clinical practice; and, second, to discuss the particular situation involving rivaroxaban, which has been approved for use in patients with an acute coronary syndrome in Europe but not in North America, is discussed.

**Table** outlines the characteristics of these trials. In comparison with dual antiplatelet therapy alone, the addition of either dabigatran, rivaroxaban, apixaban, and darexaban to dual antiplatelet therapy have all been associated with dose-dependent increases in risk of bleeding. There was no increase in bleeding risk at the dose ranges studied for ximelagatran and letaxaban. The ESTEEM trial included patients who were taking only ASA whereas the other trials recruited patients with either single or dual antiplatelet therapy. Over 75% of the patients in the APPRAISE and ATLAS ACS TIMI-46 trials, and over 95% of the patients in the REDEEM and RUBY-I trials were receiving dual antiplatelet therapy.

Within the dose ranges studied, there was no indicator of any significant clinical benefit with the addition of dabigatran (all-cause mortality,
| Phase-2 trials | Interventions | N | antiplatelets (single:dual) | bleeding risk | Indicator of efficacy |
|----------------|---------------|---|-----------------------------|--------------|---------------------|
| ESTEEM<sup>4</sup> | ximelagatan, 24, 36, 48, or 60 mg bid or placebo | 1900 | 100:0 | major bleeding (ISTH): | all-cause mortality, nonfatal MI, or severe recurrent ischemia: |
| | | | | placebo: 1% | placebo: 16% |
| | | | | ximelagatan, 24 mg bid: 2% | ximelagatan, 24 mg bid: 12% |
| | | | | ximelagatan, 36 mg bid: 1% | ximelagatan, 36 mg bid: 14% |
| | | | | ximelagatan, 48 mg bid: 3% | ximelagatan, 48 mg bid: 12% |
| | | | | ximelagatan, 60 mg bid: 2% | ximelagatan, 60 mg bid: 13% |
| | | | | ximelagatan (combined): 2% | ximelagatan (combined): 13% |
| APPRAISE<sup>7</sup> | apixaban 2.5 mg bid, 10 mg od or placebo | 1715 | 24:76 | major or clinically relevant nonmajor bleeding (ISTH): | CV death, MI, severe recurrent ischemia or ischemic stroke: |
| | | | | placebo: 3% | placebo: 8.7% |
| | | | | apixaban, 2.5 mg bid: 5.7% | apixaban, 2.5 mg bid: 7.6% |
| | | | | apixaban, 10 mg od: 7.9% | apixaban, 10 mg od: 6.0% |
| ATLAS ACS-TIMI46<sup>6</sup> | rivaroxaban 5 mg od, 2.5 mg bid, 10 mg od, 5 mg bid, 15 mg od, 7.5 mg bid, 20 mg od, 10 mg bid or placebo | 3462 | 25:75 | clinically significant bleeding (TIMI major bleeding, TIMI minor bleeding, or bleeding requiring medical attention): | death, MI, stroke or severe recurrent ischemia requiring revascularisation up to 6 months from enrolment: |
| | | | | placebo: 3.3% | placebo: 7.0% |
| | | | | rivaroxaban, 5 mg od: 7.4% | rivaroxaban, 5 mg od: 8.7% |
| | | | | rivaroxaban, 10 mg od: 10.8% | rivaroxaban, 10 mg od: 5.3% |
| | | | | rivaroxaban, 20 mg od: 16.0% | rivaroxaban, 20 mg od: 5.2% |
| | | | | rivaroxaban, 2.5 mg bid: 4.8% | rivaroxaban, 2.5 mg bid: 5.3% |
| | | | | rivaroxaban, 5 mg bid: 11.0% | rivaroxaban, 5 mg bid: 4.4% |
| | | | | rivaroxaban, 10 mg bid: 14.6% | rivaroxaban, 10 mg bid: 8.5% |
| REDEEM<sup>5</sup> | dabigatran 50, 75, 110, 150 mg bid or placebo | 1861 | 2:98 | major bleeding (ISTH): | CV death, nonfatal MI, or nonhemorrhagic stroke: |
| | | | | placebo: 0.5% | placebo: 3.8% |
| | | | | dabigatran, 50 mg bid: 0.8% | dabigatran, 50 mg bid: 4.6% |
| | | | | dabigatran, 75 mg bid: 0.3% | dabigatran, 75 mg bid: 4.9% |
| | | | | dabigatran, 110 mg bid: 2.0% | dabigatran, 110 mg bid: 3.0% |
| | | | | dabigatran, 150 mg bid: 1.2% | dabigatran, 150 mg bid: 3.5% |
| RUBY-1<sup>8</sup> | darexaban 10 mg od, 5 mg bid, 30 mg od, 15 mg bid, 60 mg od, 30 mg bid or placebo | 1279 | 5:95 | major and clinically relevant nonmajor bleeding (modified ISTH): | nonfatal MI, nonfatal stroke, severe recurrent ischemia, or all-cause death: |
| | | | | placebo: 2.8% | placebo: 4.4% |
| | | | | darexaban, 5 mg bid: 5.7% | darexaban, 5 mg bid: 3.8% |
| | | | | darexaban, 15 mg bid: 6.3% | darexaban, 15 mg bid: 6.3% |
| | | | | darexaban, 30 mg bid: 9.8% | darexaban, 30 mg bid: 5.9% |
| | | | | darexaban, 10 mg od: 5.0% | darexaban, 10 mg od: 3.8% |
| | | | | darexaban, 30 mg od: 5.1% | darexaban, 30 mg od: 6.4% |
| | | | | darexaban, 60 mg od: 6.5% | darexaban, 60 mg od: 7.8% |
| | | | | darexaban (Combined): 5.6% | darexaban (Combined): 5.6% |
| AXIOM-ACS<sup>9</sup> | letaxaban 10 mg bid, 20 mg bid, 40 mg od, 40 mg bid, 80 mg od, 80 mg bid, 160 mg od, 120 mg bid or placebo | 2753 | NA | major bleeding (TIMI): | CV death, nonfatal MI, nonfatal stroke, and myocardial ischemia requiring hospitalization: |
| | | | | placebo: 0.5% | placebo: 4.4% |
| | | | | 10 mg bid: 0.0% | 10 mg bid: 5.2% |
| | | | | 20 mg bid: 1.2% | 20 mg bid: 2.8% |
| | | | | 40 mg od: 0.4% | 40 mg od: 4.0% |
| | | | | 40 mg bid: 1.6% | 40 mg bid: 6.7% |
| | | | | 80 mg od: 1.2% | 80 mg od: 5.2% |
| | | | | 80 mg bid: 0.8% | 80 mg bid: 5.9% |
| | | | | 160 mg od: 0.4% | 160 mg od: 5.2% |
| | | | | 120 mg od: 1.2% | 120 mg od: 3.6% |

