Chapter 4
Secondary Prevention in ACS: The Role of Novel Oral Anticoagulants

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Brief Review of Current Antithrombotic Treatment Options and Recommendations from Guidelines for Secondary Prevention of ACS

For the contemporary management of acute coronary syndromes, antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor is the benchmark antithrombotic strategy for secondary prevention after ACS. However, considering that thrombosis is one of the key steps in the pathogenesis of ACS, long-term anticoagulation has the potential to be considered as a therapeutic option, in addition to dual anti-platelet therapy, to prevent recurrent ischemic events.

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P. Avanzas, P. Clemmensen (eds.), *Pharmacological Treatment of Acute Coronary Syndromes*, Current Cardiovascular Therapy,
DOI 10.1007/978-1-4471-5424-2_4,

Parenteral or subcutaneous anticoagulants are effective for reducing cardiovascular events during acute phase of acute coronary syndrome and recommended for all ACS patients without contraindications [1–6]. Anticoagulant options during the acute treatment phase of ACS include unfractionated heparin, low molecular weight heparin, fondaparinux, and bivalirudin. These agents are recommended to be used together with dual anti-platelet therapy during the index ACS hospitalization before and during invasive procedures such as angiography, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). While treatment with low molecular weight heparins including enoxaparin and dalteparin for up to a few months after ACS has been studied in previous trials, logistical and cost considerations have limited the use of these anticoagulants in the post-discharge setting [7–9].

Warfarin, an oral anticoagulant, has been evaluated for long term secondary prevention of ACS during the past two decades. Long term anticoagulation with warfarin plus aspirin was more effective for reduction of cardiovascular events than aspirin alone in secondary prevention of ACS, but did not reduce mortality [10]. However, long term anticoagulation with warfarin, in conjunction with aspirin, was associated with a significant increased risk of bleeding. "Triple therapy" with warfarin and dual antiplatelet therapy (aspirin + clopidogrel) is associated with an even higher bleeding risk than warfarin + aspirin, but this combination of medications has not been evaluated in a large enough trial to determine if there is an efficacy advantage that could counterbalance the high bleeding risk [11]. Consequently, routine anticoagulation with warfarin after ACS, in addition to dual anti-platelet therapy, is not recommended.

Long term treatment with warfarin is only recommended for ACS patients who have indications for long term anticoagulation such as atrial fibrillation with at least a moderately high thromboembolic risk, presence of a mechanical valve prosthesis, or a concomitant venous thrombotic disorder such as a deep venous thrombosis [1–6].

The introduction of new, potent $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, in the last 5 years has further established the role of dual anti-platelet therapy for the secondary prevention of ACS as both of these agents have been shown to be superior compared with aspirin and clopidogrel [12]. Current practice guidelines endorse both prasugrel and ticagrelor, in combination with aspirin, for the secondary prevention of high risk ACS patients [2–6].

Novel Oral Anti-coagulants for the Treatment of Patients with Recent ACS

There are two classes of new oral anticoagulants; direct factor Xa inhibitors and direct thrombin inhibitors. New oral anticoagulants have more predictable pharmacokinetic and pharmacodynamic characteristics than warfarin that facilitates their use without routine monitoring of anticoagulation activities at fixed doses. While these novel oral anticoagulants have shown superior efficacy and safety profiles in comparison with warfarin for patients with atrial fibrillation [13–15], the results with these agents for the secondary prevention of ACS have been more variable. Although the new parenteral direct factor Xa inhibitor otamixaban was evaluated for acute phase of treatment of ACS [16] in a dose-finding study and is currently being evaluated in a large phase III trial, otamixaban will not be discussed in this manuscript since it is a parenteral anticoagulant.

Direct Thrombin Inhibitors

Ximelagatran

In the ‘efficacy and safety of the oral direct thrombin inhibitor ximelagatran in patients with recent myocardial damage (ESTEEM)’ trial [17], ximelagatran was with background aspirin therapy was evaluated in medically treated ACS

patients within 14 days of initial presentation. Ximelagatran significantly reduced the risk of the primary efficacy composite end point of death, myocardial infarction and recurrent severe ischemia compared with placebo (12.7 % vs. 16.3 %, hazard ratio [HR] 0.76; 95 % confidence interval [CI] 0.59–0.98, $p=0.036$). There was no dose response relationship among ximelagatran dosing groups regarding cardiovascular event reduction and there was no significant increase in major bleeding in the ximelagatran groups (1.8 % vs. 0.9 %, HR 1.97, 95 % CI 0.80–4.84). Despite these intriguing findings in this dose-ranging trial, ximelagatran was development was halted due to liver toxicity.

