REVIEW ARTICLE

Rivaroxaban: One For All, All For One

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Abstract
For the past 10 years, the introduction of rivaroxaban in clinical practice has produced dramatic changes in lives of patients affected by thrombotic disorders. Rivaroxaban exerts an effective anticoagulant action with no need for a routine monitoring of coagulation tests. Rivaroxaban can be safely used in a wide range of situations, such as moderate chronic kidney disease, whereas it should be avoided in patients with chronic hepatic diseases associated with coagulopathy and clinically significant bleeding risk. Also, the physician should be aware that some drugs frequently prescribed to patients taking anticoagulants (such as dronedarone) should not be given together with rivaroxaban because of the risk of pharmacokinetic and/or pharmacodynamic interactions. Rivaroxaban represents a very useful therapeutic option, which showed superior efficacy and equal safety to low-molecular-weight heparin (LMWH) for venous thromboembolism (VTE) prevention in orthopaedic surgery. Further, it proved non-inferior to the combination of heparin and vitamin K antagonists (VKAs) for deep vein thrombosis (DVT) and pulmonary embolism (PE) treatment as well as to warfarin for stroke prevention in non-valvular atrial fibrillation (AF). Even patients undergoing AF cardioversion or ablation may benefit of rivaroxaban's ease of use. Atherosclerotic cardiovascular disease represents the most recent field in which rivaroxaban proved effective, both after an acute coronary syndrome (ACS) and in patients with chronic coronary artery or peripheral artery disease. Even though it is highly likely that in future years we will go in the direction of personalization of antithrombotic therapies, nowadays the huge amount of evidence with rivaroxaban may represent a simple answer to many complex clinical questions.

Keywords: rivaroxaban, direct oral anticoagulants, warfarin, vitamin K antagonists, deep vein thrombosis, pulmonary embolism, venous thromboembolism, cancer, non-valvular atrial fibrillation, cardioversion, ablation, coronary artery disease, acute coronary syndrome.

Abbreviations and Acronyms: ACS: Acute Coronary Syndrome; ACT: Activated Clotting, Coagulation, Time AF: Atrial Fibrillation; aPTT: activated Partial Thromboplastin Time; BID: Bis In Die, twice a day; CAD: Coronary Artery Disease; CI: Confidence Interval; CYPs: Cytochromes P450; DAPT: Dual Antiplatelet Therapy; DOAC: Direct Oral Anticoagulant; DVT: Deep Vein Thrombosis; eGFR: estimated Glomerular Filtration Rate; FXa: Factor X activated; HR: Hazard Ratio; INR: International Normalized Ratio; LMWH: Low-Molecular-Weight Heparin; PAD: peripheral artery disease; PE: Pulmonary Embolism; P-glycoprotein: Permeability glycoprotein; PT: Prothrombin Time; aPTT: activated Partial Thromboplastin Time; QD: Quaque Die, semel in die, once a day; TEE: Transesophageal Echocardiography; THA: Total Hip Arthroplasty; TKA: Total Knee Arthroplasty; VKA: Vitamin K Antagonist; VTE: Venous Thrombo-Embolism.

1. Introduction

Factor X activated (FXa) plays a pivotal role in the coagulation cascade since it mediates the production of thrombin by acting on prothrombin.[i] Thrombin, in turn, determines the formation of the fibrin clot.

Starting from observations on people with genetic FXa deficiency,[ii] it was very early recognized that this coagulation factor could be a very convenient target for a drug which would produce an antithrombotic effect while at the same time avoiding excessive bleedings.

At first, the indirect parenteral FXa inhibitor fondaparinux was developed. Then, starting in 1998 at Bayer HealthCare, a long process of research on pharmacokinetics and structure-activity relationships led to the production of rivaroxaban, a highly potent orally available direct FXa inhibitor.[iii]

Nowadays, rivaroxaban is approved for the treatment of many diseases. In this review, we discuss rivaroxaban's pharmacokinetic properties and the expanding clinical scenarios in which it can be used.

2. Rivaroxaban's clinical pharmacokinetics

Rivaroxaban is rapidly absorbed from the gastrointestinal tract.[iv] When rivaroxaban is given at a 15 or 20 mg dose, its bioavailability is highly augmented by coadministration with food, passing from 66% to 100%. This observation is not valid for lower doses of the drug. Interestingly, rivaroxaban's bioavailability is preserved even when it is crushed and administered via a nasogastric tube, thus representing a useful option for patients unable to swallow.

After absorption, rivaroxaban distributes widely to tissues, crossing the placental barrier to a moderate degree in rat studies. It is secreted in milk but it doesn't pass the blood-brain barrier. In plasma, the drug is highly bound to proteins, mainly albumin.