Abbreviations: bid – twice daily, CV – cardiovascular, ISTH – International Society of Thrombosis and Haemostasis, MI – myocardial infarction, od – once daily, NA – nonavailable, TIMI – Thrombolysis in Myocardial Infarction
nonfatal myocardial infarction [MI] or recurrent ischemia) or letaxaban (cardiovascular [CV] death, nonfatal MI, nonfatal stroke, and myocardial ischemia requiring hospitalization) to antiplatelet therapy in patients with ACS. The RUBY-1 trial, which was underpowered, showed no decrease in the efficacy outcomes (nonfatal MI, nonfatal stroke, recurrent ischemia, or all-cause death) but a numerical increase in rates among patients treated with darexaban (≥30 mg daily dose). Based on these considerations, further development of dabigatran, darexaban, and letaxaban for this clinical indication was halted.

In the ESTEEM trial, the addition of ximelagatran to ASA therapy was associated with a significant reduction in the composite clinical endpoint of all-cause mortality, nonfatal MI, and recurrent ischemia as compared with ASA alone (12.7% vs. 16.3%; hazard ratio [HR] 0.76; 95% confidence interval [CI], 0.59–0.98; P = 0.036). However, ximelagatran was later withdrawn from clinical use because of an associated increased risk of hepatotoxicity.

In the APPRAISE trial, apixaban was associated with a trend towards a lower ischemic event (CV death, MI, recurrent ischemia, or ischemic stroke). Similarly, the ATLAS ACS TIMI-46 trial showed a reduction in the composite outcome of death, MI, or stroke for rivaroxaban compared with placebo (3.9% vs. 5.5%; HR, 0.69; 95% CI, 0.50–0.96; P = 0.027) with a trend towards a reduced composite outcome of death, MI, stroke, or recurrent ischemia requiring revascularization (5.6% vs. 7.0%; HR, 0.79; 95% CI, 0.60–1.05; P = 0.10).

