A NEW COMBINATION OF FACTOR XA INHIBITION AND STANDARD ANTIPLATELET THERAPY TO PREVENT MORE RECURRENT CARDIOVASCULAR EVENTS IN ACUTE CORONARY SYNDROME (ACS)

Summary of Presentations given at the Bayer Satellite Symposium, EuroPCR 2013: The Official Annual Meeting of EAPCI, Paris, May 22nd 2013

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Introduction and Objectives

The purpose of this symposium was to:

- Discuss the interplay between the coagulation cascade and platelets in arterial thrombus formation.
- Present the rationale for oral antiplatelet and anticoagulant therapy to reduce residual thrombotic risk in patients following Acute Coronary Syndrome (ACS).
- Discuss the significant benefits seen in patients following ACS when combining rivaroxaban 2.5 mg twice daily with standard antiplatelet therapy.
- Assess how the use of oral anticoagulation may change current standards of care and influence guidelines in patients with ACS.

Thrombin Generation and its Critical Role in Acute Coronary Syndrome: Combining Anticoagulant and Antiplatelet Therapy in the Acute Phase and in Secondary Prevention of ACS

Gabriel Steg

Coronary artery disease remains the leading cause of death worldwide.[1] There has been tremendous progress in the management of Acute Coronary Syndrome (ACS) in general and ST segment elevation myocardial infarction (STEMI) in particular. There are many examples of worldwide registry data that show this. For example, the French Registry of acute ST-elevation or non-STEMI shows a dramatic reduction in the rate of cardiovascular mortality among patients with STEMI over the last 15 years. This reduction in mortality rate is a result of reperfusion therapy, primary VCR and evidence based adjuvant therapy. This is also shown in the reduction in mortality between 1995 and 2010 for primary percutaneous coronary intervention (PCI) (8.7 to 3.2, adjusted odds ratio [OR] 0.29, 95% confidence interval [CI]: 0.15-0.58), fibrinolysis patients (8.2 to 2.1, adjusted OR 0.29, 95% CI: 0.11-0.76) and even patients with no reperfusion at all (18.9 to 8.7, adjusted OR 0.47, 95% CI: 0.32-0.70).[2] These data indicate that mortality has steadily decreased over time due to a combination of the access to reperfusion therapy, the quality of

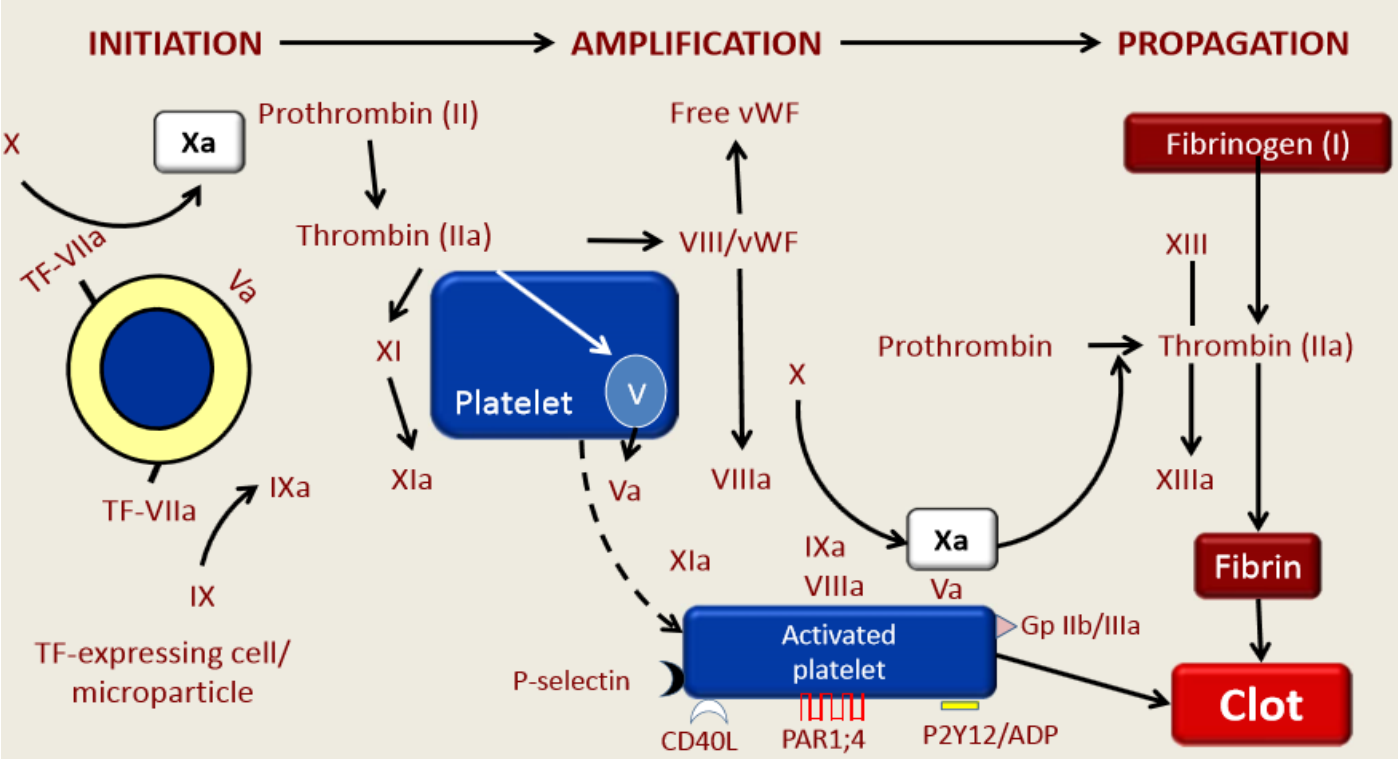

Figure 1: Thrombus formation involves both platelet activation and blood coagulation.

reperfusion therapy and the adjuvant and associated medical therapy.

However, patients still die. The perception is that once a patient has undergone primary PCI they are out of danger and within the next 42 to 72 hours will be discharged with a patent vessel and a stent, and are therefore 'cured'. This perception is incorrect because firstly, early mortality within the first 6 months after hospital discharge for ACS remains high.[3] Secondly, the 5 year death rate in a recent study (the GRACE experience in the UK and Belgium) showed that approximately 20% of ACS patients will die 5 years after having an ACS. The proportion of deaths that occur after hospital discharge are; non-STEMI patients 86%, STEMI patients 68% and unstable angina patients 97%[4] confirming that after hospital discharge, patients are not out of danger and the risk of cardiovascular death remains high.

Effective therapy is available in the acute setting and in long-term secondary prevention. In the acute setting routinely a combination of antiplatelet therapies, acetylsalicylic acid (ASA) plus adenosine diphosphate (ADP) receptor antagonist, known as dual antiplatelet therapy (DAPT) – ticagrelor or prasugrel, or clopidogrel if the other therapy is not suitable or available – are used. Furthermore, acute phase anticoagulation therapy (bivalirudin, enoxaparin, fodaprinux and unfractionated heparin) and anti-ischaemic agents (β-blockers) are given, and mechanical methods (reperfusion/revascularisation PCI, thrombolysis, coronary artery bypass grafting [CABG]) are used. In long-term secondary prevention, dual anti-platelet therapies (ASA, ADP receptor antagonists, statins, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], β-blockers) and lifestyle changes are combined to address risk factors.

