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Scientific Update™

Emerging Oral Anticoagulation Options in the Management of Acute Coronary Syndrome

A review of presentations and discussion from the American Heart Association Scientific Sessions 2011

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According to contemporary guidelines, standard antithrombotic therapy for secondary prevention of ischemic events following acute coronary syndrome (ACS) consists of dual antiplatelet therapy, namely acetylsalicylic acid (ASA) combined with a $P2Y_{12}$ receptor antagonist. However, significant residual risk remains in these patients treated with contemporary therapy, which may be mediated in part by ongoing thrombin generation. The use of oral anticoagulants, which can be used beyond the period of acute presentation, is therefore a potentially attractive strategy. Anticoagulant drugs shift the balance towards less thrombus formation; however, the cost of this benefit is increased bleeding. Development of a new anticoagulant must be considered in terms of a favourable balance between efficacy and bleeding. Studies of these oral anticoagulants in ACS, particularly the recently presented Phase III Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) Trial, and their clinical implications for practicing physicians will be reviewed in this issue of *Cardiology Scientific Update*.

Patients who suffer from an ACS remain at risk of recurrent ischemic events despite contemporary management including the use of dual antiplatelet therapy, namely acetylsalicylic acid (ASA) combined with a $P2Y_{12}$ receptor antagonist.[1,2] This residual risk may be mediated in part by excess thrombin generation that persists beyond the period of acute presentation.[3] The use of oral anticoagulants, which can be used beyond the period of acute presentation, is therefore potentially attractive. Indeed, the use of an anticoagulant for secondary prevention, in addition to antiplatelet therapy, has been explored in the past 20 years, but with limited success. For example, the vitamin K antagonists, either alone or in combination with ASA, are effective in reducing ischemic events provided that the target for the international normalized ratio (INR) was >2, but frequently at the cost of increased risking of bleeding. Furthermore, overall mortality was not affected.[4,5] Standard antithrombin therapies of non-ST-elevation ACS have included the unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), especially enoxaparin.[6,7] In patients with ST-elevation myocardial infarction (STEMI), UFH remains the primary antithrombotic regimen employed when primary percutaneous coronary intervention (PCI) is pursued. As an adjunct antithrombin to thrombolytic therapy, enoxaparin has been demonstrated to be more efficacious than UFH with comparable bleeding rates, and is widely used in practice.[8] Limitations to UFH include its variable pharmacokinetic and pharmacodynamic profile, inability to inhibit fibrin-bound thrombin, sensitivity to platelet factor 4 with risk of heparin-induced thrombocytopenia (HIT) and marked interindividual variability in therapeutic response requiring frequent monitoring and dosage titration.[9] The LMWHs have some

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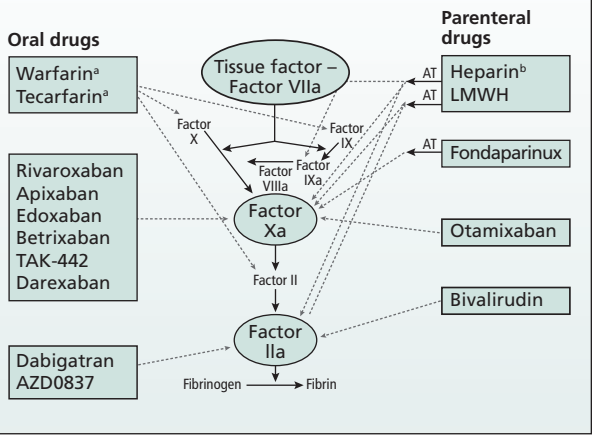
Figure 1: Pharmacological targets for anticoagulant therapy in the clotting cascade



AT = antithrombin; LMWH = low-molecular-weight heparins.
[a] Other targets for warfarin and tecarfarin are factor VII, protein C, and protein S;
[b] Other targets for heparin are factors VII, XIa, and XIIa.
Adapted from Turpie AG. *Eur Heart J.* 2008;29:155-165.

similar limitations as those of UFH, and both UFH and LMWH require parenteral administration, making them impractical for long-term use.