Rivaroxaban's half-life depends on patients' age: in young healthy subjects, it is 5-9 hours,[v] whereas it is 11-13 hours in elderly people.[vi]

Approximately 1/3 of a drug dose is eliminated unchanged by the kidney; 83% of this amount is eliminated by tubular secretion operated by P-glycoproteins and breast cancer related proteins (BCRP). P-glycoproteins are also involved in a secretion process from small-intestinal epithelial cells into the gut lumen. Therefore, P-glycoproteins represent an important interactions' determinant.

Almost 2/3 of a drug dose is subjected to metabolic conversion, mainly by hepatic cytochromes P450 (CYPs), among which CYP3A4 plays a major role. Rivaroxaban's metabolites are then eliminated by hepatobiliary and urinary routes.

Therefore, rivaroxaban should be avoided for an eGFR < 15 ml/min and should be used with caution with an eGFR of 15-29 ml/min. Also, rivaroxaban should not be used in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including Child-Pugh B and C cirrhosis.[vii]

Even though rivaroxaban has less potential interactions than the old vitamin K antagonists (VKAs), the clinician must pay particular attention to poli-pharmacy issues, which are becoming increasingly common in the elderly population taking anticoagulants.

As compared to other direct oral anticoagulants (DOACs), rivaroxaban doesn't have any significant interactions with verapamil or diltiazem and has a minor interaction with amiodarone. On the other hand, potential interactions with dronedarone, which is both a P-glycoprotein and a CYP3A4 inhibitor, could lead to increased drug levels and demand carefulness; coadministration is not recommended.

Potent metabolic inducers may lead to reduced drug levels. Thus, coadministration of rifampicin or even St. John's wort (Hypericum perforatum) is contraindicated.

Rivaroxaban and the other DOACs have the great advantage of not requiring any routine laboratory monitoring to ensure optimal anticoagulant activity and also have a wider therapeutic window when compared to VKAs. However, in emergency situations, such as in

case of bleeding or thrombotic events, need for urgent surgery, renal/hepatic insufficiency, extreme weights or coadministration with interacting drugs, a laboratory assessment of anticoagulant effect may be useful.

The activated partial thromboplastin time (aPTT) test does not give any meaningful information in patients treated with rivaroxaban, whereas the prothrombin time (PT) test is prolonged by this drug in a dose-related fashion. Nevertheless, the sensitivity of different PT reagents varies widely, and the correction of PT to international normalized ratio (INR) even increases this variability.[viii] Therefore, the INR is an unreliable indicator of anticoagulation for rivaroxaban. Rivaroxaban has a small dose-dependent effect on the ACT; however, this test does not give any reliable information on the anticoagulation status.

The anti-FXa "chromogenic assays" may be used to directly measure rivaroxaban's plasma concentrations using validated calibrators. Even though these tests may prove useful in exceptional cases, as pointed out before, their routine use in discouraged because of no evidence from clinical studies.

3. DVT prevention

3.1 Orthopaedic surgery

Deep vein thrombosis (DVT) prevention was one of the first common clinical scenarios in which Rivaroxaban was tested. Specifically, it was studied in the phase III programme RECORD (REgulation of Coagulation in ORthopaedic surgery to prevent Deep venous thrombosis and pulmonary embolism), which comprised 4 large studies including more than 12,500 patients. This programme definitely established the role of rivaroxaban 10 mg QD as an efficacious way to prevent DVT in patients undergoing total hip or knee arthroplasty (THA or TKA, respectively). In all of the studies, the primary efficacy endpoint was the composite of DVT, non-fatal pulmonary embolism (PE) and all-cause mortality and the main secondary efficacy endpoint was major venous thromboembolism (the composite of proximal DVT, non-fatal PE and all-cause mortality), whereas the primary safety endpoint was major bleeding. The four studies differed in the duration of treatment (see **table 1**) and in the comparator.

In both the RECORD1[ix] and the RECORD2[x] studies, THA candidates were randomized to oral rivaroxaban 10 mg QD (started 6-8 hours after wound closure) or subcutaneously injected enoxaparin 40 mg QD (started 12 hours before surgery and restarted 6 to 8 hours after wound closure). The study treatment with rivaroxaban was maintained for 35 days (range, 31 to 39). The 2 studies differed in the duration of the enoxaparin regimen, which was 31 to 39 days in the RECORD1 but only 10-14 days in the RECORD2.

On the day after the last dose of the study drug (day 32-40), patients underwent bilateral venography. Rivaroxaban proved superior to enoxaparin, both for the primary outcome and for the the main secondary efficacy endpoint in RECORD1 as well as in RECORD2. Moreover, rivaroxaban proved equally safe as enoxaparin.

