

## Horizons in Novel Oral Anticoagulation Therapy in Concomitant Acute Coronary Syndromes and Atrial Fibrillation

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### Abstract

Thrombus formation and coronary artery occlusion, in acute coronary syndromes, occur as a result of an atherosclerotic plaque rupture/erosion and the subsequent activation of platelets and coagulation factors. Also, cardioembolic events, in atrial fibrillation, are related to the thrombus formation and the systemic arterial embolization secondary to the blood stasis in left atrium.

Antiplatelet treatments in acute coronary syndromes and long-term oral anticoagulation in atrial fibrillation have improved prognosis by reducing ischemic events but both treatments are associated with an increase in the risk of bleeding. Furthermore, thrombin and activated factor X are the key elements in the coagulation cascade and novel oral anticoagulants act by inhibiting these coagulation factors, generating a double effect: the reduction of ischemic events and the increment in hemorrhagic events.

To date, the clinical benefit of novel oral anticoagulants, in patients presenting acute coronary syndromes and atrial fibrillation, has not well studied. For that reason, the objective of this manuscript is to explain basic clinical trials testing novel oral anticoagulants in patients with acute coronary syndromes and ongoing trials evaluating the use of new oral anticoagulants in population with acute coronary syndromes and atrial fibrillation: the PIONEER AF-PCI (Rivaroxaban), the RT-AF (Rivaroxaban) and the REDUAL-PCI (Dabigatran) trials.

**Keywords:** Acute coronary syndromes; Atrial fibrillation; Thrombin; Factor Xa; New oral anticoagulants

### Novel Oral Anticoagulants After Acute Coronary Syndromes

The ischemic risk in patients with acute coronary syndromes (ACS) persists after hospital discharge, even with proper antithrombotic therapy. The rate of cardiovascular death, non-fatal myocardial infarction (MI) or stroke during the first year after hospitalization is around 10%, despite antithrombotic and revascularization therapies [1-3].

Multiple clinical trials have been conducted to assess the benefit of classic anticoagulants after ACS. The WARIS-II study [4] showed a reduction in reinfarction and all-cause mortality in patients surviving a MI who were treated with warfarin. Despite the reduction in cardiovascular events, the treatment with classic anticoagulants at long-term was not implemented in clinical practice due to the increase in bleeding, the multiple drug interactions and the need for strict control.

Recently, the WOEST study [5] randomized 573 patients receiving classic anticoagulants who underwent to percutaneous coronary intervention (PCI) to clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy). No increase in thrombotic events was observed in double therapy group in comparison with triple therapy. There were a reduction in the primary endpoint (any bleeding episode within one year after PCI) in double therapy group compared with triple therapy group (19.4% for double therapy vs. 44.4% for triple therapy (hazard ratio (HR) [95% confidence interval (CI)]: 0.36 [0.26-0.50],  $p < 0.0001$ ).

In spite of the reduction under double therapy, long-term treatment with conventional anticoagulants was associated with a high rate of bleeding. It is also noteworthy that after ACS, thrombin and activated Factor X (FXa) remain high at long-term. For these reasons, novel oral anticoagulants (NOAC) are being studied as alternative treatments for patients who have overcome the acute phase of an ACS.

NOAC selectively inhibits thrombin or FXa (Figure 1 and Table 1) [6,7]. Direct thrombin inhibitors (DTI) are attractive because they directly bind the active site of the thrombin, generating the subsequent inhibition of thrombin and soluble fibrin. FXa is another attractive target because it is at the beginning of the common coagulation pathway. Some groups have postulated that the selective inhibition of coagulation factors above thrombin could present an optimal risk-benefit balance, because a few quantity of coagulation factors escape from inhibition allowing that small amounts of thrombin can still be generated, and therefore the treatment with FXa inhibitors may protect against ischemic events without greatly increase in the risk of bleeding [6,7].