In the past few years, new antithrombins have been investigated in patients with ACS (Figure 1).[10] Based on favourable data obtained from large prospective, randomized, controlled trials, the indirect anti-Xa inhibitor fondaparinux and the direct thrombin inhibitor bivalirudin have been included into the updated guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC).[1,11-14] Fondaparinux is selective for factor Xa inhibition, unlike UFH and LMWHs. However, like these agents, it does not directly inhibit factor Xa or platelet-bound factor Xa. Fondaparinux has a long half-life (17–21 hours), has no direct reversal agent, and may require additional heparin boluses during PCI to prevent coronary-guided catheter thrombus formation.[11] Bivalirudin is currently the only parenteral direct thrombin inhibitor approved for use in PCI in patients with HIT and thrombosis syndrome. It has a half-life of 20–30 minutes, but requires reconstitution for administration, as well as dosage adjustments in patients with renal dysfunction. Both fondaparinux and bivalirudin must be administered parenterally.

To overcome some of the limitations of traditional parenteral and oral antithrombotics, there has been continual interest in the development of new agents that are highly selective for specific coagulation factors blocking the synthesis of thrombin. The impetus has been to develop anticoagulant drugs with the ability to bind clot-bound coagulation factors, have predictable pharmacological profiles that allow for oral dosing and negate the need for frequent monitoring, have fixed and convenient dosing regimens, and have rapid onset of action with the potential for high efficacy and low bleeding risk. Among agents under investigation for use in ACS, and potentially with these properties, direct inhibitors of thrombin and factor Xa appear to fit these criteria, with good bioavailability and reliable anticoagulant effects shown for the prevention of deep venous thrombosis and thromboembolism.[15] However, none of these newer agents are yet approved by Health Canada for the treatment of patients with ACS.

Dabigatran Etexilate

The reversible oral direct thrombin inhibitor dabigatran is administered in double prodrug form (dabigatran etexilate), which undergoes esterase conversion through 2 intermediate prodrugs to dabigatran.[16,17] Dabigatran etexilate is absorbed rapidly, but oral bioavailability is low (~6.5%).[17] Dabigatran etexilate was evaluated in ACS patients in the double-blind, placebo-controlled, dose-escalation RE-DEEM trial.[18] Subjects (N=1861) were randomized within a mean of 7.5 days after either a STEMI or non-STEMI (NSTEMI) to either one of the 4 bid doses – 50 mg, 75 mg, 110 mg, or 150 mg – or to placebo. During the 6-month study period, the primary outcome – a composite of major or clinically relevant minor bleeding – was increased in a dose-dependent fashion in the dabigatran groups compared with placebo (Table 1). Hazard ratios (HRs) of primary outcome events ranged from 1.77 (95% confidence interval [CI], 0.70 to 4.50) for the 50-mg group to 4.27 (95% CI, 1.86 to 9.81) in the 150-mg group. The rates of the secondary efficacy outcome – a composite of cardiovascular (CV) death, nonfatal MI, and stroke – were not

Table 1: RE-DEEM Trial:[18] Occurrence of major events at 6 months (intention-to-treat analysis)

Event	Placebo (n=371)	Dabigatran 50 mg bid (n=369)	Dabigatran 75 mg bid (n=368)	Dabigatran 110 mg bid (n=406)	Dabigatran 150 mg bid (n=347)
Primary endpoint[a]	2.4%	3.5%	4.3%	7.9%	7.8%
Major bleeding[b]	0.5%	0.8%	0.3%	2.0%	1.2%
Secondary outcome[c]	3.8%	4.6%	4.9%	3.0%	3.5%

[a] Composite of major or clinically relevant minor bleeding;
[b] International Society of Thrombosis and Haemostasis criteria;
[c] Composite of cardiovascular death, nonfatal myocardial infarction, and stroke

significantly improved with dabigatran (4.6% with 50 mg, 4.9% with 75 mg, 3.0% with 110 mg, and 3.5% with 150 mg) compared with placebo (3.8%). Median D-dimer concentrations were significantly (P<0.001) lower after 1 and 4 weeks in all 4 dabigatran dose groups, compared with placebo.