Data from the PLATO trial[5] showed using one of the most effective treatments available for ACS (ASA and ticagrelor), that at 1 year follow up there is still a 10% event rate. In addition, the PROSPECT study[6] evaluated patients post ACS that underwent successful uncomplicated PCI; both the culprit and non-culprit lesions were studied. A number of these patients experienced recurrent events following their index ACS; the study found that these recurrences could be attributed to the index lesion or to other lesions. At the 3 year follow up, a 20% risk of cardiac death, cardiac arrest, myocardial infarction (MI) or re-admission for unstable angina was seen. Approximately half of these events were culprit related and half were non-culprit related and were therefore related to other lesions or progression of disease. This shows that treating the culprit lesion does not ensure the patient's complete

recovery. In an equal proportion of cases, non-culprit lesions will cause further events despite optimal medical therapy.

Thrombosis appears to be the precipitating factor for both acute and recurrent events. Anti-thrombotic treatments are inexpensive, however coagulation is complicated and it is a cascade phenomenon which is notoriously challenging. There are 3 intertwined phases of coagulation; initiation, amplification and propagation that involve a complex set of events (Figure 1).[7] It is generally thought that clots are purely platelets (white clots) or purely fibrin (red clots) however, clot formation involves both platelet activation and blood coagulation.

In vivo, arterial thrombosis involves platelet aggregation, tissue factor generation and fibrin formation. Falati et al (2002)[8] showed real-time *in vivo* imaging of arterial thrombus formation in the mouse after laser-induced vascular injury, and within seconds of the laser injury the tissue factor bursts and is followed by the rapid formation of fibrin and platelets concurrently. This quickly occludes the vessel and the well-known phenomenon of cyclical variation occurs as the tail of the clot embolises and patency re-establishes. This is followed by more fibrin generation and platelet activation causing re-occlusion. A study[9] that compared thrombin generation in ACS, healthy control subjects and coronary artery disease found that thrombin generation in ACS was both faster and greater than in the other groups. This is predictable because in the generation of the clot, thrombin is found in several places in the sequence of events. Thrombin participates in fibrin formation, which is sometimes beneficial due to its involvement in haemostasis. Thrombin is also important because it can activate platelets; there are specific thrombin receptors on the platelet surface (protease-activated receptor [PAR]-1 and PAR-4) and these receptors play a key role in platelet activation and clot formation which can be targeted for platelet inhibition therapy.[10]

Silvain et al (2011)[11] studied the thrombus composition in acute MI. The thrombus was retrieved and electron micrograph scanning was performed; it showed a mixture of fibrin and platelets. A typical 'early' thrombus (ischaemic time [time from symptom onset to thrombus retrieval] ≤ 1 hour) showed mainly platelet aggregates with a few cholesterol crystals and a typical 'late' thrombus (ischaemic time > 3 hours) showed mainly erythrocytes trapped in fibrin mesh with only a few platelet aggregates. The faster and greater thrombin response in ACS is not only

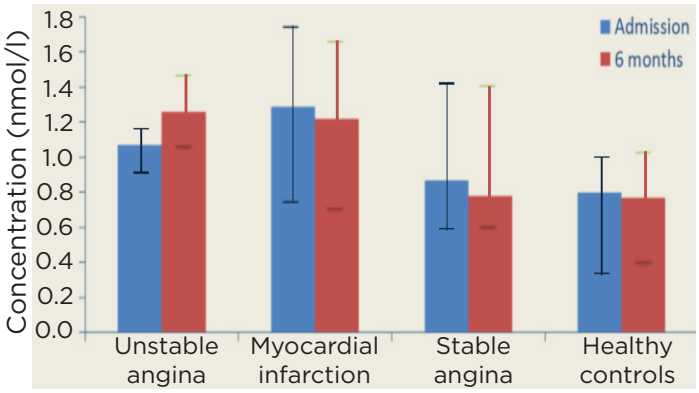

Figure 2: Increased thrombin levels persist in ACS patients at least 6 months after admission.

seen in the acute phase but also persists long-term.[12] Merlini et al (1994)[13] studied plasma concentrations of prothrombin fragment 1+2 (F_{1+2}, a cleavage product of prothrombin) in patients with ACS and found that at 6 months follow up there was persistent plasma concentration elevation in patients with MI compared with healthy controls or patients with stable angina ($p<0.001$) (Figure 2).

In the acute phase of ACS generally two antiplatelet agents (ASA, clopidogrel, prasugrel, ticagrelor, anti-glycoprotein IIb/IIIa or cangrelor) are combined with an anticoagulant (unfractionated heparin, low molecular weight heparin, bivalirudin or fondaparinux).[14,15] Unfortunately, the anticoagulants are injectable so they are not easy to use long-term. It is possible to use low molecular weight heparin long-term but it does generate substantial bleeding and the clinical benefits are uncertain. There have been attempts to combine long-term antiplatelet and anticoagulation therapy. The early studies used warfarin, which is a drug that has a narrow therapeutic margin, combined with ASA. The WARIS II (pre-clopidogrel era) study[16] compared warfarin alone, ASA alone or a combination of warfarin and ASA. The results of the study showed a statistically significant reduction ($p<0.001$) in secondary events in the combination arm, however this was associated with a higher risk of bleeding. This study pertains to the pre-reperfusion and pre-angioplasty era therefore most of the patients had not undergone mechanical intervention or stenting. The applicability of these results in the era of wide spread stenting and dual antiplatelet therapy is uncertain. The other issue with the early studies is that because of the narrow therapeutic margin there was often unacceptable bleeding. Meta-analysis of the early trials[17] that combine ASA and warfarin

showed that in the studies with good International Normalised Ratio (INR) control (therapeutic range of 2-3); a substantial mortality reduction was seen or cardiovascular outcomes improved by approximately 25% in cardiovascular death, MI and stroke. However, there was an increased risk of major bleeding events, extracranial bleeds and a possible signal for intracranial bleeds. The conclusion was that outcomes can be improved long-term post ACS or post MI by combining an antiplatelet agent and an anticoagulant; however this was done at the expense of increased bleeding, including increased intracranial bleeding.

Despite major progress there remains a high unmet need in secondary prevention of ACS. The existing options of anticoagulation with vitamin K antagonists combined with antiplatelet therapy are fraught with poor efficacy, poor therapeutic margins and safety. There is a solid rationale and compounding evidence for targeting platelets and thrombin, not only in the acute phase but also in secondary prevention.

New Era of Anticoagulation: Reducing Mortality and Preventing Stent Thrombosis in Acute Coronary Syndrome (ACS) Patients When Combining Rivaroxaban 2.5 mg Bid and Standard Antiplatelet Therapy – the ATLAS ACS 2 TIMI 51 Trial

Sarah Richardson
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Summary of a presentation given by Professor Gilles Montalescot (Hôpital de la Pitié-Salpêtrière, Paris, France).

