

New plasmatic anticoagulants after acute coronary syndromes

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Summary

Acute coronary syndrome (ACS) and its sequelae continue to be the major cause of death in developed countries resulting in a high toll of fatalities and health care expenditure. The treatment of ACS has dramatically evolved over the last decade leading to a much more aggressive invasive approach in ST- and Non-ST-elevation myocardial infarction. Despite fast reperfusion strategies and optimal anti-atherosclerosis prophylaxis most patients will experience a progression of the disease in the years following diagnosis of coronary heart disease (CHD). Interestingly enough, thrombin generation markedly increases after acute cardiac events and persists for months after clinical stabilisation, suggesting a role of anticoagulant strategies beyond the use in the acute setting. New anticoagulants have been developed with the goal of reducing cardiovascular events in CHD patients while minimising the risk of bleeding. The new oral Xa-inhibitor, rivaroxaban, is the first out of a large selection of new anticoagulant agents to show a statistically significant reduction of a composite endpoint of cardiovascular death, myocardial infarction and stroke in patients with ACS, compared to standard therapy.

Key words: acute coronary syndrome; therapy; prevention; anticoagulants

Introduction

The acute coronary syndrome (ACS) is a complication of coronary artery disease (CHD), and resides among the most prevalent non-communicable diseases in the world. It develops from sudden thrombosis superimposed on atherosclerotic coronary lesions. ACS and its sequelae account for a large toll of fatalities in developed countries. In addition, CHD and its disabling complications have emerged as a major source of morbidity and disability and result in high national health expenditures. The treatment of ACS has dramatically evolved over the last ten years to favor a much more aggressive and earlier invasive approach in patients suffering ST- (STEMI) or non-ST-elevation myocardial infarction (NSTEMI).

Funding / potential competing interests:

No financial support and no other potential conflict of interest relevant to this article was reported.

Despite fast reperfusion strategies and optimal anti-atherosclerosis prophylaxis most patients will experience a progression of the disease in the years following diagnosis of CHD. Several interventions have proven beneficial in the secondary prevention of myocardial infarction, including angiotensin-converting enzyme inhibitors, lipid lowering with statins, aspirin® and beta-blockers. Interestingly enough, after acute cardiac events, a marked thrombin generation persists for months after clinical stabilisation, suggesting a role for anticoagulant strategies beyond the use in the acute setting. Consequently, a variety of anticoagulant agents have undergone clinical evaluation in randomised trials over the past decades. As a general rule, their overall benefit depends on a delicate trade-off between a reduction in recurrent ischaemic events and cardiovascular death versus an increased risk of fatal or life-threatening bleeding, a problem that has to be faced by all new anticoagulant agents. Additionally, antiplatelet regimes and reperfusion strategies have changed considerably over the past decades, thus much of the evidence from older studies has questionable relevance in contemporary practice. In the present review, we summarise the available published evidence on old and new anticoagulant agents after ACS.

Long-term versus acute anticoagulation

Anticoagulants are being used for the treatment of ACS, regardless whether patients are treated with reperfusion therapies such as thrombolysis or more recently with percutaneous coronary interventions (PCI) or not. However, available anticoagulants (such as vitamin-K antagonists) are characterized by several limitations and a large unmet clinical need is present.

On one hand, we have excellent multiple drugs at our disposal that rapidly and effectively block the coag-

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ulation cascade and are used in the acute setting to facilitate PCI. In addition to unfractionated heparin (UFH) and low molecular weight heparins [1], fondaparinux and bivalirudin have emerged as potent anticoagulants leading to improved clinical outcomes.

In patients with STEMI undergoing primary PCI, the initial treatment with bivalirudin alone compared to heparin plus GPIIb/IIIa inhibitors at three years resulted in a significant 36% reduction in major bleeding and a significant 24% reduction in reinfarction, with non-significantly different rates of stent thrombosis, target vessel revascularisation and stroke. In addition a significant 44% reduction in cardiac mortality and a 25% reduction in all-cause mortality was observed, the latter representing 18 lives saved per 1000 patients treated with bivalirudin (numbers needed to treat [NNT] = 56 to save 1 life) was seen.