Rivaroxaban

Rivaroxaban is an oral, reversible direct factor Xa inhibitor that is rapidly absorbed and has high bioavailability (~100% for the 10-mg dose). Maximum concentrations are reached within 2–4 hours and a half-life of 5–13 hours in healthy and elderly subjects.[19] In the Phase II dose-finding trial, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome –Thrombolysis in Myocardial Infarction 46 (ATLAS ACS – TIMI 46),[20] rivaroxaban was tested in 3491 patients with a recent ACS at total daily doses ranging from 5 mg to 20 mg. Compared with placebo, rivaroxaban reduced the primary efficacy endpoint (a composite of death, MI, stroke, or severe recurrent ischemia requiring revascularization during 6 months; relative risk reduction [RRR] 21%; P=0.1) and significantly reduced the secondary endpoint (death, MI, or stroke; RRR 31%; P=0.027), with the lowest ratios seen at the lowest bid doses. There was a dose-dependent increase in bleeding events (HR 2.21 for 5 mg, 3.35 for 10 mg, 3.60 for 15 mg, and 5.06 for 20 mg; P<0.0001).

Based on these observations, a Phase III trial to evaluate bid rivaroxaban at doses of 2.5 mg and 5 mg as adjunctive therapy in patients with a recent ACS, with the aim of determining a clinically effective low-dose regimen, was undertaken.[21]

ATLAS ACS 2 – TIMI 51 Trial

The results of ATLAS ACS 2 – TIMI 51, completed in September 2011, were presented during a Late-breaking Clinical Trials session at the 2011 AHA Scientific Sessions.[22] This trial included patients presenting with symptoms suggestive of an ACS (N=15 526) in whom STEMI (50.3%), NSTEMI (25.6%), or unstable angina (24.0%) were diagnosed. Patients were randomly assigned (mean 4.7 days after the index event) in a 1:1:1 ratio to rivaroxaban 2.5 mg bid or 5 mg bid, or placebo. All patients were to receive standard medical therapy, including low-dose ASA with or without a thienopyridine (clopidogrel or ticlopidine), according to national guidelines. The primary efficacy endpoint was a composite of CV death, MI, or stroke. The primary safety endpoint was TIMI major bleeding unrelated to coronary-artery bypass grafting (CABG).

The mean duration of treatment with a study drug was 13.1 months. Among patients who received at least 1 dose of a study drug, premature discontinuation of treatment occurred in 26.9% of patients receiving the 2.5-mg dose of rivaroxaban, 29.4% receiving the 5-mg dose of rivaroxaban, and 26.4% receiving placebo. Baseline characteristics of the patients reflected contemporary practice of the management of ACS and were similar in the study groups (Table 2).

Efficacy endpoints

Rivaroxaban reduced the primary composite efficacy endpoint of death from CV causes, MI, or stroke, as compared with placebo, with rates of 8.9% and 10.7% respectively (HR 0.84; 95% CI, 0.74 to 0.96; P=0.008; Figure 2). These results were consistent in the intention-to-treat analysis (P=0.002). In the evaluation of the individual components of the primary efficacy endpoint, rivaroxaban reduced the risk for CV death, MI, but not for stroke. The reduction in the primary efficacy endpoint with rivaroxaban was consistent among the subgroups except for patients with a history of stroke or transient ischemic attack. Both rivaroxaban doses reduced the primary efficacy endpoint: the HRs were 0.84 (95% CI, 0.72 to 0.97; P=0.02) and 0.85 (95% CI, 0.73 to 0.98; P=0.03) in the 2.5-mg and 5-mg doses, respectively. The 2.5-mg dose of rivaroxaban significantly reduced the risk of CV death (HR 0.66; 95% CI, 0.51 to 0.86; P=0.002) and the risk of death from any cause (HR 0.68; 95% CI, 0.53 to 0.87; P=0.002). No such significant reductions were observed with the 5-mg group for CV death (HR 0.94; P=0.63) or death from any cause (HR 0.95; P=0.66), and results differed significantly from the 2.5-mg dose of rivaroxaban (P=0.009 for both comparisons).

Rivaroxaban also reduced the secondary composite efficacy endpoint (death from any cause, MI, or stroke), as compared with placebo, by 9.2% and 11.0%, respectively (HR 0.84; 95% CI, 0.74 to 0.95; P=0.006). In addition, rivaroxaban reduced the risk of stent thrombosis (HR 0.69; 95% CI, 0.51 to 0.93; P=0.02).