Dabigatran

Dabigatran is a pro-drug which has direct thrombin inhibitor activity with a serum half-life of 12–17 h and is excreted renally. The phase II Dose Finding Study for Dabigatran Etexilate in Patients with Acute Coronary Syndrome (REDEEM) trial evaluated the safety of dabigatran in stabilized 1,861 ACS patients who were enrolled within 14 days after index ACS event and treated with dual antiplatelet therapy. Dabigatran was associated with a dose-dependent increase in the primary safety endpoint of ISTH major or clinically relevant minor bleeding during the 6 month treatment period [18]. There was a dose-dependent increase of bleeding with dabigatran (twice daily at dose of 50 mg: 3.5 %, 75 mg: 4.3 %, 110 mg: 7.9 %, and 150 mg: 7.8 % vs. placebo: 2.2 %, $p<0.001$ for trend among dabigatran groups) during 6 months follow up. However there was no significant difference in the composite efficacy endpoint of cardiovascular death, non-fatal myocardial infarction, or non-haemorrhagic stroke between groups (dabigatran 50 mg: 4.6 %, 75 mg: 4.9 %, 110 mg: 3.0 %, 150 mg: 3.5 % vs. placebo: 3.8 %). However the two high dose groups (110, 150 mg) showed numerically lower event rates compared with the two low dose groups. All dabigatran doses were associated with significant further decreases of D-dimer level without dose-response relationship during first 4 weeks

after treatment compared with placebo. Based upon these findings, further development of dabigatran for an ACS indication has not been pursued.

Direct Factor Xa Inhibitors

Darexaban

Darexaban is a direct factor Xa inhibitor with a terminal half-life of 14–18 h and equally gut and renal excretion. A randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban following acute coronary syndrome (RUBY-1) trial evaluated the safety of darexaban for secondary prevention of 1,279 high risk ACS patients who were enrolled within 7 days after index event and treated with dual antiplatelet therapy [19]. There was a dose-dependent increase of ISTH major and clinically relevant non-major bleeding event rates in the combined darexaban groups vs. placebo (pooled HR 2.275; 95 % CI 1.13–4.60, P = 0.022) (P = 0.009 for trend across darexaban dosing groups). The rate of all cause death, nonfatal myocardial infarction, nonfatal stroke, and severe recurrent ischemia was similar between the pooled darexaban groups vs. placebo (darexaban: 6.5 % vs. placebo: 5.2 %). Given these findings, darexaban has not been developed further for an ACS indication.

Apixaban

Apixaban is a direct factor Xa inhibitor with half-life of 12 h and predominantly eliminated by non-renal mechanisms. Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE-1) trial was a phase II trial, which evaluated apixaban in stabilized recent ACS patients within 7 days with at least one risk factor for recurrent ischemic event [20]. There was a dose dependent increase of bleeding risk across the 4 dosing regimens of apixaban and the two higher dose

groups with 10 mg twice daily or 20 mg once daily were discontinued prematurely because of excessive total bleeding. Apixaban 2.5 mg twice daily (HR 1.78; 95 % CI 0.91–3.48, P = 0.09) and 10 mg once daily (HR 2.45; 95 % CI 1.31–4.61, P = 0.005) also resulted in an increased risk of ISTH major or clinically relevant non-major bleeding. The increase in bleeding with the higher 2 doses of apixaban was more evident in patients taking clopidogrel. The two dosing groups, Apixaban 2.5 mg twice daily (HR 0.73; 95 % CI 0.44–1.19, P = 0.21) and 10 mg once daily (HR 0.61; 95 % CI 0.35–1.04, P = 0.07),were both associated with lower rates of the composite ischemic endpoint of cardiovascular death, myocardial infarction, severe recurrent ischemia, or ischemic stroke compared with placebo. These promising results led to a large, phase III trial for the ACS indication.

The efficacy of apixaban for the secondary prevention of ACS was evaluated in 7,392 stabilized recent, high risk ACS patients with 2 or more risk factors in the APPRAISE-2 trial [21]. This trial was terminated prematurely because of excessive increase in major bleeding events with apixaban, including a higher risk for intracranial hemorrhage. During an average follow-up period of 8 months, apixaban did not reduce the primary outcome of cardiovascular death, myocardial infarction, or ischemic stroke (apixaban: 7.5 % vs. placebo: 7.9 %, HR 0.95; 95 % CI 0.80–1.11, P = 0.51). Additionally, the risk of Thrombolysis in Myocardial Infarction (TIMI) major bleeding was more common in the apixaban group (1.3 %) compared with the placebo group (0.5 %, HR 2.59; 95 % CI 1.50–4.46, P = 0.001).