The new generation of anticoagulation therapy is important in the field of Acute Coronary Syndrome (ACS) and primary percutaneous coronary intervention (PCI); it has become increasingly apparent that one antiplatelet agent is not sufficient to treat ACS patients. Two or sometimes three antiplatelet agents are required for successful treatment. In addition, anticoagulation is also required for both the acute and the chronic phases of ACS.

Despite antiplatelet therapy being the long-term standard of care in ACS[14,15] there is a 10% risk of a recurrent cardiovascular (CV) event in the 12-15 months after ACS.[5,18,19] The data available is

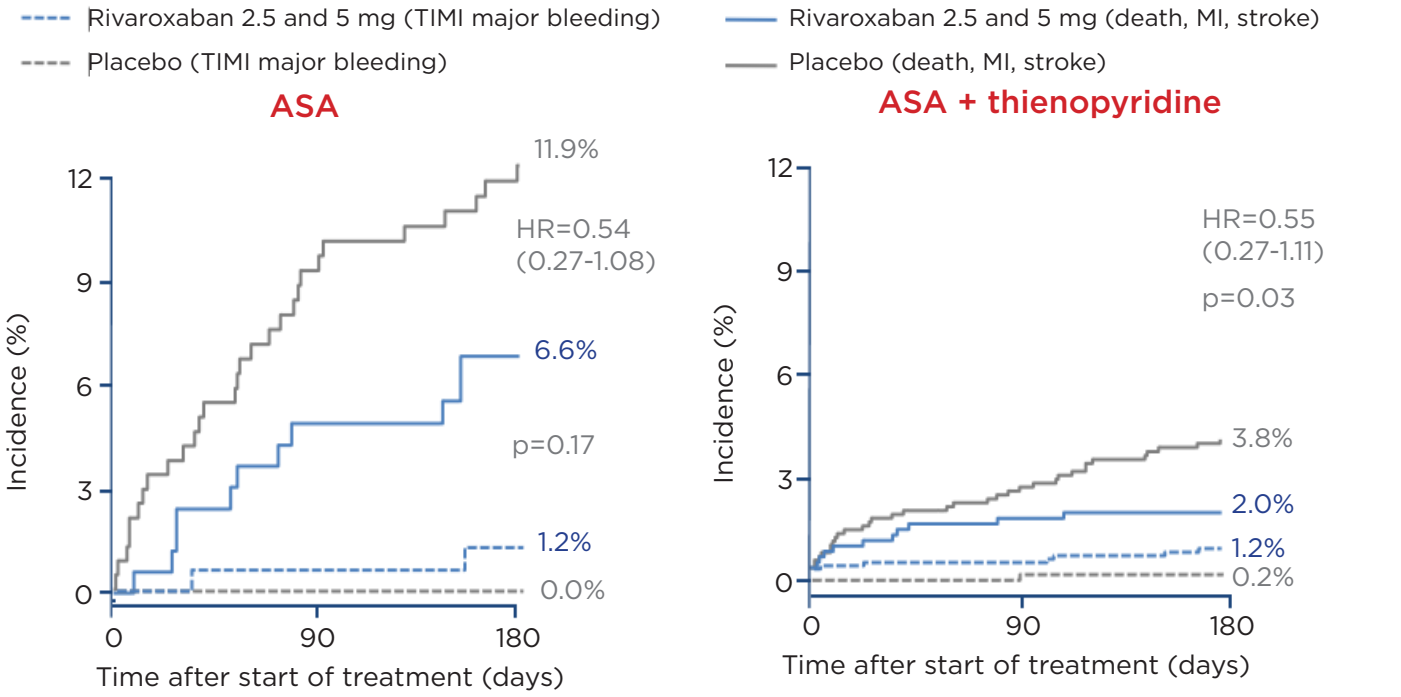


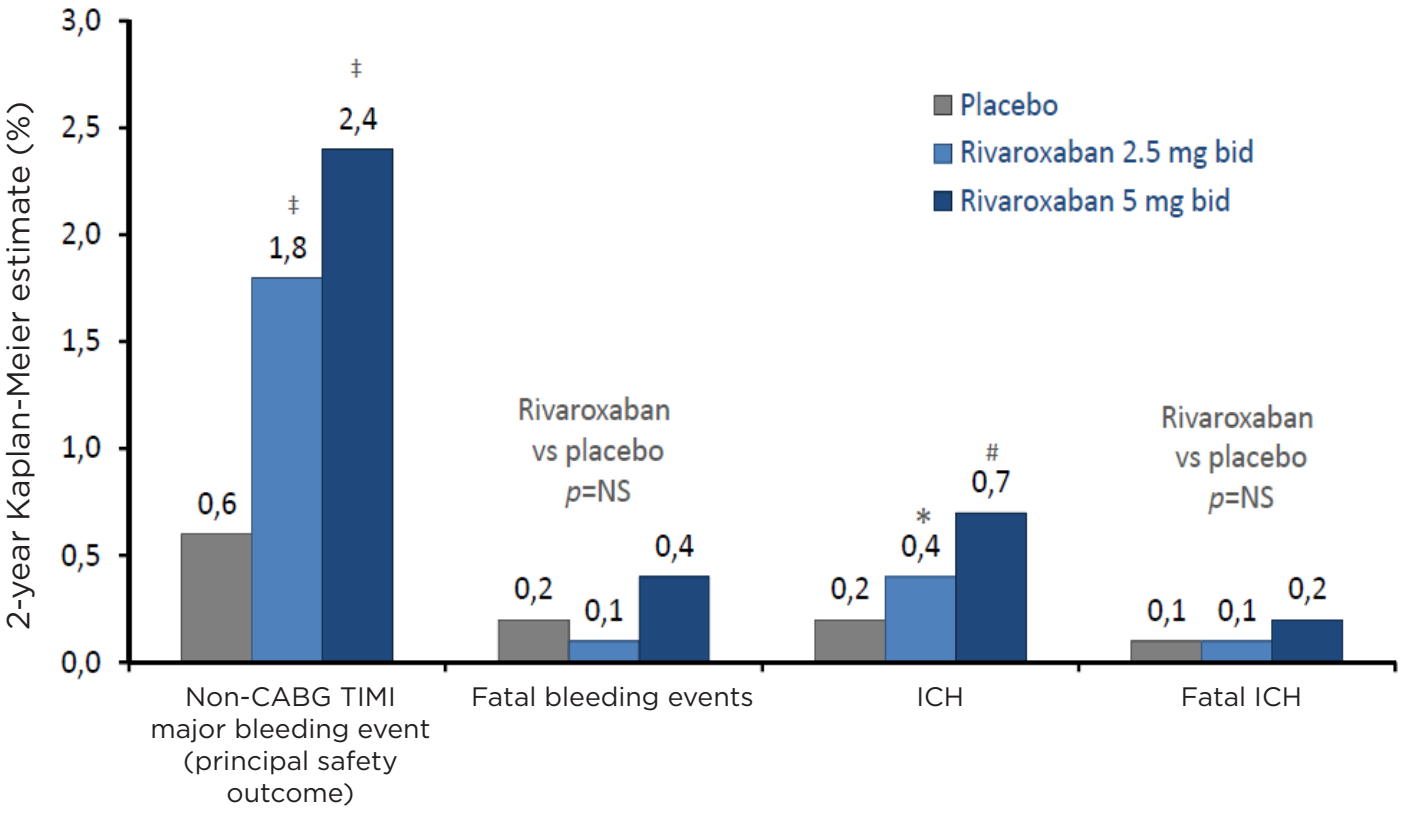
Figure 3: ATLAS ACS TIMI 46: 2.5 and 5 mg twice daily doses showed a favourable efficacy-safety profile.