Safety endpoints

Rivaroxaban significantly increased the rate of TIMI major bleeding unrelated to CABG, as compared with placebo, with rates of 2.1% and 0.6%, respectively (HR 3.96; 95% CI, 2.46 to 6.38; P<0.001). There were no significant interactions between the measured characteristics of patients and the study group. Also greater in the combined rivaroxaban group, as compared with placebo, were rates of TIMI minor bleeding (1.3% versus 0.5%; P=0.003), TIMI bleeding requiring medical attention (14.5% versus 7.5%; P<0.001), and intracranial hemorrhage (0.6% versus 0.2%; P=0.009). However, there was no significant difference in the rates of fatal bleeding associated with rivaroxaban as compared with placebo (0.3% versus 0.2%; P=0.66).

In the comparison between the 2 doses of rivaroxaban, the rates of TIMI major bleeding unrelated to CABG tended

Table 2: ATLAS ACS 2 – TIMI 51 Trial:[22] Baseline patient characteristics

Characteristic	Rivaroxaban 2.5 mg bid (n=5174)	Rivaroxaban 5 mg bid (n=5176)	Placebo (n=5176)
Age			
Mean — yr	61.8±9.2	61.9±9.0	61.5±9.4
≥65 yr — no. (%)	1905 (36.8)	1921 (37.1)	1835 (35.5)
≥75 yr — no. (%)	466 (9.0)	441 (8.5)	498 (9.6)
Male sex — no. (%)	3875 (74.9)	3843 (74.2)	3882 (75.0)
Medical history — no. (%)			
Previous MI	1363 (26.3)	1403 (27.1)	1415 (27.3)
Hypertension	3470 (67.1)	3499 (67.6)	3494 (67.5)
Diabetes	1669 (32.3)	1648 (31.8)	1647 (31.8)
Hypercholesterolemia	2498 (48.3)	2544 (49.1)	2496 (48.2)
Index diagnosis — no. (%)			
STEMI	2601 (50.3)	2584 (49.9)	2632 (50.9)
NSTEMI	1321 (25.5)	1335 (25.8)	1323 (25.6)
Unstable angina	1252 (24.2)	1257 (24.3)	1221 (23.6)
PCI or CABG for index event — no. (%)	3138 (60.6)	3123 (60.3)	3126 (60.4)
Medications — no. (%)			
ASA	5105 (98.7)	5099 (98.5)	5108 (98.7)
Thienopyridine	4790 (92.6)	4812 (93.0)	4811 (92.9)
Beta-blocker	3426 (66.2)	3394 (65.6)	3444 (66.5)
ACE inhibitor or ARB	2022 (39.1)	1977 (38.2)	2050 (39.6)
Statin	4304 (83.2)	4342 (83.9)	4321 (83.5)
Calcium-channel blocker	820 (15.8)	742 (14.3)	764 (14.8)

* Plus–minus values are means ± standard deviation. There were no significant differences among the 3 groups.

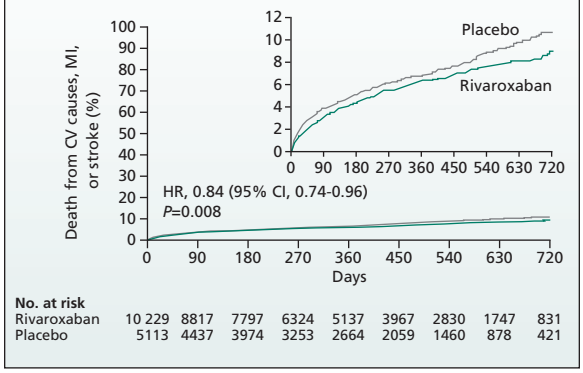
ATLAS ACS 2 – TIMI 51 = Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction; MI = myocardial infarction; STEMI = ST-segment elevation MI; NSTEMI = non-STEMI; PCI = percutaneous coronary intervention; CABG = coronary-artery bypass grafting; ASA = acetylsalicylic acid; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker

to be lower in patients receiving the 2.5-mg dose than in those receiving the 5-mg dose (1.8% versus 2.4%; *P*=0.12), and the lower dose resulted in significantly lower rates of TIMI minor bleeding (0.9% versus 1.6%; *P*=0.046), TIMI bleeding requiring medical attention (12.9% versus 16.2%; *P*<0.001), as well as fatal bleeding (0.1% versus 0.4%; *P*=0.04).