### Direct thrombin inhibitors

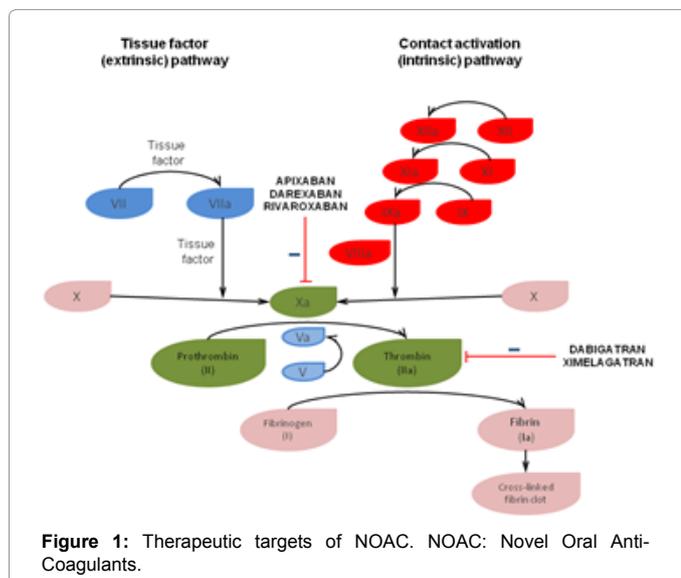
Ximelagatran was the first drug of a new generation of oral anticoagulants being studied in ACS setting. The ESTEEM [8] was a phase II, randomized, placebo-controlled trial that evaluated 1883 patients with ST-segment elevation MI or non-ST-segment elevation MI. The treatment was initiated within 14 days after the event and prolonged for six months. The patients were randomized to receive placebo or Ximelagatran at different doses twice daily (bid) (24 mg, 36

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**Figure 1:** Therapeutic targets of NOAC. NOAC: Novel Oral Anti-Coagulants.

mg, 48 mg or 60 mg) in combination with low-dose of aspirin.

The primary endpoint was a composite including all-cause death, non-fatal MI or severe recurrent ischemia showing a significant reduction in the primary endpoint when all treatment groups were grouped and compared to placebo (12.7% for combined Ximelagatran groups vs. 16.3% for placebo; HR [95% CI]: 0.76 [0.59-0.98]). There were no significant differences between treatment doses. Regarding secondary safety endpoints, the rate of major hemorrhagic events was very low, with no significant differences between groups (1.8% for combined Ximelagatran groups vs. 0.9% for placebo; HR [95% CI]: 1.97 [0.80-4.84]).

Later, Ximelagatran did not receive the Food and Drug Administration approval due to cases of severe hepatic toxicity, and therefore it was not marketed [9].

Dabigatran Etexilate was tested in the RE-DEEM trial [10], a phase II, randomized, placebo-controlled, dose-ranging study evaluating the safety of Dabigatran. The RE-DEEM included 1861 patients with ST-segment elevation MI or non-ST-segment elevation MI. The treatment was initiated on average 7.5 days after the event and continued for six months.

The patients were randomized to receive placebo or different doses of Dabigatran bid (50 mg, 75 mg, 110 mg, 150 mg). Almost all patients (99.2%) were under dual antiplatelet therapy with low-dose aspirin and clopidogrel. The primary endpoint was a composite of major bleeding or clinically relevant minor bleeding. A dose-dependent increase in primary endpoint with Dabigatran in comparison with placebo was observed (HR [95% CI]: 1.77 [0.70-4.50] for 50 mg; 2.17 [0.88-5.31] for 75 mg; 3.92 [1.72-8.95] for 110 mg; and 4.27 [1.86-9.81] for 150 mg). Respect to secondary efficacy endpoints, the combined rate of death, MI or stroke was 3.8% in placebo group compared with 4.6% in 50 mg, 4.9% in 75 mg, 3.0% in 110 mg and 3.5% in 150 mg Dabigatran group.

Furthermore, a substudy of the RE-LY trial [11] evaluated the efficacy and safety of Dabigatran compared to Warfarin in patients with non-valvular atrial fibrillation (AF) receiving concomitant antiplatelet therapies (not specifically ACS patients). From a total of 18113 patients included in the RE-LY trial, 6952 patients (38.4%) received concomitant aspirin or clopidogrel at some time during the

study. The absolute risks of thrombotic and hemorrhagic events were lower with Dabigatran 110 mg bid in comparison with Dabigatran 150 mg bid or Warfarin.

In comparison with Warfarin, Dabigatran 110 mg presented similar risks for stroke and systemic embolism (HR [95% CI]: 0.93 [0.70-1.25] for patients with antiplatelet treatment vs. 0.87 [0.66-1.15] for patients without antiplatelet treatment; interaction  $p=0.738$ ); and lower risk for major bleeding (HR [95% CI]: 0.82 [0.67-1.00] for patients who used antiplatelets vs. 0.79 [0.64-0.96] for patients who did not; interaction  $p=0.794$ ), whether patients received antiplatelet therapy or not.