Otamixaban, a selective and direct inhibitor of factor Xa, was investigated in patients undergoing non-urgent percutaneous coronary intervention in the SEPIA-PCI trial [2]. In a double-blind, double-dummy, parallel-group, dose-ranging trial, 947 patients were randomly assigned to either 1 of 5 weight-adjusted otamixaban regimens or weight-adjusted unfractionated heparin before percutaneous coronary intervention. Otamixaban reduced prothrombin fragments 1+2 significantly more than UFH at the highest dose regimen, whereas no significant difference in the incidence of TIMI bleeding was observed between the otamixaban and unfractionated heparin groups. These results set the stage for adequately powered clinical outcome trials of selective direct factor Xa inhibition in patients with acute coronary syndromes. These medications, once administered on top of double or triple antiplatelet agents such as aspirin[®], ADP-receptor antagonists and platelet glycoprotein IIb/IIIa inhibitors might, however, significantly increase the risk of bleeding associated with PCI or coronary artery bypass grafting. This aspect is potentially still underestimated and could be more apparent since the new more potent anti-platelets strategies are increasingly used.

On the other hand anticoagulant strategies are emerging in secondary prevention after ACS. In fact, another unmet clinical need is the prevention of disease progression and re-infarction. Vitamin K antagonists are of proven efficacy and are superior to monotherapy with aspirin[®], however, are rarely used by cardiologists in secondary prevention because of the need for long-term laboratory monitoring and the perceived high-risk of bleeding. New anticoagulants have been, therefore, developed with the goal of reducing cardiovascular events in CHD patients by minimising the risk of bleeding. For the longest time, the cardiological community has been waiting for an oral anticoagulant drug with no laboratory monitoring requirement and minimised risk of bleeding that could be safely associated to dual antiplatelet therapy. The new oral Xa-in-

hibitor rivaroxaban was the first to show a statistically significant reduction of the composite endpoint of cardiovascular death, myocardial infarction and stroke in patients with ACS, compared to standard therapy.

Evidence for oral anticoagulant drugs in the secondary prevention therapy

Aspirin[®] therapy is generally recommended in secondary prevention and primary prevention if the risk for developing CHD exceeds 1.5% per year. The oral anticoagulant warfarin has also been shown to reduce the risk in secondary prevention. However, the potential benefit of adding aspirin[®] is outweighed by the increased risk of major bleeding [3]. The ATACS trial first demonstrated the benefits of long-term anticoagulant therapy (with an international normalised ratio (INR) ranging 2.0 to 3.0) when compared to aspirin[®] alone [4]. These results were consecutively confirmed in the APRICOT-2 [5] and ASPECT-2 [6] trials. The analysis of the pooled data of this trials showed that 3 death/reinfarction are prevented at the cost of 1 major bleeding; the reduction of ischaemic stroke is even higher with no excess haemorrhagic strokes [7]. In the WARIS-II trial anticoagulant therapy with INR 2.0–2.5 in addition to low-dose aspirin[®] (75 mg) significantly reduced the combined endpoints death, MI and stroke when compared to aspirin[®] (160 mg) however the combination was also associated with slight increase in bleeding complications [8]. In a randomised, multicentre trial including 3630 patients, 1216 were randomised to receive warfarin (in a dose intended to achieve an INR of 2.8 to 4.2), 1206 to receive aspirin[®] (160 mg daily), and 1208 to receive aspirin[®] (75 mg daily) combined with warfarin (in a dose intended to achieve an INR of 2.0 to 2.5). The mean duration of observation was four years. The primary outcome, a composite of death, nonfatal reinfarction, or thromboembolic cerebral stroke, occurred in 20% patients receiving aspirin[®], in 16.7% in patients receiving warfarin (hazard ratio [HR] of 0.81; 95% CI = 0.69–0.95; $p = 0.03$ as compared with aspirin[®]), and in 15% in those receiving warfarin and aspirin[®] (HR of 0.71; 95% CI = 0.60–0.83; $p = 0.001$ as compared with aspirin[®]). The difference between the two groups receiving warfarin was not statistically significant. Episodes of major, nonfatal bleeding were observed in 0.62% of patients per treatment-year in both groups receiving warfarin and in 0.17% of patients receiving aspirin[®] ($p < 0.001$). Similar results were obtained in the ASPECT-2 trial [6]. The authors concluded that warfarin, in combination with aspirin[®] or given alone, was superior to aspirin[®] alone in reducing the incidence of composite events after an acute myocardial infarction but was associated with a higher risk of bleeding [8]. A metaanalysis including data from the MEDLINE published between 1990 and 2005 indicated that for patients with the ACS