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor with half-life of 5–7 h and eliminated by renal and gut excretion. In the phase II ‘Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in

Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 46 (ATLASACS-1)' trial [22], rivaroxaban was evaluated in 3,491 stabilized recent ACS patients. The combined rivaroxaban dosing groups demonstrated a non-significant increase in the risk of the primary safety endpoint compared with placebo (composite of TIMI major, minor or requiring medical attention: 7.0 % vs. 5.6 %: p = 0.10). There were dose dependent increases of bleeding (p < 0.0001 for trend) with rivaroxaban treatment both with aspirin and aspirin + clopidogrel. An unexpected finding was that a reduced risk of the efficacy endpoint was demonstrated in the combined rivaroxaban groups (composite of death, myocardial infarction, or stroke: 3.9 % vs. 5.5 %: p = 0.027). Additionally, a significant reduction in the net clinical benefit (composite of death, myocardial infarction, stroke, severe recurrent ischemia requiring revascularisation, TIMI major bleeding, or TIMI minor bleeding) was demonstrated with rivaroxaban compared with placebo only in patients treated with aspirin monotherapy (HR 0.56; 95 % CI 0.35–0.88), but not in the entire cohort (HR 0.99; 95 % CI0.76–1.29) and not in patients treated with dual antiplatelet therapy (HR 1.29; 95 % CI 0.93–1.81).. For the low dosing groups (2.5 mg or 5 mg of rivaroxaban twice daily), the net clinical benefit with rivaroxaban compared with placebo showed a potential signal for benefit with an HR of0.72 (0.46–1.12) in the entire cohort.

Based upon the ATLAS ACS-1 findings, the ALTAS ACS-2 trial was conducted in 15,526 stabilized recent ACS patients (within 7 days) who were treated with twice daily doses of either 2.5 mg or 5 mg of rivaroxaban vs. placebo for a mean of 13 months [23]. The combined rivaroxaban groups were shown to have a significant reduction in the risk of the primary composite efficacy end point of cardiovascular death, myocardial infarction, or stroke compared with placebo (8.9 % vs. 10.7 %, HR 0.84; 95 % CI 0.74–0.96, P = 0.008), with similar results both the twice daily 2.5 mg dose (9.1 % vs. 10.7 %, P = 0.02,) and the twice daily 5 mg dose (8.8 % vs.

10.7 %, P = 0.03,). Unexpectedly, the twice daily 2.5 mg dose of rivaroxaban was associated with a significant reduction in the risk of cardiovascular death (2.7 % vs. 4.1 %, P = 0.002) and all-cause death (2.9 % vs. 4.5 %, P = 0.002). However, the combined rivaroxaban dosing groups were associated with increased rates of major bleeding not related to CABG (2.1 % vs. 0.6 %, P < 0.001,) and intracranial hemorrhage (0.6 % vs. 0.2 %, P = 0.009) compared with placebo. Currently, rivaroxaban is undergoing regulatory review in both Europe and the United States for an ACS indication.

Safety Data with the Use of Novel Oral Anticoagulants for the Treatment of Patients with Recent ACS

Across 7 trials with 5 different medications, new oral anticoagulants have shown a consistent dose response relationship for bleeding risks. In general, doses of new anticoagulants used for patients with atrial fibrillation were associated with excessive bleeding in ACS patients primarily due to the fact that oral anticoagulant was usually evaluated as adjunct to mono- or dual-antiplatelet therapy. In theAPPRAISE-2 trial [21], the 5 mg twice daily dose of apixaban, which was same dose used in the ARISTOTLE trial for atrial fibrillation [14], resulted in excessive bleeding without concomitant efficacy benefit leading to premature trial termination. A dose response in bleeding risk was also observed in the ATLAS ACS-2 trial, despite using cumulative doses of rivaroxaban lower than those used in the ROCKET trial for atrial fibrillation (2.5, 5.0 mg twice daily vs. 15/20 mg once daily) [15, 23]. Interestingly, the higher dose of rivaroxaban showed no efficacy advantage compared with the lower dose of rivaroxaban that was associated with a significant reduction in the risk of mortality.