Thus, these 2 trials proved that rivaroxaban is more effective than enoxaparin for venous thromboembolism (VTE) prevention in THA candidates and that an extended thromboprophylaxis (5 weeks) is more effective than a short-term (10-14 days) enoxaparin regimen, confirming previous trials and meta-analyses of short vs long term thromboprophylaxis.[xixii] Further, these benefits were obtained with no significant increase in major bleedings.

The RECORD3[xiii] and the RECORD4[xiv] studies included TKA candidates which were randomized to rivaroxaban 10 mg QD or enoxaparin. In RECORD3, the 2 drugs starting times were the same as in the RECORD1 or 2 trials, whereas in RECORD4 enoxaparin was started 12-24 hours after wound closure. In both RECORD3 and RECORD4, the study drugs were maintained for 10 to 14 days. These 2 studies differed for the enoxaparin regimen: in RECORD3, enoxaparin was given at a 40 mg QD dose, whereas in RECORD4 it was given at

a 30 mg BID dose, a regimen specifically approved in North America for the prevention of VTE after TKA. Patients underwent a bilateral venography to assess DVTs between day 11 and day 15. Again, rivaroxaban proved more effective than enoxaparin for the primary efficacy endpoint, with similar major bleeding rates. Also, rivaroxaban resulted superior to enoxaparin for major VTE (the main secondary efficacy endpoint) in RECORD3 but only non-inferior in RECORD4.

Thus, rivaroxaban is the only DOAC which proved non-inferior (and even superior) to enoxaparin 30 mg BID for thromboprophylaxis after TKA.

Table 1: DVT prevention in orthopaedic surgery trials overview

Study	Type of surgery	Number of patients	Treatment in experimental group	Treatment in control group	Day of venography	Primary efficacy endpoint for rivaroxaban vs control in the intention to treat population	Primary safety endpoint for rivaroxaban vs control
RECORD1[9]	THA	3029 (per protocol population), 3153 (modified intention to treat population).	Rivaroxaban 10 mg QD for 31-39 days	Enoxaparin 40 mg QD for 31-39 days	32-40	1.1% vs 3.7% (95% CI, 1.5 to 3.7; P<0.001)	0.3% vs 0.1%
RECORD2[10]	THA	1733 (modified intention to treat population)	Rivaroxaban 10 mg QD for 31-39 days	Enoxaparin 40 mg QD for 10-14 days	32-40	2% vs 9.3% (95% CI, 5·2 to 9·4; p<0·0001)	0.01% vs 0.01%
RECORD3[13]	TKA	1702 (modified intention to treat population)	Rivaroxaban 10 mg QD for 10-14 days	Enoxaparin 40 mg QD for 10-14 days	11-15	9.6% vs 18.9% (95% CI, 5.9 to 12.4; P<0.001)	0.6% vs 0.5%
RECORD4[14]	TKA	1742 (per protocol population), 1924 (modified intention to treat population)	Rivaroxaban 10 mg QD for 10-14 days	Enoxaparin 30 mg BID for 10-14 days	11-15	6.9% vs 10.1% (95% CI 0·71 to 5·67; p=0·0118)	0.7% vs 0.3% (95% CI 0·09 to 0·88; p=0·1096)

3.2 Medically ill patients

A different setting in which thromboprophylaxis with rivaroxaban was evaluated pertains to patients suffering an acute medical illness, such as stroke, myocardial infarction or active cancer. Parenteral anticoagulants proved effective in clinical trials when administered up to 14 days in this population.[xvxvixviixviiixix] Given that thromboembolic risk can persist even after hospital discharge, a randomized controlled trial was conducted in order to evaluate the effectiveness and safety of rivaroxaban for extended prophylaxis in medical patients, the MAGELLAN (Multicenter, rAndomized, parallel Group Efficacy and safety study for the prevention of VTE in hospitalized medically iLL patients comparing rivaroxabAN with enoxaparin) study.[xx]

In this trial, Rivaroxaban 10 mg QD for 35 days was compared to enoxaparin 40 mg QD for 10 days. The population in study included 8,101 subjects 40 years of age or older who had been hospitalized for a specified medical illness less than 72 hours before randomization and had reduced mobility. There were 2 coprimary efficacy endpoints: a composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE or death related to VTE from day 1 to day 10 (day 10 analysis), and this same composite outcome from day 1 to 35 (day 35 analysis). The former analysis was prespecified to be a noninferiority analysis whereas the second one a superiority analysis. The main safety outcome was clinically relevant bleeding, a composite of major bleeding and clinically relevant nonmajor bleeding. Only about 7% of patients had active cancer and about 1 out of 3 had heart failure. In the day 10 analysis, rivaroxaban proved noninferior to enoxaparin, whereas in the day 35 analysis it proved superior for the primary outcome with a 23% relative risk reduction. However, the number of main safety events was higher with rivaroxaban, both at 10 and at 35 days. There was no net clinical benefit with rivaroxaban in this clinical context, a finding possibly attributable to the higher age of patients included as compared to the trials in orthopaedics. Therefore, rivaroxaban was not approved for this clinical indication.