who are at low or intermediate risk for bleeding, the cardiovascular benefits of warfarin outweigh the bleeding risks.

However, after coronary stenting the use of dual antiplatelet treatment (with aspirin® and ticlopidin) proved superior to aspirin® and oral anticoagulation with warfarin or phenprocoumon with a significant 59% reduction in the 30-day composite endpoint of cardiac death, nonfatal MI and repeat revascularization. A favorable effect, albeit not statistically significant, was also observed with dual antiplatelet therapy with regard to the occurrence of major haemorrhages and stent thrombosis on angiography [9].

How to minimise the risk of bleeding complications in CHD patients requiring anticoagulation

Considering the individual patient risk of bleeding and the potential benefit of a combined antiplatelet and anticoagulant therapy, the optimisation of the anticoagulation control within the INR target was, till recently, the only reasonable approach. The risk of major bleeding with aspirin® alone is about 0.13% per person-year, while in combination with oral anticoagulation the risk is increased 1.5 times.

There are three patient-conditions in which adding aspirin® to an anticoagulant is favourable:

1. In ACS patients the guidelines recommend starting aspirin® after myocardial infarction even if the INR is in the therapeutic range, especially if a PCI is performed [10, 11].
2. After PCI with stent implantation dual antiplatelet therapy with aspirin® and a thienopyridine is superior to aspirin® and/or warfarin in reducing the risk of stent thrombosis and major cardiovascular events such as myocardial infarction (MI) or urgent revascularisation [9, 12]. If the patient has an indication for long-term anticoagulation, a triple combination should be considered in order to reduce the risk of stent thrombosis [11]. The INR should be maintained between 2.0 and 2.5. The type of stent implanted guides the duration of the triple combination. Table 1 shows recommendations for the duration of triple antithrombotic treatment in patients undergoing coronary stenting. New stents have been designed to reduce the period of triple therapy with the goal of reducing it to one month.
3. In patients with mechanical heart valves especially in those who experienced a thrombotic complication while on therapeutic INR range or who have a history of cerebrovascular or peripheral vascular disease, a hypercoagulable state or CHD [13–15]. In such patients adding aspirin® has dem-

Table 1

Recommendations for duration of triple antithrombotic treatment in patients after coronary stenting with an indication for oral anticoagulation. Adapted from Consensus Document of the ESC WG on Thrombosis, endorsed by EHRA and EAPCI [29].

Haemorrhagic risk	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin® ≤100 mg/day + clopidogrel 75 mg/day Lifelong: warfarin (INR 2.0–3.0) alone
		Drug eluting	3 (olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin® ≤100 mg/day + clopidogrel 75 mg/day Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin® 100 mg/day)* Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal / drug eluting	6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin® ≤100 mg/day + clopidogrel 75 mg/day Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin® 100 mg/day)* Lifelong: warfarin (INR 2.0–3.0) alone
High	Elective	Bare metal [†]	2–4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin® ≤100 mg/day + clopidogrel 75 mg/day Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal [†]	4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin® ≤100 mg/day + clopidogrel 75 mg/day Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin® 100 mg/day)* Lifelong: warfarin (INR 2.0–3.0) alone

INR denotes international normalised ratio; ACS = acute coronary syndrome.

*Combination of warfarin (INR 2.0–2.5) + aspirin® ≤100 mg/day may be considered as an alternative. [†] Drug-eluting stents should be avoided.

onstrated a reduction of the frequency of thromboembolism [16].