Apixaban

Apixaban, another oral, reversible direct factor Xa inhibitor, has a bioavailability of 66%, and C_{max} is reached ~3 hours after administration.[19,23] In the Apixaban for Prevention of Acute Ischemic Events 1 (APPRAISE-1) trial[24] apixaban demonstrated a trend towards a reduction in CV events. However, the Phase III APPRAISE-2 trial[25] concluded that the addition of 5 mg bid of apixaban to antiplatelet therapy in patients with ACS increased the number of major bleeding events (HR 2.59; 95% CI, 1.50 to 4.46; *P*=0.001) without a significant reduction in the rate of recurrent ischemic events (HR 0.95; 95% CI, 0.80 to 1.11; *P*=0.51). As a result, the trial was stopped prematurely.

Figure 2: ATLAS ACS 2 – TIMI 51 Trial:[22] Primary efficacy endpoint – CV death, MI, or stroke



Absolute risk reduction 1.8%. Primary endpoint would be prevented in 1 patient if 56 patients were treated for 2 years with rivaroxaban. The *P* value is for the modified intention-to-treat analyses; *P*=0.002 for the intention-to-treat analysis.

CV = cardiovascular; HR = hazard ratio; CI = confidence interval

Darexaban

Darexaban exhibits similar pharmacokinetic properties as the other oral factor Xa inhibitors, namely rapid absorption (C_{max} in ~2 hours) and an elimination half-life ranging from 18–20 hours.[26] Bioavailability is highly variable (25%–82%). The randomized, double-blind, placebo-controlled Phase II RUBY-1 trial[27] evaluated the efficacy and safety of 6 doses of darexaban – 5 mg bid, 10 mg qd, 15 mg bid, 30 mg qd, 30 mg bid, and 60 mg qd – in 1279 patients with recent high-risk STE or NSTE ACS. While darexaban was observed to dose-dependently increase the primary outcome of major or clinical relevant nonmajor bleeding events (*P*=0.002 for 30 mg bid), it did not confer a benefit in the main efficacy outcome (composite of death, stroke, MI, systemic thromboembolism, and severe recurrent ischemia); in fact, patients in the 30-mg and 60-mg groups experienced increases in these outcomes. No Phase III trial is underway.

Discussion of Trial Results and their Clinical Implications

Anticoagulant drugs shift the balance towards significantly lower thrombus formation at the cost of increased bleeding. The clinical usefulness of an anticoagulant therefore depends on its efficacy to prevent thrombosis in relation to its effect to induce bleeding projected on the background of the absolute thromboembolic risk from the underlying disease for which the agent is intended to treat. Clinical trial data are accumulating on the efficacy and safety of novel oral anticoagulants in patients who have experienced an ACS. The relative effectiveness of these agents to reduce further CV events are highly variable, and as previously discussed, all Phase II programs investigating these oral anticoagulants revealed dose-dependent increases in bleeding.

ATLAS ACS 2-TIMI 51 is the first Phase III trial to demonstrate efficacy of an oral new anticoagulant in patients with ACS, albeit with increased bleeding. Results of the ATLAS ACS 2–TIMI 51 trial demonstrate that in patients who suffer a recent ACS, both rivaroxaban doses reduce the primary endpoint of CV death, MI and stroke, but perhaps at the cost of increased bleeding rates. The rates of adverse events, other than bleeding events, are similar in the combined rivaroxaban group and the placebo group. The 2.5-mg bid dose appears to have a better benefit to risk ratio, significantly reducing CV and total mortality, with a lower bleeding risk than the 5-mg twice-daily dose. This 2.5-mg bid regimen appears to produce the efficacy benefit with a modest increase in major bleeds and no significant increase in fatal bleeding events. The overall number needed to treat to prevent one all-cause death is 63, which is favourable and with a substantially lower number than that needed to produce harm.

While these results are relevant to the vast majority of patients with recent ACS who are treated with ASA and clopidogrel, the safety of oral anticoagulation in the growing number of patients with ACS treated with the newer and more powerful antiplatelet drugs prasugrel and ticagrelor is still unclear. The safety and efficacy of rivaroxaban when added to treatment with prasugrel or ticagrelor will need to be addressed in future studies. For the majority of patients with ACS, the balance favours a net benefit from adding rivaroxaban to standard therapy.

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