predominately from old studies, and shows warfarin + aspirin (ASA) versus ASA alone reduces the risk of CV events but at the expense of increased bleeding risk.[17] More effective drugs are needed with an increased safety profile. The phase II/III ATLAS ACS programme evaluated the addition of rivaroxaban to antiplatelet therapy for the prevention of recurrent CV events in patients with ACS.[20,21]

The phase II dose finding study[20,22] stratified patients to use ASA only or ASA + thienopyridine, and within each stratum patients were randomised to receive placebo or rivaroxaban (5-20mg). The results showed that death, myocardial infarction (MI) or stroke occurred in 11.9 % (hazard ratio [HR] 0.54; confidence interval [CI] 0.27-1.08) in the ASA + placebo arm compared with 3.8% (HR 0.55; CI 0.27-1.11) in the ASA + thienopyridine arm. Rivaroxaban + ASA + thienopyridine showed a significant reduction in death, MI or stroke (2.0% [p=0.03]) compared with the ASA + placebo arm (6.6% [p=0.17]) (Figure 3). Based on the favourable efficacy and safety results of this study, 2.5 mg and 5 mg twice daily (bid) doses were chosen for the phase III study.

The phase III ATLAS ACS 2 TIMI 51 trial[21,23] randomised 15,526 hospitalised patients with ACS. The physicians decided whether or not patients were to receive thienopyridine, accordingly they were assigned to stratum 1: ASA alone, or stratum 2: ASA + thienopyridine. Within each stratum patients were randomised to either the placebo, rivaroxaban 2.5 mg or rivaroxaban 5 mg arm. The primary efficacy endpoint was CV death, MI or stroke versus placebo in both strata. The results showed that rivaroxaban significantly reduced the primary efficacy end point compared with placebo. 8.9% in the rivaroxaban arm (HR 0.84; CI 0.74-0.96) compared with 10.7% in the placebo arm.[20] Rivaroxaban did not increase fatal bleeding or fatal intracranial haemorrhage (Figure 4). The 2.5 mg bid dose significantly reduced CV death compared with placebo (2.7% vs. 4.1%, p=0.002) and from any cause (2.9% vs. 4.5%, p=0.002).

The trial identified 7,817 patients that presented with ST segment elevation myocardial infarction (STEMI); these patients were randomised to 2.5 mg bid rivaroxaban, 5 mg rivaroxaban or placebo arms. The patients who received 2.5 mg bid rivaroxaban showed a significant reduction in CV events and death compared with patients that received placebo. The primary efficacy endpoint, CV death, MI or



*p=0.04 vs placebo; #p=0.005 vs placebo; ‡p<0.001 vs placebo

Figure 4. Rivaroxaban did not increase fatal bleeding or fatal intracranial haemorrhage.

stroke was 8.8% in the 2.5 mg bid rivaroxaban arm compared with 9.7% in the placebo arm (intention to treat [ITT]population: HR 0.81; 95% CI 0.65-1.00; modified intention to treat [mITT] population: HR 0.85; 95% CI 0.68-1.06). All-cause death was 2.5% in the rivaroxaban 2.5 mg arm compared with 4.3% in the placebo arm (ITT: HR 0.63; 95% CI 0.45-0.89; mITT: HR 0.60; 95% CI 0.41-0.87). These results show that in patients with recent STEMI, rivaroxaban reduced CV events.[24]

Stent thrombosis still represents a rare but often serious complication of PCI. The incidence of stent thrombosis with second generation drug-eluting stents is 1.0-2.5%[25] and in-hospital mortality is 2-9%, depending on whether stent thrombosis presents as unstable angina, non-STEMI or STEMI.[26] Approximately 1 in 5 survivors experience a recurrent stent thrombosis within 3 years.[27] The ATLAS ACS 2 TIMI 51 trial found that rivaroxaban significantly reduced stent thrombosis,[28] the combined data of both rivaroxaban doses in both strata showed an estimated cumulative incidence of 2.3% 24 months after randomisation compared with 2.9% in the placebo stratum (HR=0.69, relative risk reduction 31%; mITT: p=0.02; ITT: p=0.008). Rivaroxaban 2.5 mg bid stratum 2 showed a reduction in CV mortality in stented patients when compared with placebo, 1.35% versus 2.27% (HR 0.56; mITT: p=0.014; ITT: p=0.039).

In the ATLAS ACS 2 TIMI 51 study, a subgroup of patients with elevated cardiac biomarkers constituted 80% of the trial population therefore a subpopulation analysis was performed. The analysis of this subpopulation showed that 2.5 mg rivaroxaban was effective in patients with elevated biomarkers, without prior stroke or transient ischaemic attack, when compared with placebo (Table 1).[29]

The ATLAS ACS 2 TIMI 51 study demonstrates that rivaroxaban 2.5 mg bid plus standard antiplatelet therapy reduced CV mortality by 34% (p=0.002) and all-cause mortality by 32% (p=0.002). The results showed that there was no increase in fatal bleeding or fatal intracranial haemorrhage ICH and similar findings were reported in patients with STEMI. Rivaroxaban 2.5 mg bid reduced stent thrombosis by 35% compared with antiplatelet therapy alone (p=0.02), in addition CV mortality was significantly reduced in stented patients. These results were confirmed in those patients with elevated biomarkers without prior stroke or transient ischaemic attack.[21,30]

There is a clear rationale for targeting both platelet activation and thrombin generation in patients with ACS. The ATLAS ACS 2 TIMI 51 data indicated the rivaroxaban 2.5 mg bid combined with dual antiplatelet therapy significantly reduces mortality and stent thrombosis in patients with ACS. Selecting the right patient is critical; patients with high ischaemic risk but a low risk of bleeding will benefit most from this combined anticoagulant-antiplatelet therapy. Future studies with rivaroxaban will provide the basis for expanding the use of this combined strategy to other patient groups.

Parameter	2.5 mg N=4104 n (%)	Placebo N=4160 n (%)	HR (95%CI)	Log-rank p-value
Primary	256 (6.2)	327 (7.9)	0.80 (0.68, 0.94)	0.007
CV Death	68 (1.7)	127 (3.1)	0.55 (0.41, 0.74)	<0.001
MI	176 (4.3)	204 (4.9)	0.88 (0.72, 1.08)	0.215
Stroke	35 (0.9)	29 (0.7)	1.23 (0.75, 2.02)	0.403

CI=Confidence Interval; CV=Cardiovascular; HR=Hazard Ratio; MI=Myocardial Infarction; N=Total patient population; n=Number of patients

Table 1. Efficacy of rivaroxaban in patients with elevated cardiac biomarkers.