There are two conditions in which anticoagulation alone may be sufficient:

1. In primary prevention of coronary disease in patients on long-term anticoagulant the benefit of adding aspirin[®] to anticoagulation is outweighed by the increase risk of major bleeding [3].
2. In stable CHD patients without mechanical heart valves and at least 6–12 months after coronary stent implantation (tab. 1) anticoagulation alone is sufficient.

Several large randomised studies demonstrated the efficacy of anticoagulants in secondary prevention [6, 17], while the combination of aspirin[®] with anticoagulants did not add any benefit, but significantly increased the risk of bleeding in these patients [8].

The need for safer and more effective combination therapies has led to the development of anticoagulants with a more predictive efficacy. Factor Xa initiates the final common pathway of the coagulation cascade and results in the formation of thrombin, which catalyses additional coagulation-related reactions and promotes platelet activation. Direct and selective inhibition of the factor Xa is, therefore, an appealing strategy to increase antithrombotic efficacy by limiting the risk of bleeding. In the setting of ACS new oral Xa-inhibitors, providing potent antithrombotic activity through selective inhibition of factor Xa by high-affinity binding to antithrombin III have been recently tested.

The oral Xa-inhibitors

Since factor Xa plays a central role in thrombosis, the inhibition of factor Xa might improve cardiovascular outcomes in patients with a recent ACS. The orally active, selective, direct factor Xa inhibitor apixaban (under joint development by Bristol Meyer Squibb and Pfizer) has been the subject of intense interest in the recent years. It has been shown to reduce the incidence of venous thromboembolism in patients undergoing orthopaedic surgery or in acutely ill patients who had congestive heart failure or respiratory failure or other medical disorders and at least one additional risk factor for venous thromboembolism in comparison to enoxaparin and to prevent thromboembolic events in patients with atrial fibrillation in comparison with vitamin-K antagonist therapy [18–21].

In patients with ACS treated with aspirin[®] or aspirin[®] plus clopidogrel, treatment with apixaban at doses of 5 to 20 mg daily resulted in dose-related increases in bleeding events and a trend toward fewer ischaemic events [22]. In July 2011 the announcement of the APPRAISE-2 (Apixaban for Prevention of Acute Ischaemic Events-2) results with apixaban in ACS appeared to dash hopes that oral anticoagulant therapy could be added to dual antiplatelet therapy in ACS.

APPRAISE-2 was a phase 3 trial comparing apixaban to placebo in ACS patients already receiving standard antiplatelet therapy and who had at least 2 additional risk factors for recurrent ischaemic events. The trial planned to enroll 10 800 patients and was stopped prematurely after 7392 patients enrolled because of an increase in major bleeding events in patients receiving apixaban [23]. After a medial follow-up of 241 days, the primary endpoint of combined rate of cardiovascular death, MI or ischaemic stroke was seen in 7.5% of the patients treated with apixaban and in 7.9% in the placebo group (HR 0.95, CI 1.5–4.46, $p = 0.51$, fig. 1).