Concomitant antiplatelet therapy is also an important determinant for bleeding risk with new oral anticoagulants in

the post-ACS setting. Increases in bleeding were more evident when oral anticoagulants were used with dual antiplatelet therapy than aspirin alone [20, 22, 24].

Balancing Ischemic Vs. Bleeding Risks

The clinical usefulness for the adjunctive use of new oral anticoagulants should be discussed in terms of net clinical benefit. To justify the use of anticoagulants, absolute clinical benefit from ischemic event reduction should outweigh the expected increase in bleeding events. We already have noticed similar trade-off between ischemic event reduction and increase in bleeding with prasugrel and ticagrelor vs. clopidogrel in high risk ACS patients. For example, prasugrel prevented 19 ischemic events at the cost of 6 major TIMI non CABG bleeding during an average 14.5 months of treatment [12]. Ticagrelor prevented 22 ischemic events at the cost of 6 major TIMI non CABG bleeding during an average 9 months of treatment [25]. In comparison, the 2.5 mg twice daily dose of rivaroxaban prevented 16 major ischemic events at the cost of 12 major TIMI non CABG bleeding [26]. A recently published meta-analysis reported that new oral anticoagulants in the post ACS setting prevented 13 major ischemic event at the cost of 9 TIMI major bleeding [27]. Thus, the net clinical benefit with adjunctive oral anticoagulants dose not compare favourably with dual antiplatelet therapy and thus does not justify the routine use of new oral anticoagulants for the secondary prevention of ACS.

Nonetheless, further study of shorter durations of anticoagulation may be warranted as previous meta-analyses for the use of warfarin with aspirin in ACS patients showed that the greatest absolute net clinical benefit was observed during the first 3 months of therapy [10]. Shorter durations of treatment with new oral anticoagulants may improve the risk vs. benefit calculations for these agents in the post-ACS setting, but may not be attractive from a commercial standpoint for the pharmaceutical industry (Tables 4.1 and 4.2).

Table 4.1 Profiles of the clinical trials

	Phase of clinical trial	Number of patients	Duration of study	Dual antiplatelet	Treatments
ESTEEM [17]	II	1,883	6 months	0 %	Ximelagatran 24, 36, 48, 60 mg twice daily or placebo
REDEEM [18]	II	1,861	6 months	99 %	Dabigatran 50, 75, 110 or 150 mg twice daily or placebo
RUBY-1 [19]	II	1,279	6 months	95 %	Darexaban 5, 15, 30 mg twice daily, 10, 30, 60 mg once daily or placebo
APPRAISE-1 [20]	II	1,715	6 months (10 mg twice daily and 20 mg once daily: terminated early)	76 %	Apixaban 2.5, 10 mg twice daily, 10, 20 mg once daily or placebo
APPRAISE-2 [21]	III	7,392	8 months (prematurely terminated)	81 %	Apixaban 5 mg twice daily or placebo
ATLAS ACS-1 TIMI46 [22]	II	3,491	6 months	75 %	Rivaroxaban 2.5, 5, 10 mg twice daily or 5, 10, 20 mg once daily with aspirin, or rivaroxaban 2.5, 5, 7.5, 10 mg twice daily or 5, 10, 15, 20 mg once daily with dual antiplatelet or placebo
ATLAS ACS-2 TIMI51 [23]	III	15,526	13 months	93 %	Rivaroxaban 2.5 or 5 mg twice daily or placebo