Translating Survival Benefit into Clinical Practice in Patients Following Acute Coronary Syndrome (ACS): Choosing the Right Patient

Robert Welsh

Integrating scientific advances into clinical practice – a case history

A 65-year old female patient with known multi-vessel coronary disease and Acute Coronary Syndromes presented at 7.30 am with sudden occurrence of crushing chest pain. The patient did not respond to nitroglycerin and reported that she had experienced intermittent chest pressure following significant exertion for the past 4 months (intermittent angina).

The patient's medical history included a non-ST elevation myocardial infarction (NSTEMI) 9 years ago with three coronary artery bypass grafts (CABGs) and 5 years ago the patient experienced a STEMI leading to a stent implantation with a drug-eluting stent (DES) in the left circumflex artery (LCX). In addition the patient had controlled hypertension, diabetes mellitus and hypercholesterolaemia. There was no prior documented history of cerebral vascular or peripheral vascular disease.

On physical examination the patient was moderately obese (BMI 30 kg/m^2) with vital signs within normal range (blood pressure 136/88, heart rate 86, respiratory rate 16 and oxygen saturation 96%). On clinical examination the patient did not appear to be in heart failure (jugular venous pressure 4 cm above sternal angle, heart sounds normal and normal respiratory examination). The electrocardiogram (ECG) showed normal sinus rhythm with ST elevation in the inferior leads greater than 3 mm in II, III and AVF; creatinine clearance was 72 ml/min and haemoglobin was within normal range.

This patient was diagnosed with an inferior wall STEMI and taken for immediate cardiac catheterisation with the intent of primary PCI. The angiographic findings showed severe proximal right coronary artery stenosis with a visible thrombus and an occluded vein graph to the distal right coronary artery. The previous stent in the LCX was patent with 50% in-stent stenosis. Compared with a coronary angiogram performed 5 years previously, the patient showed significant overall moderate disease progression comprising left ventricular ejection fraction of 45% and inferior hypokinesis, consistent with the presentation.

The acute treatment the patient received was very typical; aspirin (ASA), clopidogrel and heparin and primary PCI with a DES implantation in the proximal right coronary artery with a good angiographic result.

This patient is high-risk with previous ACS events, multi-vessel coronary disease with moderate in-stent restenosis and multiple co-morbidities including diabetes mellitus. In this situation it is difficult to

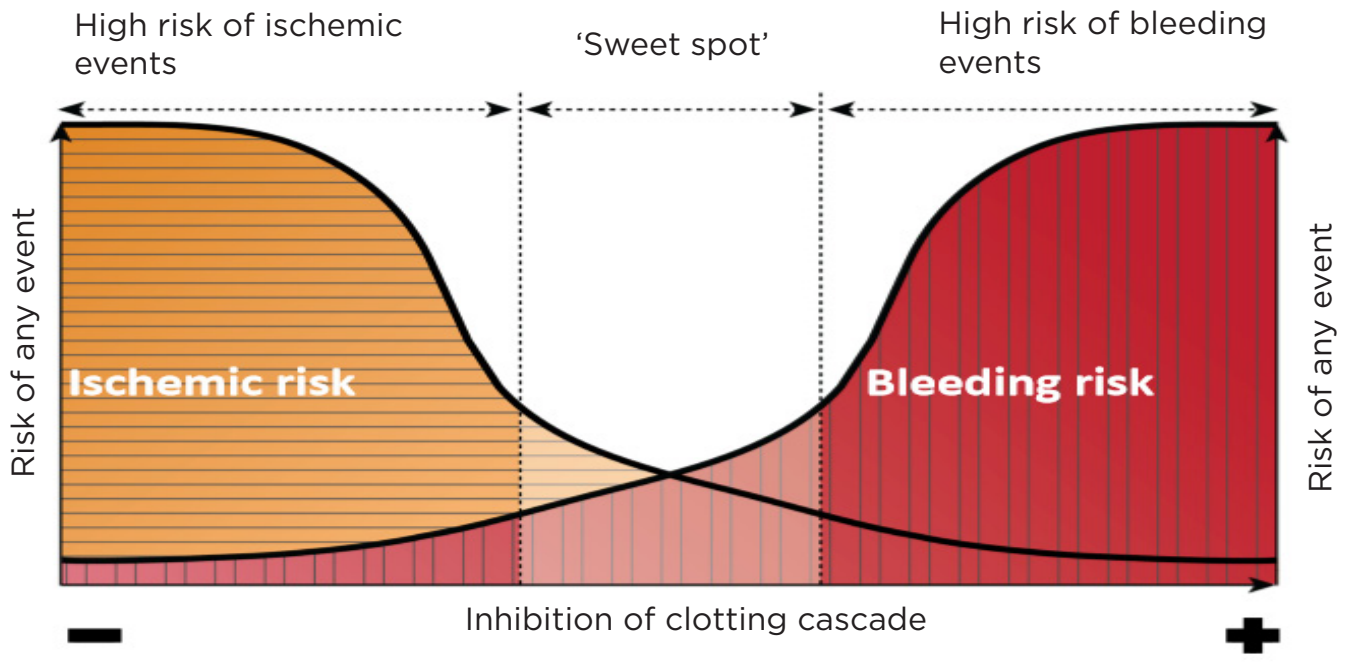


Figure 5. Balancing safety and efficacy.

predict which vessel may cause a recurrent event; it could be the current culprit or other lesions. In these circumstances clinicians must maximize evidence based care to minimize the patient's risk of future events. The best strategy for treatment requires assessment of both ischemic risk and potential bleeding risk and should take into consideration the new antiplatelet and antithrombotic agents (Figure 5).[31] This specific patient has an obvious high-risk of recurrent ischemic events but does not have features suggestive of increased bleeding risk.

Figure 5 outlines a theoretical model, but the clinician has a dilemma balancing ischaemic and bleeding risks, in addition the therapeutic 'sweet spot' is not easy to identify in clinical practice. In many clinical situations balancing an individual patients risk is challenging. The unfortunate reality is that for a clinician many of the things that predict bleeding are exactly the same variables that predict ischaemic risk.[32] For example, presenting with an elevated heart rate, high systolic blood pressure, poor kidney function or heart failure all predict an increased risk of bleeding (CRUSADE)[33] and an increased ischaemic risk (GRACE)[34] this poses a challenge for treatment.

The ATLAS ACS 2 TIMI 51 trial[21,28] showed that rivaroxaban 2.5 mg bid in conjunction with standard antiplatelet therapy had a 16% reduction in the composite endpoint of cardiovascular (CV) death, MI and stroke (p=0.002). There was a 34% reduction in CV mortality, 32% reduction in all-cause mortality and a 35% reduction in-stent thrombosis (p=0.002).[28] These benefits were associated with an increase in non-CABG-related thrombolysis in myocardial infarction (TIMI) major bleeding (hazard ration (HR): 3.46; p<0.001) but no increase in fatal bleeding or fatal intracranial haemorrhage.