Phase-3 trials of novel oral anticoagulants in patients with an acute coronary syndrome

**Apixaban**

In the APPRAISE-2 trial, the addition of apixaban, 5 mg twice daily (bid), started 6 days (median) after ACS, to dual antiplatelet therapy in patients with ACS was associated with a significantly increased risk of major bleeding as compared with placebo (1.3% vs. 0.5%; HR, 2.59; 95% CI, 1.50–4.46; P = 0.001). There was also a significant increase in intracranial and fatal bleeding with apixaban. There was no statistically significant difference in the primary composite outcome of CV death, MI, or ischemic stroke between the 2 groups (7.5% vs. 7.9%; HR, 0.95; 95% CI, 0.80–1.11; P = 0.51). Overall, the increase in major bleeding coupled with the lack of efficacy at the dose studied resulted in the termination of the trial following the recruitment of 7392 patients and a median follow-up of 241 days.

**Rivaroxaban**

The ATLAS ACS-2 TIMI-51 trial randomized 15,526 patients with an ACS to rivaroxaban, 2.5 mg bid or 5 mg bid, or placebo, starting 4.7 days (median) after diagnosis of ACS, for a mean duration of 13 months (>91% of the patients were on dual antiplatelet therapy). Rivaroxaban significantly reduced the composite outcome of death from CV causes, MI, or stroke as compared with placebo (8.9% vs. 10.7%; HR, 0.84; 95% CI, 0.74–0.96; P = 0.008). Rivaroxaban, 2.5 mg bid (but not 5 mg bid), significantly lowered the rates of CV death (2.7% vs. 4.1%; P = 0.002) and all-cause mortality (2.9% vs. 4.5%; P = 0.002). The combined analysis of both doses of rivaroxaban revealed that compared with placebo, rivaroxaban also significantly increased rates of noncoronary artery bypass grafting major bleeding (2.1% vs. 0.6%; P < 0.001) and intracranial bleeding (0.6% vs. 0.2%; P = 0.009), with a similar risk of fatal bleeding (0.3% vs. 0.2%, P = 0.66). There was significantly less fatal bleeding events with the 2.5 mg bid than the 5 mg bid dose (0.1% vs. 0.4%; P = 0.04).

In patients with an ST-segment elevation myocardial infarction, rivaroxaban significantly reduced the composite of CV death, MI, or stroke (8.4% vs. 10.6%; HR: 0.81; 95% CI, 0.67–0.97; P = 0.019). This reduction was evident by day 30 (1.7% vs. 2.3%; P = 0.042). Rivaroxaban, 2.5 mg bid (but not 5 mg bid) reduced CV death (2.5% vs. 4.2%; P = 0.006). Compared with placebo, rivaroxaban (combined group) significantly increased the non-coronary artery bypass grafting TIMI major bleeding (2.2% vs. 0.6%; P < 0.001) and intracranial bleeding (0.6% vs. 0.1%; P = 0.015) but not fatal bleeding (0.2% vs. 0.1%; P = 0.51).

Rivaroxaban significantly reduced the incidence of stent thrombosis among stented ACS patients treated with dual antiplatelet therapy (combined doses vs. placebo: 1.9% vs. 1.5%; HR, 0.65; P = 0.017; and 2.5 mg bid vs. placebo (1.9% vs. 1.5%; HR 0.61; P = 0.023). There was a trend toward a reduction in the 5 mg bid group as compared with placebo (1.9% vs. 1.5%; HR, 0.70; P = 0.089). Rivaroxaban, 2.5 mg bid, was associated with a reduction in mortality as compared with placebo in patients on dual antiplatelet therapy (HR 0.56; 95% CI: 0.35–0.89; P = 0.014).

**Pooled analyses of studies assessing novel oral anticoagulants in acute coronary syndromes**

A meta-analysis involving 31,286 patients showed that NOACs conferred a statistically significant reduction in both the composite ischemic events (death, MI, ischemic stroke, or severe recurrent ischemia) (odds ratio [OR]: 0.86; 95% CI: 0.79–0.94; P < 0.001) and stent thrombosis (OR: 0.73; 95% CI: 0.54–0.98; P = 0.04). However, when compared with placebo, NOACs conferred a statistically significant increased risk for TIMI major bleeding events (OR 3.03; 95% CI, 2.20–4.16; P < 0.001) with no effect on overall mortality (OR 0.90; 95% CI, 0.76–1.06; P = 0.22). Another meta-analysis of 30,866 patients with an ACS showed that adding a NOAC to dual antiplatelet therapy as compared with NOAC and a single antiplatelet agent resulted in a significant reduction in major adverse CV events (HR: 0.87; 95% CI, 0.80–0.95 vs. HR: 0.70; 95% CI, 0.59–0.84) but with substantially higher clinically significant bleeding risk (HR, 2.34; 95% CI, 2.06–2.66; vs. HR, 1.79; 95% CI, 1.54–2.09).
The case of rivaroxaban and decisions by the United States Food and Drug Administration and European Medicines Agency for acute coronary syndrome