Table 4.2 Key results of the clinical trials

	Efficacy endpoint (anticoagulant vs. placebo)	All cause death (anticoagulant vs. placebo)	Bleeding endpoint (anticoagulant vs. placebo)
ESTEEM [17]	composite of all cause death, non-fatal myocardial infarction, and severe recurrent ischemia = 12.7 % (24, 36, 48, 60 mg: 11.7 %, 13.5 %, 11.6 %, 12.7 %) vs. 16.3 %	1.4 % (all) vs. 4.1 %	ISTH major bleeding: 1.8 % (1.9 %, 0.7 %, 3.2 % 1.5 %) vs. 0.9 %
REDEEM [18]	composite of cardiovascular death, non-fatal myocardial infarction, and non-hemorrhagic stroke = 50, 75, 110, 150 mg: 4.6 %, 4.9 %, 3.0 %, 3.5 % vs. 3.8 %	2.1 % (all) vs. 3.8 %	ISTH major or clinically relevant minor bleeding: 1.1 % (3.5 %, 4.3 %, 7.9 %, 7.8 %) vs. 2.2 %
RUBY-1 [19]	composite of all-cause death, nonfatal myocardial infarction, non-fatal stroke, and severe recurrent ischemia = 5.6 % (5, 15, 30 mg twice daily, 10, 30, 60 mg once daily; 3.8 %, 6.3 %, 5.9 %, 3.8 %, 6.4 %, 7.8 %) vs. 4.4 %	0.7 % (all) vs. 0.6 %	ISTH major or clinically relevant minor bleeding = 5.7 %, 6.3 %, 9.8 %, 5.0 %, 5.1 %, 6.5 % vs. 2.8 %
APPRAISE-1 [20]	composite of cardiovasculardeath, MI, severe recurrent ischemia, or ischemic stroke = 2.5 mg twice daily, 10 mg once daily: 7.6 %, 6.0 % vs. 8.7 %	2.5 mg twice daily, 10 mg once daily: 3.5 %, 1.6 % vs. 2.0 %	ISTH major or clinically relevant minor bleeding = 2.5 mg twice daily, 10 mg once daily, 10 mg twice daily, 20 mg once daily: 5.0 %, 5.6 %, 7.8 %, 7.3 % vs. 0.8 %

(continued)

Table 4.2 (continued)

	Efficacy endpoint (anticoagulant vs. placebo)	All cause death (anticoagulant vs. placebo)	Bleeding endpoint (anticoagulant vs. placebo)
APPRAISE-2 [21]	Composite of cardiovascular death, myocardial infarction, or ischemic stroke = 7.5 % vs. 7.9 %	4.2 % vs. 3.9 %	TIMI major bleeding = 1.3 % vs. 0.5 %
ATLAS ACS-1 TIMI46 [22]	the time to the first episode of death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularization (Kaplan Meier event rate) = 2.5, 5, 10 mg twice daily or 5, 10, 20 mg once daily; 5.3 %, 4.4 %, 6.5 %, 8.7 %, 5.3 %, 5.2 % vs. 7.0 %	Not available	Clinically significant bleeding (TIMI major, TIMI minor, or requiring medical attention) = 2.5, 5, 10 twice daily or 5, 10, 20 mg once daily; 4.8 %, 11.0 %, 14.6 %, 7.4 %, 10.8 %, 16.0 % vs. 3.3 %
ATLAS ACS-2 TIMI51 [23]	Composite of cardiovascular death, myocardial infarction, or stroke = 8.9 % (2.5 , 5 mg twice daily:9.1 %, 8.8 %) vs. 10.7 %	3.7 % (2.5, 5 mg: 2.9 %, 4.4 %) vs. 4.5 %	TIMI major non-CABG bleeding: 2.1 % (1.8 %, 2.4 %) vs. 0.6 %

- ISTH: International Society of Thrombosis and Haemostasis
- ISTH major bleeding: fatal bleeding; clinically overt bleeding associated with a fall in haemoglobin of at least 20 g/L or leading to transfusion of two or more units of whole blood or erythrocytes; bleeding in areas of special concern, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or atraumatic intra-articular bleeding
- Clinically relevant minor bleeding: a clinically overt bleed that did not meet the criteria for major bleed but prompted a clinical response
- TIMI: thrombolysis in myocardial infarction
- TIMI major bleeding: any intracranial bleeding, clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15 % absolute decrease in haematocrit, or fatal bleeding
- TIMI minor bleeding: clinically overt, resulting in hemoglobin drop of 3 to <5 g/dL or ≥10 % decrease in haematocrit, or no observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12 % decrease in haematocrit, any overt sign of hemorrhage requiring intervention or prompting evaluation, or leading to or prolonging hospitalization and does not meet criteria for a major bleeding event

Suggested Choices Based on Current Evidence

Regarding combination therapy, anticoagulation in conjunction with dual antiplatelet therapy is associated with an increased risk of bleeding and potential lower reduction in the risk of ischemic events compared with use of these agents with aspirin alone. Additionally, data regarding the use of new anticoagulants in conjunction with or in comparison with potent $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) are not available. Thus, it is not recommended to use new oral anticoagulants together with or in place of prasugrel or ticagrelor. However, using new oral anticoagulants in ACS patients who have an indication for long term anticoagulation, in which warfarin is typically used, may be considered as a reasonable approach, but requires further study in dedicated trials that are just starting.

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