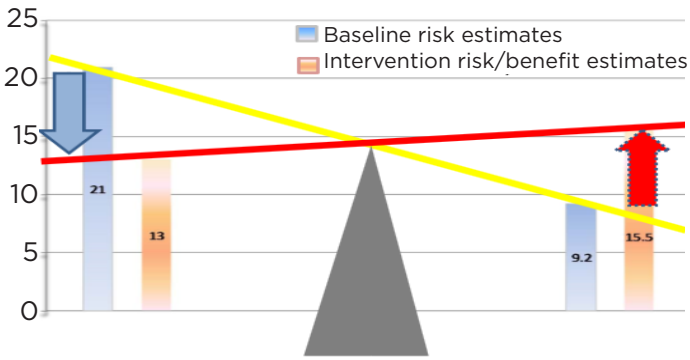


Figure 6. Blancing ischaemic and bleeding risks.

Many clinicians and researchers have stressed the importance of mortality reduction in clinical trials before novel therapy is incorporated into current clinical practice. The ATLAS trial shows a very impressive mortality reduction of over 30% in both CV death and all-cause mortality. Although there is continued debate about how to incorporate new therapies, this mortality reduction mandates consideration of this add on therapy for secondary prevention in ACS. When analysing a clinical trial of novel therapies, the scientific approach is to evaluate the overall trial results and assess major subgroups to identify consistent results with restraint regarding over interpretation of subgroup results. However, with an add-on therapy with an associated bleeding risk, clinicians need to judiciously implement therapy to maximize benefit and manage risk. Within the ATLAS study; the subgroup of patients with prior ischaemic stroke or transient ischaemic attack had a compelling signal of increased risk and represent a group where this therapy would not be considered.

Gibson et al. (2012)[30] evaluated fatal irreversible ischaemic events (non-bleeding CV death, MI), ischaemic stroke and fatal irreversible haemorrhagic events (fatal bleeding or ICH). Low dose (2.5.mg bid) rivaroxaban showed a significant reduction in ischaemic events; 105 (95% CI6-204) fatal or irreversible events were prevented per 10, 000 patient years versus placebo. There was a small increase in fatal bleeding and ICH (10 events per 10,000 patient years versus placebo). Nonetheless rivaroxaban shows favourable results, this is shown by the number needed to treat (87 subjects [patient-years] to prevent 1 fatal/irreversible ischaemic event) compared with the number needed to harm (984 subjects [patient-years] to cause 1 fatal/irreversible harm event). To put these results in perspective the number of irreversible ischaemic events occurs approximately 200 times more frequently than the irreversible bleeding events, which is a compelling reason to at least consider new therapies.

The European Society of Cardiology (ESC) 2012 STEMI guidelines[15] recommendation for the use of rivaroxaban following STEMI: 'In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk (Class IIb Level C)' This is the first step in understanding how to use this therapy. However, the clinician's dilemma of understanding the balancing of bleeding and ischaemic risk remains. In addition to formal risk

scoring discussed early, there are some predictable indicators for bleeding (low haemoglobin, prior vascular disease, diabetes, female sex) and ischaemic risk (cardiac arrest on admission, advanced age, ST-segment deviation and elevated biomarkers). The GRACE registry further informs predictors of major bleeding with a past history of bleeding as one of the principal predictors of subsequent major bleeding. If a patient has had a major bleed in the past it appears logical to exclude the patient from this new add-on therapy. Furthermore, we must acknowledge that many of the excess bleeding risks are caused by treatment to reduce ischaemic risk. Thrombolysis, intravenous or subcutaneous anticoagulant therapy, glycoprotein IIb/IIIA blockers and inotropic agents used early in the course of hospitalization with ACS are all associated with increased bleeding risk. Due to the fact that rivaroxaban is added following medical stabilisation and revascularisation many of these inotrogenic bleeding risks have past. The risk/benefit balance is to decide when to intensify therapy to obtain the best results.

The Committee for Medicinal Products for Human Use (CHMP) issued an opinion on rivaroxaban use in patients with ACS on 21st March 2013.[35] CHMP recommended the use of rivaroxaban 2.5 mg bid following ACS in patients with elevated cardiac biomarkers for the prevention of atherothrombotic events, and that rivaroxaban should be co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine in these patients. This opinion is supported by a retrospective analysis assessing outcomes in the majority of the trial population with exclusion of those with prior stroke or TIA and those without elevated biomarkers. The analysis of this group which represent approximately 80% of the trial study population showed a favourable net clinical benefit in the efficacy and safety profile with the 2.5 mg dose (Table 2).[36] These results indicate that this sub-population of patients will benefit the most from rivaroxaban treatment.

As clinicians patient predictors for recurrent ischaemic events and stent thrombosis using the GRACE[34] risk score includes parameters such as age, diabetes, prior MI, prior PCI and smoking status. Additionally there are important procedural variables during PCI which include baseline TIMI flow 0/1 and final TIMI flow <3, which is typically in a STEMI situation.[37] Likewise poor angiographic outcomes post PCI has been related to an increased risk of stent thrombosis. These predictors are important in assessing which patient will get the greatest benefit from rivaroxaban therapy.

Finally when initiating therapy it should be acknowledged that the treatment effect has been shown to remain constant over the entire treatment period.[29] Long term therapy should be considered once a commitment is made to using rivaroxaban whilst continuing to re-assess the risk of individual patients for bleeding.

For instance, the case history patient presents a 65-year-old female patient with high risk features,

	Subgroup	Primary Composite Endpoint (CV death/MI/ Stroke)	CV death	Net Clinical Benefit ** Efficacy: non-bleed CV death, MI, ischemic stroke events prevented; Safety: Fatal Bleeding, symptomatic ICH
1	Overall ATLAS ACS 2 TIMI 51 Study Population	HR 0.84 CI: 0.72– 0.97 (ARR: 1.6%) NNT: 63	HR 0.66 CI: 0.51– 0.86 (ARR: 1.4%) NNT: 71	Efficacy: -125 Safety: +10
2	Excluding Prior Stroke/TIA	HR 0.81, CI: 0.69–0.94 (ARR: 1.8%) NNT: 56	HR 0.63, CI: 0.48–0.82 (ARR: 1.5%) NNT: 67	Efficacy: -143 Safety: +8
3	**Targeted population with Elevated Biomarkers, Excluding prior Stroke/TIA**	**HR 0.80, CI: 0.68–0.94 (ARR: 2.1%) NNT: 48**	**HR 0.55 CI: 0.41–0.74 (ARR: 2.0 %) NNT: 50**	**Efficacy: -159 Safety: +3**

ARR=absolute risk reduction based on 2-year KM estimates; NNT=number needed to treat
** Excess number of events in 10,000 patient years .

Table 2. ATLAS ACS 2 TIMI 51: Rivaroxaban in patients with ACS and elevated cardiac biomarkers.

including prior ACS, CABG, and PCI, who presented with on-going chest pain, and has both ST deviation with an inferior wall STEMI and positive biomarkers. Although patient's features for bleeding risk were considered to be relatively neutral, the CRUSADE bleeding score was 6.5% (low risk), but the GRACE risk score was much higher with a 4% risk of in-hospital mortality and 31% risk of death or repeat MI at 6 months, therefore this was a high ischaemic risk patient. Therefore, this patient was deemed 'attractive' for intensified secondary prevention treatment with an add on treatment such as rivaroxaban.