### Factor Xa inhibitors

Apixaban was evaluated in the APPRAISE-2 trial [12], a phase III, randomized, placebo-controlled study evaluating patients with high-risk ACS. Almost all patients were under aspirin treatment (97%) and the majority was receiving dual antiplatelet therapy with low-dose aspirin and P2Y12 inhibitors (81%), predominantly clopidogrel.

The treatment was initiated within the first seven days after the ACS and subjects were randomized to Apixaban 5-mg bid or placebo. The study was terminated prematurely after recruiting 7392 patients due to an increase in major bleeding related with Apixaban. The mean follow-up period was 241 days. There were no differences in the primary efficacy endpoint (combination of cardiovascular death, MI or ischemic stroke) (7.5% for Apixaban vs. 7.9% for placebo; HR [95% CI]: 0.95 [0.80-1.11]). The primary safety endpoint was major bleeding (1.3% for Apixaban vs. 0.5% for placebo; HR [95% CI]: 2.59 [1.50-4.46]). Furthermore, a greater number of intracranial and fatal bleeding events occurred with Apixaban as compared with placebo.

Darexaban has been tested in the RUBY-1 trial [13]. The RUBY-1 trial was a phase II, randomized, placebo-controlled, dose-ranging study that recruited 1279 patients presenting ST-segment elevation MI or high-risk non-ST-segment elevation MI. The treatment was initiated the first week after the event and prolonged for 26 weeks.

Patients were randomized to receive placebo or Darexaban at different doses (5 mg bid, 10 mg once daily [od], 15 mg bid, 30 mg od, 30 md bid, or 60 mg od) in combination with dual antiplatelet therapy. The primary endpoint was a composite of major bleeding or clinically relevant minor bleeding. The combined analysis of Darexaban showed an increase in hemorrhagic risk (HR [95% CI]: 2.275 [1.13-4.60]) as compared to the bleeding rate in placebo group (3.1%). A dose-response relationship ( $p=0.009$ ) was observed for increased bleeding with incremental Darexaban doses. No significant decrease was demonstrated in secondary efficacy endpoint (combination of death, stroke, MI, systemic embolism and severe recurrent ischemia) with Darexaban and an even an increment in this endpoint was observed with 30 mg and 60 mg doses.

Rivaroxaban was investigated in ATLAS ACS 2-TIMI 51 studies [14]. 15526 patients were randomized to receive Rivaroxaban at doses of (2.5-mg or 5-mg) bid or placebo (scheme 1:1:1) for a mean of 13 months and up to 31 months. This trial was a phase III, randomized, placebo-controlled, double-blind trial evaluating Rivaroxaban in patients with recent ACS. All patients received standard medical therapy including low-dose aspirin (98.7% in 2.5 mg group and 98.5% in 5 mg group) and thienopyridines: clopidogrel or ticlopidine (92.6% in 2.5 mg group and 93% in the 5 mg). The primary efficacy endpoint was a combination of cardiovascular death, MI or stroke. A significant reduction in the combined analysis of Rivaroxaban doses in comparison with placebo was observed (8.9% for combined Rivaroxaban groups vs.

Anticoagulants	Target	Pro-drug	Bioavailability	Half-life	Renal excretion	Routine monitoring
Ximelagatran	Thrombin	Yes	23 %	4-5 hours	80%	No
Dabigatran	Thrombin	Yes	6.5 %	9-13 hours	80%	No
Apixaban	FXa	No	66 %	8-15 hours	25%	No
Darexaban	FXa	No	50 %	9-11 hours	35%	No
Rivaroxaban	FXa	No	80 %	7-11 hours	66%	No

**Table 1:** Pharmacokinetics of long-term NOAC tested in ACS and AF. Ximelagatran was not approved by FDA for medical use due to cases of severe hepatic toxicity; NOAC: Novel Oral Anti-Coagulants; ACS: Acute Coronary Syndromes; AF: Atrial Fibrillation; FXa: Activated Factor X; FDA: Food and Drug Administration.