This issue is noteworthy because of different interpretations of the results of the ATLAS ACS-2 TIMI-51 trial by the Food and Drug Administration (FDA) and European Medicines Agency (EMA). The FDA assigned a Priority Review designation on February 27, 2012, to the supplemental new drug application filed on December 29, 2011, by Janssen Research & Development, LLC (JRD), and Bayer Healthcare for Xarelto® (rivaroxaban). On May 23, 2012, the FDA Cardiovascular and Renal Drugs Advisory Committee voted against the approval (6 to 4 with 1 abstention) of rivaroxaban to reduce the risk of secondary cardiovascular events in patients with ACS in combination with standard antiplatelet therapy. While the FDA was not bound by the advisory group’s decision, it issued a complete response letter on June 21, 2012, to Janssen and Bayer outlining a request for further information pertaining to the ATLAS ACS-2 TIMI 51 trial and the reasons for its lack of approval.

The panel’s decision focused on concerns regarding early patient withdrawals from the study and missing data. Approximately 12% of the patients had incomplete follow-up, with a total of 1294 subjects discontinuing the trial prematurely. Of this number, investigators were only able to contact 183 patients, of which 177 were confirmed to be alive. Given the large number of patients with unknown vital status, the small relative difference in mortality rates between groups, and the potential for differential event rates after dropout, the studies reported differences in mortality rates and overall mortality benefit were deemed to be unreliable. An additional concern was raised regarding the mortality benefit with the 2.5 mg bid dose but no mortality benefit with the 5 mg bid dose, especially as this mortality difference could not be accounted for by an increase in fatal bleeds with the 5 mg bid dose.

On September 6, 2012, Janssen presented new data to the FDA in an attempt to address questions regarding missing data on patients who had withdrawn from the trial. The study sponsors confirmed the vital status for 843 patients (63%) with a previously unknown vital status. New events were distributed equally between the 3 treatment groups and there was no difference in initially observed mortality benefit. Despite this, the FDA issued a second complete response letter to Bayer Healthcare/Janssen Pharmaceuticals on March 4, 2013, regarding their supplemental new drug application for rivaroxaban, and currently it remains unapproved in patients with ACS. The FDA remains concerned that the overall rate of unknown vital statuses in the trial (3.2%) still remains significantly higher than other contemporary trials. Other persisting concerns include the lack of an expected dose response as the 5 mg dose did not have a greater efficacy (8.8% in relative terms) compared with the 2.5-mg dose (9.1%) for the primary outcome. Finally, there was a divergent impact of the 2 doses on ischemic endpoints. The 2.5-mg dose of rivaroxaban compared with placebo reduced the risk of death from cardiovascular causes (2.7% vs. 4.1%; HR 0.66; 95% CI, 0.51–0.86; \( P = 0.002 \)) and the risk of death from any cause (2.9% vs. 4.5%; HR, 0.68; 95% CI, 0.53–0.87, \( P = 0.002 \)). The 5 mg dose of rivaroxaban did not significantly reduce the risk of CV death (HR 0.94; \( P = 0.63 \)) or any causes (HR, 0.95; \( P = 0.66 \)) and differed significantly from the 2.5-mg dose (\( P = 0.009 \) for both comparisons).

Since the second complete response letter from the FDA, rivaroxaban has received a “positive opinion” from the EMA Committee for Medicinal Products for Human Use for treatment in patients with ACS. This decision on March 22, 2013, was based on similar data presented to the FDA with the committee finding the overall benefit of rivaroxaban exceeding the risks. While similar concerns regarding the robustness of data from the ATLAS ACS-2 TIMI-51 trial were raised, the reviewers were satisfied with the supplemental data provided by the study sponsors. The approved dose was 2.5 mg twice-daily, which was associated with a reduction in CV and all-cause mortality, but also conferred an increased risk of major and intracranial bleeding. The 5-mg dose of rivaroxaban twice daily was not approved because of an increased risk of bleeding which outweighed its benefits.