In conclusion, the ATLAS ACS 2 TIMI 51 trial demonstrated rivaroxaban had a consistent efficacy benefit across all major subgroups but at the cost of increased risk of bleeding. Clinicians should carefully consider benefit and risk when selecting appropriate patients. Patients at a high risk of recurrent ischaemic events with low to moderate bleeding risk are most likely to benefit from rivaroxaban therapy. This concept has recently been adopted by CHMP giving a positive opinion for rivaroxaban use following ACS in patients with elevated cardiac biomarkers. Compared with the overall trial population, rivaroxaban demonstrated greater benefit and enhanced safety in these patients.

Rivaroxaban: Proven Experience and New Clinical Activities

Christoph Bode

Overall, 41, 000 patients have been analysed in four large studies[21,38-40] of cardiovascular (CV) prevention in patients with atrial fibrillation (AF) and acute coronary syndrome (ACS) using rivaroxaban therapy. This demonstrates impressive experience in terms of the safety profile of rivaroxaban (Figure 8).

The use of rivaroxaban in the prevention of stroke in patients with atrial fibrillation was evaluated in the ROCKET AF trial.[38] The per-protocol on treatment analysis showed that rivaroxaban was superior to warfarin (Figure 8) with a cumulative event rate per year of 1.7% in the rivaroxaban group compared with 2.2% in the warfarin group (hazard ratio [HR] 0.79;95% confidence interval [CI] 0.66-0.96; p<0.001 [non-inferiority]).

The ATLAS trial[39] showed that rivaroxaban therapy in secondary prevention after ACS reduced all-cause mortality by 1.8% over a period of 2 years.

These two trials with different indications showed encouraging results; rivaroxaban appears to be the only drug that has shown effective results in AF and ACS treatment. The problem is how to treat

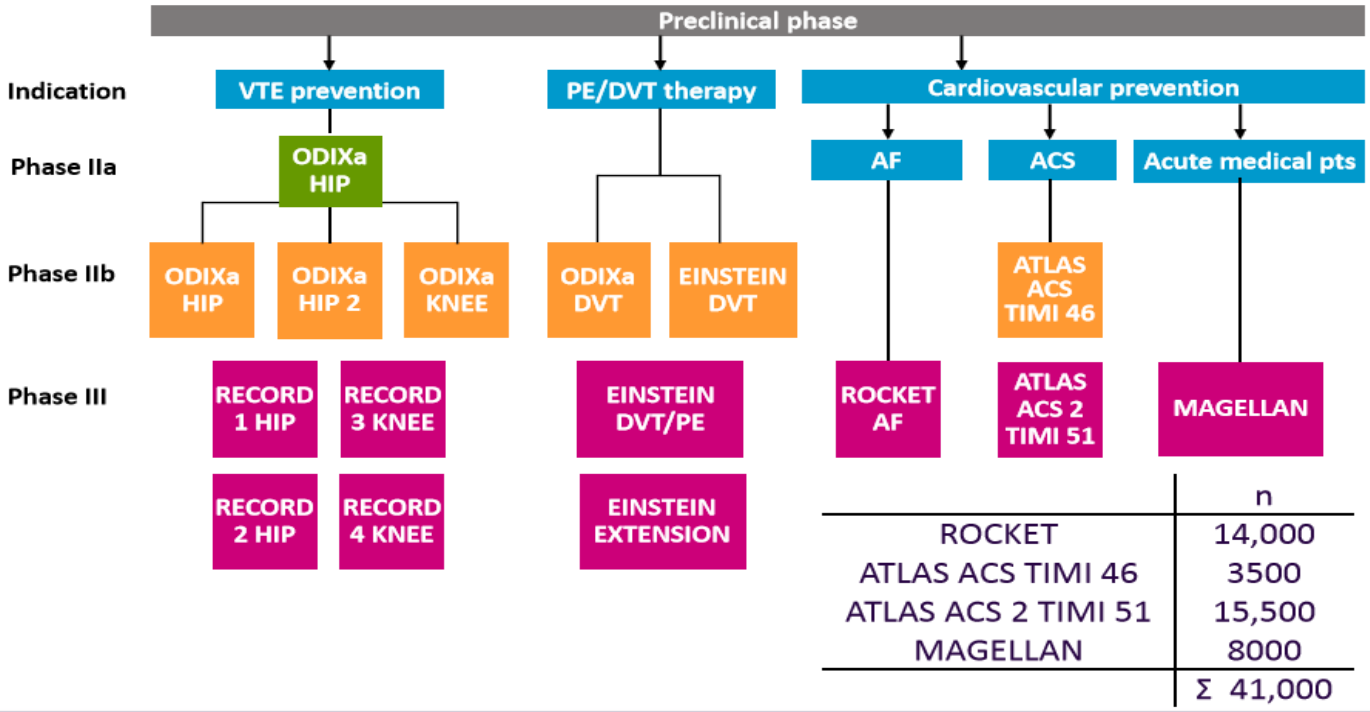
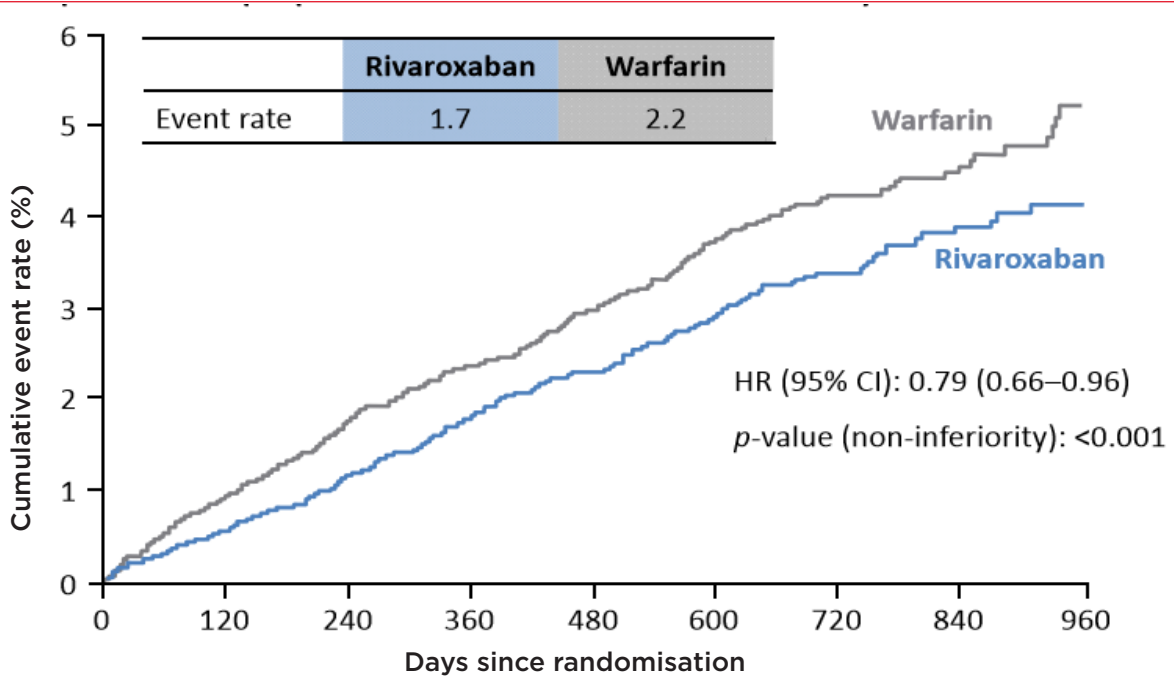


Figure 7: Rivaroxaban: Study Experience.