10.7% for placebo; HR [95% CI]: 0.84 [0.74-0.96]), as well as individual Rivaroxaban doses (9.1% for 2.5-mg Rivaroxaban vs. 10.7% for placebo;  $p=0.02$ ) and (8.8% for 5 mg Rivaroxaban vs. 10.7% for placebo,  $p=0.03$ ). Furthermore, 2.5 mg Rivaroxaban reduced death from cardiovascular causes (2.7% for 2.5mg Rivaroxaban vs. 4.1% for placebo;  $p=0.002$ ) and death from any cause (2.9% for 2.5 mg Rivaroxaban vs. 4.5% for placebo;  $p=0.002$ ). This benefit in survival was not observed with 5 mg Rivaroxaban. With regard to safety, the combined analysis of Rivaroxaban showed an increase in major bleeding (2.1% for combined Rivaroxaban group vs. 0.6% for placebo;  $p<0.001$ ) and intracranial hemorrhage (0.6% for combined Rivaroxaban groups vs. 0.2% for placebo;  $p=0.009$ ) but no significant increase in fatal bleeding (0.3% for combined Rivaroxaban group vs. 0.2% for placebo;  $p=0.66$ ) in comparison with placebo.

It was also noted in Rivaroxaban groups that 2.5 mg dose showed a lower rate of fatal bleeding as compared to 5 mg dose the dose of (0.1% for 2.5 mg Rivaroxaban vs. 0.4% for 5 mg Rivaroxaban;  $p=0.04$ ).

### Ongoing Trials in Concomitant Acute Coronary Syndromes and Atrial Fibrillation

Rivaroxaban is being tested in the PIONEER AF-PCI [15] (NCT01830543) and RT-AF [16] (NCT02334254) studies that compare Rivaroxaban vs. vitamin K Antagonists (VKA) in patients with non-valvular AF undergoing percutaneous coronary intervention with stent implantation (bare metal or drug-eluting stents).

The PIONEER AF-PCI is a randomized, multicentric, clinical trial evaluating the safety of three different treatment strategies recruiting approximately 2,100 patients (including ACS or stable angina) in a 1:1:1 scheme to receive:

a) Rivaroxaban 15 mg once-daily treatment strategy: Rivaroxaban 15 mg od plus P2Y12 inhibitor (clopidogrel 75 mg, ticagrelor 90 mg or prasugrel 10 mg) for 12 months.

b) Rivaroxaban 2.5 mg twice-daily treatment strategy: Rivaroxaban 2.5 mg bid plus dual antiplatelet therapy at investigator discretion (1,6 or 12 months) with low-dose aspirin and P2Y12 inhibitor (clopidogrel 75 mg, ticagrelor 90 mg or prasugrel 10 mg) followed by Rivaroxaban 15 mg od plus low-dose aspirin until completing 12 months

c) Dose-adjusted VKA treatment strategy: VKA (International Normalized Ratio [INR] 2.0-3.0) plus double antiplatelet therapy at investigator discretion (1, 6 or 12 months) with low-dose aspirin and P2Y12 inhibitor (clopidogrel 75 mg, ticagrelor 90 mg or prasugrel 10 mg) followed by VKA plus aspirin at low doses until the twelfth month.

The primary endpoint (clinically significant bleeding) is a composite of the rate of TIMI major bleeding [17], bleeding requiring medical attention, and minor bleeding at 12-months. Secondary endpoints include the incidence of each component of the composite clinically significant bleeding (TIMI major bleeding, bleeding requiring medical attention and minor bleeding), the composite of adverse cardiovascular

events (cardiovascular death, MI, and stroke), as well as cardiovascular death, MI, stroke, and stent thrombosis.

The RT-AF study is a randomized, clinical trial enrolling patients in five centres comparing the safety of two therapeutic strategies recruiting approximately 420 patients (with ACS or stable angina). The endpoints will be evaluated at 12-month follow-up. The two treatment arms are:

a) Rivaroxaban plus Ticagrelor strategy: Rivaroxaban 2.5 or 5 mg od (depending on patient clinical characteristics) plus ticagrelor 90 mg for 12 months. Ticagrelor therapy is mandatory at least 1 month after bare metal stents and 6 months after drug-eluting stents.

c) Triple antithrombotic therapy strategy: Dose-adjusted VKA (INR 1.8-2.5) plus dual antiplatelet treatment with low doses of aspirin and clopidogrel 75 mg.

The primary safety end point is the rate of the composite of ISTH major bleeding [18] or clinically relevant non-major bleeding. Secondary endpoints include efficacy items like the rate of the composite of all-cause death, MI, stent thrombosis or ischemic stroke, as well as the same individual endpoints.

Dabigatran Etexilate is being tested in REDUAL-PCI study [19] (NCT02164864), assessing the efficacy and the safety of three strategies of antithrombotic therapy in patients with AF and ischemic heart disease (ACS or stable angina) that undergo to stent placement with bare metal or drug-eluting stents.