The clinical use of rivaroxaban for an ACS remains unclear in the United States, irrespective of the decision from the EMA. A recent subgroup analysis from the ATLAS ACS-2 TIMI-51 trial showed that a 2.5 mg bid rivaroxaban dose reduced definite or probable stent thrombosis in patients who had a stent placed before or at the time of their index ACS (1.9% vs. 1.5; HR 0.61; \( P = 0.023 \)). Additionally, among stented patients receiving dual antiplatelet therapy, there was a mortality reduction with rivaroxaban 2.5 mg bid (HR 0.56; 95% CI, 0.35–0.89; \( P = 0.014 \)). Nonetheless, the FDA has rejected a supplemental new drug application from Janssen Pharmaceuticals seeking approval for rivaroxaban for the indication of preventing stent thrombosis in patients with ACS. This appears to signal that any future decision on rivaroxaban will depend on either the manufacturer’s ability to provide additional data from the ATLAS ACS-2 TIMI-51 trial or to develop additional clinical trials evaluating its use. Given the lack of supportive external evidence for the incremental benefit of adding rivaroxaban to dual antiplatelet therapy in ACS (ATLAS ACS-2 TIMI-51) and evidence of unfavourable benefit/risk balance with adding other anticoagulants such as dabigatran (REDEEM),1 apixaban (APPRAISE-2),16 and vorapaxar (TRACER)17 to dual antiplatelet therapy, it appears some jurisdictions will proceed carefully before adopting the addition of a NOAC to dual antiplatelet therapy for patients with an ACS.4,6
Summary  Patients with an ACS remain at risk for recurrent cardiovascular events despite standard medical therapy. The present review highlights the current evidence regarding the use of NOACs as an adjunctive therapy to dual antiplatelet therapy in the setting of an ACS. All the NOACs studied to date, with the exception of rivaroxaban, have not been approved for the secondary prevention of an ACS because of either the lack of efficacy or increased risk of bleeding. On the other hand, rivaroxaban was approved by the EMA Committee for Medicinal Products for Human Use but not the FDA. These divergent decisions are based on opinions regarding the robustness of missing data related to the vital status of a substantial number of patients in the ATLAS ACS-2 TIMI-51 trial.

For the practicing clinician, the role of NOACs remains unclear and patterns of use will depend on a number of factors. In jurisdictions including Poland where rivaroxaban is approved for secondary prevention an ACS prevention appropriate patient selection and an understanding of the eligibility and exclusion criteria in the previously mentioned trials will dictate practice patterns. Additionally, with the introduction and widespread utilization of antiplatelet agents such as ticagrelor and prasugrel, careful attention to individual bleeding risks on a case-by-case basis will become necessary. In jurisdictions where rivaroxaban has not yet been approved for this indication, similar efficacy and safety considerations are needed when deciding on antiplatelet therapy. However, the use of rivaroxaban remains unapproved and until further data is available, should not be considered for patients after ACS in these jurisdictions.

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ARTYKUŁ POGŁĄDOWY

Rola nowych doustnych antykoagulantów w leczeniu chorych z ostrym zespołem wieńcowym

Przegląd badań klinicznych

Aaron Liew, Saeed Darvish-Kazem, James D. Douketis

SŁOWA KLUCZOWE
apiksaban, dabigatran,
nowe doustne antykoagulanty, ostre zespoły wieńcowe,
rywaroksaban

STRESZCZENIE
Nowe doustne antykoagulanty, w tym dabigatran, rywaroksaban i apiksaban, stanowią obiecującą alternatywę dla antagonistów witaminy K w prewencji [ew. zapobieganiu udarowi] udaru mózgu w przebiegu migotaniu przedsionków oraz dla heparyny małocząsteczkowej w profilaktyce zakrzepowo-zatorowej po artroplastyce stawów biodrowych i kolanowych. Rywaroksaban został także zarejestrowany do leczenia żyłnej choroby zatorowo-zakrzepowej. Natomiast rola tych leków w leczeniu chorych z ostrym zespołem wieńcowym nie jest do końca jasna. Celem tej pracy przeglądowej było podsumowanie badań z randomizacją oceniających efekty stosowania nowych doustnych antykoagulantów u chorych z ostrym zespołem wieńcowym oraz prób odpowiedzi na pytanie, dlaczego nie weszły one do codziennej praktyki klinicznej. Ponadto omówiono zagadnienia związane z zastosowaniem rywaroksabanu, który został zarejestrowany do stosowania w leczeniu pacjentów z ostrym zespołem wieńcowym w Europie, ale nie w Stanach Zjednoczonych.