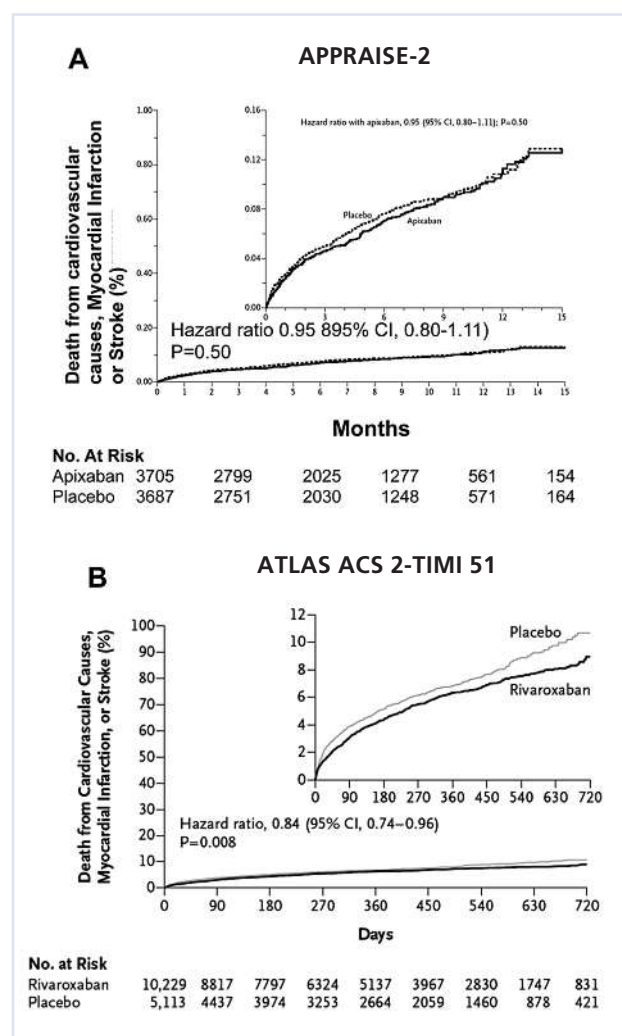


Figure 1

Kaplan-Meier curves for the primary efficacy outcome in the APPRAISE-2 (panel A, reproduced from [23]: Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med.* 2011;365:699–708. © Massachusetts Medical Society, Waltham, MA, USA. Reprint with kind permission) and ATLAS ACS 2-TIMI 51 (panel B, reproduced from [25]: Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012;366:9–19. © Massachusetts Medical Society, Waltham, MA, USA. Reprint with kind permission.). In both studies the primary efficacy outcome was the composite of cardiovascular death, myocardial infarction, or ischaemic stroke. The inset shows the same data on an enlarged y axis.

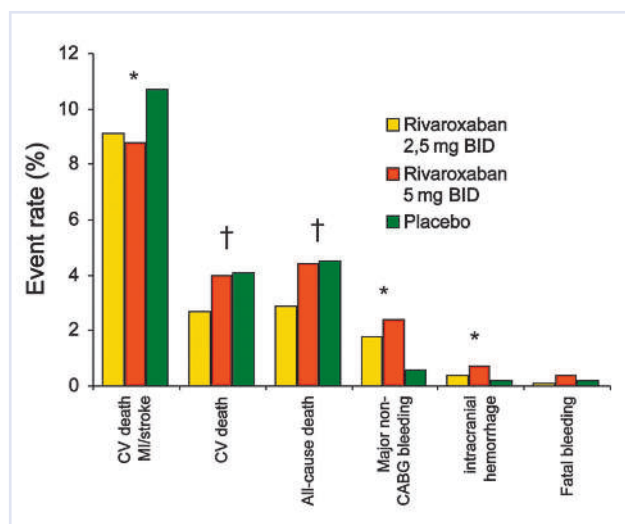


Figure 2

Event rates for efficacy and safety endpoints in the ATLAS ACS 2 - TIMI 51 study (Rivaroxaban in Patients with a Recent Acute Coronary Syndrome). [25].

* $p < 0.05$ for pairwise comparison of both, 2.5 mg BID rivaroxaban vs placebo and 5 mg BID rivaroxaban vs placebo.

† $p < 0.05$ for pairwise comparison of 2.5 mg BID rivaroxaban vs placebo, but $p = ns$ for pairwise comparison of 5 mg BID rivaroxaban vs placebo.

Major bleeding occurred more frequently in the apixaban arm (1.3%) compared to placebo (0.5%, $p = 0.001$). This APPRAISE-2 study therefore failed to confirm the promising results seen in 3 phase 2 trials suggesting that oral anticoagulants when added to antiplatelet therapy in ACS patients would reduce recurrent events without causing a large excess of bleeding complications. These results raised doubts about whether meaningful incremental efficacy can be achieved with an acceptable risk of bleeding by combining long-term anticoagulant with both aspirin® and a P2Y₁₂-receptor antagonist. This dilemma was however solved later on with the presentation of the data of another ACS trial using low-dose rivaroxaban.