The REDUAL-PCI study is a randomized, multicentric, clinical trial that includes approximately 8,250 subjects with a 30-month follow-up. The three regimens of treatment are:

a) Dabigatran 110 mg twice-daily treatment strategy: Dabigatran 110 mg bid plus P2Y12 inhibitor (clopidogrel 75-mg or ticagrelor 90 mg).

b) Dabigatran 150 mg twice-daily treatment strategy: Dabigatran 150 mg bid plus P2Y12 inhibitor (clopidogrel 75-mg or ticagrelor 90 mg).

c) Dose-adjusted VKA treatment strategy: VKA (INR 2.0-3.0) and dual antiplatelet therapy with P2Y12 inhibitor (clopidogrel 75 mg or ticagrelor 9 mg) plus low-dose aspirin.

In this study, there exist two primary endpoints. The primary safety endpoint will be determined by comparing a composite of the rate of overall death, MI, stroke or systemic embolism. The primary safety endpoint will compare the rate of major bleeding using the ISTH classification. Secondary endpoints include the rate of the composite endpoint of all-cause death, MI or stroke, as well as the following individual endpoints: all-cause death, cardiovascular death, non-cardiovascular death, MI, stroke, systemic embolism, stent thrombosis and repeat revascularization (Table 2).

	PIONEER AF-PCI	RT-AF	REDUAL-PCI
NOAC	Rivaroxaban	Rivaroxaban	Dabigatran Etxilate
Population	AF and ACS or Stable Angina undergoing PCI + Stent (BMS or DES)	AF and ACS or Stable Angina undergoing PCI + Stent (BMS or DES)	AF and ACS or Stable Angina undergoing PCI + Stent (BMS or DES)
Treatment arms	a) Rivaroxaban 15-mg qd + Clopidogrel or Ticagrelor or Prasugrel b) Rivaroxaban 2.5-mg bid + Clopidogrel or Ticagrelor or Prasugrel + ASA → Rivaroxaban 2.5-mg bid + ASA c) VKA (INR 2-3) + Clopidogrel or Ticagrelor or Prasugrel + ASA → VKA (INR 2-3) + ASA	a) Rivaroxaban 2.5 or 5-mg bid + Ticagrelor b) VKA (INR 1.8-2.5) + Clopidogrel + ASA	a) Dabigatran 110-mg bid + Clopidogrel or Ticagrelor b) Dabigatran 150-mg bid + Clopidogrel or Ticagrelor c) VKA (INR 2-3) + Clopidogrel or Ticagrelor + ASA
Follow-up	12 months	12 months	30 months
Sample size (n)	2100	420	8520
Primary endpoints	- Safety: Composite of TIMI major bleeding, bleeding requiring medical attention, and minor bleeding	- Safety: Composite of ISTH major bleeding or clinically relevant non-major bleeding	- Efficacy: Composite of all-cause death, MI, stroke or systemic embolism - Safety: ISTH major bleeding
Study characteristics	Randomized Intention-to-treat Open label	Randomized Intention-to-treat Open label	Randomized Intention-to-treat Open label

**Table 2:** Comparison in design of the PIONEER AF-PCI, the RT-AF and the RE-DUAL PCI trials. NOAC: Novel Oral Anticoagulants; AF: Atrial Fibrillation; ACS: Acute Coronary Syndromes; PCI: Percutaneous Coronary Intervention; BMS: Bare Metal Stent; DES: Drug-Eluting Stent; qd: once daily; bid: twice daily; VKA: Vitamin-K Antagonists; ASA: Aspirin; INR: International Normalized Ratio; TIMI: Thrombolysis in Myocardial Infarction; ISTH: International Society of Thrombosis and Hemostasis; MI: Myocardial Infarction.

## Conclusion

ACS and AF have become cardiovascular epidemics in the twenty-first century. Because both conditions present the thrombosis as central axis, long-term therapy with NOAC can operate as a cardinal therapy in patients with concomitant ACS and AF.

The feasibility of long-term therapy with NOAC was demonstrated as a result of studies with Ximelagatran. The safety of fixed dosing without routine coagulation monitoring is the key point for the treatment with IDT or FXa inhibitors. The hepatotoxicity of Ximelagatran has not been observed with other NOAC, enabling these new drugs have been evaluated in AF and ACS settings.

The PIONEER AF-PCI (Rivaroxaban), the RT-AF (Rivaroxaban) and the REDUAL-PCI (Dabigatran) trials may shed light on the safety and efficacy of long-term therapy with these new drugs in patients simultaneously presenting both diseases.

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