Event rates are % per year.
CI=confidence interval; HR=hazard ratio

Figure 8. Per-protocol population analysis of rivaroxaban and warfarin.

'overlapping' patients with both AF and ACS. This dilemma exists because two different doses of rivaroxaban were trialled in the ROCKET AF and ATLAS trials. In the ROCKET AF trial a large dose was used (20 mg once a day), and in the ATLAS trial a smaller dose was used (2.5 mg twice daily [bid]). This provides two different populations, two different dosages but the same drug and until now the only drug that has performed well in both indications.

Data suggest that dabigatran therapy may increase the risk of MI; a meta-analysis evaluated the risk of myocardial infarction in seven trials.[41] Overall, an increased risk of myocardial infarction (MI) was shown, even though cumulative data from six of the seven trials showed that mortality was reduced by 0.19%.

In addition, a phase III study of apixaban failed to demonstrate a favourable benefit/risk profile in patients with ACS[42] the study showed that apixaban increased bleeding by at least 2-fold and did not reduce the ischaemic endpoint.

The European Society for Cardiology guidelines suggest that patients with AF who have ACS and/or percutaneous coronary intervention (PCI) with stenting are recommended oral anticoagulant therapy with single or dual antiplatelet therapy in the short term.[43,44]

The results of the previous rivaroxaban trials have encouraged new clinical investigations. The PIONEER AF-PCI study[45] was an exploratory study; the objective was to assess the safety of two rivaroxaban treatment strategies and a dose-adjusted vitamin K antagonist (VKA) treatment after PCI (with stent placement) in subjects with non-valvular AF.[45] The study population comprised 2,100 patients with AF who had undergone PCI. The patients were randomised to three arms. The first arm: treatment with VKA and a P2Y12 inhibitor (clopidogrel 75 mg daily, alternatively prasugrel 10 mg daily or tricagrelor 90 mg bid capped at 15%) for 12 months or if the patients International Normalised Ratio (INR) was 2.0-3.0, VKA plus aspirin plus P2Y12 inhibitor for 1 or 6 months as decided by the investigator. The second arm: treatment with rivaroxaban 2.5 mg bid plus aspirin plus P2Y12 inhibitor for 12 months or 2.5 mg bid plus aspirin plus P2Y12 inhibitor for 1 or 6 months. The third arm: treatment with rivaroxaban 15 mg daily plus P2Y12 inhibitor for 12 months. The primary endpoint of the study was the composite of thrombolysis in myocardial infarction (TIMI), major bleeding, minor bleeding and bleeding requiring medical attention. The secondary endpoints were events of CV death, MI or stroke. The study has provided useful information regarding the difficulties that arise when deciding the most appropriate course of treatment, this included whether one antiplatelet agent can be dropped from the treatment regimen,

if low dose rivaroxaban plus double antiplatelet therapy is enough to prevent a stroke and indicated the bleeding risk with the new antiplatelet agents in combination with different dosages of rivaroxaban. However there were no definitive conclusions because the study was only powered for safety.

The WOEST trial evaluated clopidogrel plus VKA (double therapy) versus clopidogrel plus VKA plus aspirin (ASA) (triple therapy) in patients undergoing PCI.[46] The double therapy resulted in similar efficacy benefits, significantly less bleeding and significantly less mortality compared with triple therapy.

PIONEER AF-PCI will further evaluate the role of ASA.[45] The ATLAS ACS 2 TIMI 51 trial was initiated prior to the availability of prasugrel and ticagrelor[21] therefore their use was not permitted in the trial. For this reason, limited prasugrel or tricagrelor use with rivaroxaban 2.5 mg bid or 15 mg daily will be evaluated in PIONEER AF-PCI as alternatives to clopidogrel capped at 15% of the study population.

The COMPASS study[47] involves the treatment of patients with coronary artery disease (CAD) and peripheral artery disease (PAD). CAD is the most common cause of cardiovascular disease (CVD) and PAD is a risk marker. Globally CVD is a major cause of death.[48] The questions that have been raised are; if the marker is treated, is CAD being treated? Is coronary death being prevented if patients with overt PAD are treated? The COMPASS study will investigate these issues. The objective of the study is to evaluate the efficacy and safety of rivaroxaban alone compared with low-dose rivaroxaban plus ASA or ASA alone in reducing the risk of MI, stroke or CV death in patients with a history of CAD or PAD.[46]

The COMMANDER-HF trial proposes to study rivaroxaban in patients with heart failure. Heart failure is a prothrombotic disease and it has been suggested that subjects with heart failure have higher circulating levels of pro-coagulants.[49] Approximately 70% of patients with heart failure have known significant CAD with sudden death being a major cause of mortality.[50] Studies have shown that patients with heart failure who died suddenly had high rates of MI or acute coronary events.[51] Overall, approximately half of all patients with heart failure die within 4 years of diagnosis[52] therefore heart failure has a very poor prognosis. COMMANDER-HF will assess the safety and efficacy of 2.5 mg of rivaroxaban twice daily versus placebo in patients with chronic heart failure and significant CAD following hospitalisation.[53] The primary efficacy outcome of the trial is the composite of all-cause mortality, MI or stroke, and the principal safety outcome is the composite of fatal bleeding or bleeding into a critical space with the potential of permanent disability. The patient population consists of 5,000 patients who will receive rivaroxaban 2.5 mg or placebo in addition to standard care.

The new trials for rivaroxaban are built on the strong foundation of the COMPASS and COMMANDER trials and the use of rivaroxaban in PAD and heart failure. The trials will incorporate a study expert for patients that undergo cardioversion and ablation and for those patients who have AF and a stent placed, this will expand the rivaroxaban programme substantially.

Rivaroxaban has been developed through a very large and rational trial programme built on comprehensive phase II dose finding studies. ATLAS 1 is the key to the success of ATLAS 2. 3,500 patients were studied in ATLAS 1 to find the correct dose. ATLAS 2 randomly assigned 15,526 patients to receive either 2.5 mg or 5 mg bid of rivaroxaban or placebo. The results showed that the 2.5 mg bid dose resulted in fewer fatal bleeding events than the 5 mg bid dose (0.1% versus 0.4%, p=0.04).[21] Having completed trials in patients with AF and ACS, rivaroxaban is uniquely placed to answer some of the outstanding key questions in cardiology. By the time these new studies are completed more than 100,000 patients will have participated globally in the trial programme. This will provide a significant evidence base, especially in terms of the safety of rivaroxaban, and considerably expand our knowledge in treating this group of patients.

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