Rivaroxaban is an oral anticoagulant that directly and selectively inhibits factor Xa. It was discovered in Bayer HealthCare's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Janssen Research & Development (a Johnson and Johnson, J&J company). In the US, J&J holds marketing right for rivaroxaban. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for routine coagulation monitoring, and a limited potential for pharmacokinetic interaction. Rivaroxaban is marketed under the brand name of Xarelto. Convincing data have demonstrated superior efficacy compared to LMWH in the prevention of deep venous thrombosis following elective hip or knee replacement. Thus, it has rapidly obtained approval for this indication in more than 110 countries. In Europe, it was approved by the EMA on

December 19 2010, and in US received FDA approval on July 2011. In addition, rivaroxaban has been more recently approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

The 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) was a phase 2 dose-finding trial that enrolled 3491 patients with a recent acute coronary syndrome [24]. Rivaroxaban was tested at total daily doses ranging from 5 to 20 mg and, as compared with placebo, reduced the composite end point of death, myocardial infarction, or stroke with the lowest hazard ratios noted for the lowest twice-daily doses, whereas there was a dose-dependent increase in bleeding events.

With the aim of determining a clinically effective low-dose regimen, and on the base of the observations made in ATLAS ACS-TIMI 46, a phase 3 trial to evaluate twice-daily rivaroxaban at doses of 2.5 mg and 5 mg twice daily as adjunctive therapy in patients with a recent acute coronary syndrome was conceived. The ATLAS ACS 2-TIMI 51 study was designed to test the efficacy of rivaroxaban compared to placebo in preventing cardiovascular death, myocardial infarction and stroke in patients after an episode of ACS [25]. Patients were given standard antiplatelet therapy plus rivaroxaban dosed at 2.5 mg or 5 mg BID, or a placebo for a mean of 13 months and up to 31 months. These doses represent 25% and 50% respectively, of the daily dose tested in the setting of atrial fibrillation [26]. A total of 15 526 patients were randomised. The vast majority (93%) received aspirin® plus a thienopyridine agent in addition to the study drug or placebo. The study design was double blind, randomised, placebo-controlled. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (HR in the rivaroxaban group 0.84; 95% CI 0.74 to 0.96; $p = 0.008$, fig. 1), with significant improvement for 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%, $p = 0.03$). Rivaroxaban showed, therefore, a significant 16% reduction of the primary endpoint. The twice-daily 2.5-mg dose reduced the rates of death from cardiovascular causes (2.7% vs 4.1%, $p = 0.002$) and from any cause (2.9% vs 4.5%, $p = 0.002$), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary artery bypass grafting (2.1% vs 0.6%, $p < 0.001$) and intracranial haemorrhage (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. 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%, $p = 0.04$). The authors concluded that in patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite endpoint of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial haemorrhage but not the risk of fatal bleeding.

Potential difference between APPRAISE-2 and ATLAS ACS 2-TIMI 51

One difference that may turn out to be key is that patients enrolled in ATLAS ACS 2-TIMI 51 were stratified based upon whether the investigator planned to give aspirin[®] alone or aspirin[®] plus thienopyridine such as clopidogrel or prasugrel. In contrast to the atrial fibrillation trial ROCKET AF, rivaroxaban was given in the ATLAS ACS 2-TIMI 51 twice a day with lower dose (2.5 or 5 mg BID in ATLAS ACS versus 10 g BID in ROCKET AF [27, 28]).

Conclusion

Long-term anticoagulation (alone or in combination with antiplatelet agents) is beneficial in a subgroup of patients with CHD, however, the risks of increased major bleeding events has to be weighed against the potential reduction in ischaemic events. New anti-thrombotic drugs have shown impressive result in the setting of ACS. More potent anti-platelets and plas-matic anticoagulants were tested in NSTEMI and STEMI patients treated with or without PCI. The new oral anti Xa rivaroxaban showed a 16% relative risk reduction in primary efficacy end point, as compared with placebo. The twice-daily 2.5-mg dose of rivaroxaban tested in the ATLAS significantly reduced the rates of death from cardiovascular causes and from any cause, a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary artery bypass grafting and intra-cranial haemorrhage, without a significant increase in fatal bleeding or other adverse events. The risk of bleeding was dose-dependent. These results are of great clinical relevance as the study demonstrated a relevant cardiovascular risk reduction during the first year after an ACS on top of effective antiplatelet therapy. The decision to use low doses of rivaroxaban in the context of an ACS appears to make sense and shows some analogy to the OASIS-5 study, in which low dose fondaparinux (2.5 mg/d) showed a good effectiveness and save profile. It is, however, premature to claim that rivaroxaban has a definitive role in secondary prevention. In fact, the ATLAS ACS 2-TIMI 51 study was performed in a selected population and elderly patients (>75 years old), women and patients with renal failure

were underrepresented. This aspect appears particularly relevant if the save spectrum of a triple therapy is considered. In addition, prasugrel and ticagrelor (two potent antiplatelet agents) were recently introduced in the clinical practice in the treatment of ACS and these substances have been shown to be more effective than clopidogrel. Therefore, the benefit of adding rivaroxaban could be less impressive in the setting of dual antiplatelet therapy with either prasugrel or ticagrelor, and the risk of major bleeding even more pronounced. Based on the large number of new anti-thrombotics reaching the clinical stage, several new studies in secondary prevention are expected. This is of great importance as the event rate in the first year following an ACS is still in the range of 10%.

References

- 1 Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med.* 1997;337:447–52.
- 2 Cohen M, Bhatt DL, Alexander JH, et al. Randomized, double-blind, dose-ranging study of otamixaban, a novel, parenteral, short-acting direct factor Xa inhibitor, in percutaneous coronary intervention: the SEPIA-PCI trial. *Circulation.* 2007;115:2642–51.
- 3 Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. *Arch Intern Med.* 2007;167:117–24.
- 4 Cohen M, Xiong J, Parry G, et al. Prospective comparison of unstable angina versus non-Q wave myocardial infarction during antithrombotic therapy. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. *J Am Coll Cardiol.* 1993;22:1338–43.
- 5 Brouwer MA, van den Bergh PJ, Aengevaeren WR, et al. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRI-COT)-2 Trial. *Circulation.* 2002;106:659–65.
- 6 van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet.* 2002;360:109–13.
- 7 Verheugt FWA, Marc A Brouwer MA, Van Es RF, Ezekowitz MD, Fiore L, Fuster V. Risks versus benefit of oral anticoagulation on top of aspirin following unstable angina or myocardial infarction: a meta-analysis. *Circulation.* 2001;104:II–88.
- 8 Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med.* 2002;347:969–74.
- 9 Rubboli A, Milandri M, Castelvetro C, Cosmi B. Meta-analysis of trials comparing oral anticoagulation and aspirin versus dual antiplatelet therapy after coronary stenting. Clues for the management of patients with an indication for long-term anticoagulation undergoing coronary stenting. *Cardiology.* 2005;104:101–6.
- 10 Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol.* 2004;44:671–719.
- 11 Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2999–3054.

- 12 Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527–33.
- 13 Bonow RO, Carabello BA, Chatterjee K, et al. Focused update incorporated into the 2 American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2008;118:e523–661.
- 14 Nishimura RA, Carabello BA, Faxon DP, et al. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2008;118:887–96.
- 15 Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J*. 2007;28:230–68.
- 16 Turpie AG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med*. 1993;329:524–9.
- 17 Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA*. 1999;282:2058–67.
- 18 Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*. 2010;375:807–15.
- 19 Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*. 2010;363:2487–98.
- 20 Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med*. 2011;365:2167–77.
- 21 Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–92.
- 22 Alexander JH, Becker RC, Bhatt DL, et al. 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;119:2877–85.
- 23 Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011;365:699–708.
- 24 Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet*. 2009;374:29–38.
- 25 Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9–19.
- 26 Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–91.
- 27 Ahrens I, Lip GY, Peter K. What do the RE-LY, AVERROES and ROCKET-AF trials tell us for stroke prevention in atrial fibrillation? *Thromb Haemost*. 2011;105:574–8.
- 28 Cleland JG, Coletta AP, Buga L, et al. Clinical trials update from the American Heart Association meeting 2010: EMPHASIS-HF, RAFT, TIM-HF, Tele-HF, ASCEND-HF, ROCKET-AF, and PROTECT. *Eur J Heart Fail*. 2011;13:460–5.
- 29 Lip GY, Huber K, Andreotti F, et al. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: executive summary – a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2010;31:1311–8.