More recently, rivaroxaban proved again disappointing for thromboprophylaxis in medically ill patients in the MARINER trial,[xxi] which differed in many respects from the MAGELLAN trial. In MARINER (Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolism Risk), rivaroxaban was given to patients recently hospitalized for 3 to 10 days for an acute medical illness, excluding cancer but including heart failure with reduced ejection fraction (HFrEF), acute respiratory insufficiency, stroke, infectious or inflammatory diseases, who were believed to be at a higher risk of VTE based on the IMPROVE (International Medical Prevention Registry On Venous Thromboembolism) risk score[xxii] and on D-dimer levels. Patients were randomized to rivaroxaban or placebo. 2 different rivaroxaban doses were given: 10 mg QD for patients with an eGFR ≥50 ml/min or 7.5 mg QD for patients with an eGFR < 50 ml/min and ≥30 ml/min. Randomization was performed on the day of the discharge or the day after, and treatment was started as soon as possible and no later than the next day and was maintained for 45 days; this duration of treatment was chosen because previous studies showed that 75% of post-hospital discharge VTE events occur within 45 days after discharge.[xxiii] The primary efficacy outcome was the composite of any symptomatic VTE or death related to VTE; the primary safety outcome was major bleeding. Rivaroxaban did not significantly reduce the primary outcome but proved as safe as placebo. An exploratory analysis showed that the number of VTE related death was not reduced in rivaroxaban group, whereas the number of symptomatic VTE events was.

Indeed, medically ill patients are at a high risk of VTE events, both during the hospitalization and after discharge; nonetheless, our ability to identify who is at the highest risk and the best

way to prevent VTE events in these patients will require further research.

4. VTE treatment

4.1 Acute and long term therapy

VTE comprises two very important clinical entities: DVT, which carries a 25% risk of recurrence in the first 6 to 12 months,[xxiv] and PE, which can be fatal.[xxv] These two conditions are frequently associated. For half a century and until 2010, the only treatment available for VTE was anticoagulation with VKAs.[xxvi] This therapy is limited by the need for an initial bridge with parenteral heparin and by an unpredictable anticoagulant effect, which must be monitored via the INR test. Moreover, VKAs suffer from multiple interactions with other drugs.

The efficacy and safety of rivaroxaban for patients with VTE was established in the EINSTEIN programme, which comprised 3 randomized trials: the Acute DVT study, the Acute PE study and the Continued Treatment Study.[xxviixxviii]

The first two studies were open label in design. They compared oral rivaroxaban (at a dose of 15 mg BID for 3 weeks, then 20 mg QD) with standard therapy, consisting of enoxaparin and a VKA (with enoxaparin given for at least 2 consecutive days after reaching an INR ≥ 2 and for a total of at least 5 days). The use of the 15 mg BID dose of rivaroxaban for the first 3 weeks was justified by the higher risk of recurrence in this period coupled with the evidence of higher trough drug levels and better thrombus resolution with this regimen in phase 2 studies.[xxixxxx]

Patients enrolled had acute symptomatic DVT (in the Acute DVT study) or PE (in the Acute PE study). Patients could not be included if they had been treated with fibrinolysis, vena cava filters or thrombectomy for the current VTE event. Another exclusion criterion regarded patients receiving parenteral anticoagulants for more than 48 hours or more than 1 dose of VKA. Further, the eGFR needed to be ≥30 ml/min. Treatment could be maintained for 3, 6 or 12 months at the discretion of the clinician.

The primary efficacy outcome in both studies was symptomatic recurrent VTE, defined as a composite of DVT or nonfatal or fatal PE. These events had to be ascertained by means of objective criteria (e.g., using CT scan, pulmonary angiography or lung scanning for PE and using US or venography for DVT). The main safety outcome was a composite of major and clinically relevant non-major bleedings.

Rivaroxaban proved non-inferior to the conventional treatment of heparin-VKA for both the primary efficacy outcome and the primary safety outcome. Further, in the Acute PE study, rivaroxaban was associated with significantly less major bleedings, a predefined secondary outcome. These results were confirmed in all major subgroups included in the trials, without raising any concerns inherent the use of a fixed dose of rivaroxaban.

These observations were confirmed and further expanded in a broader patient population in the prospective non-interventional XALIA (XA inhibition with rivaroxaban for Long-term and Initial Anticoagulation in venous thromboembolism) study,[xxxi] which was conducted after rivaroxaban's authorization for DVT treatment indication. The XALIA study included 5,142 patients with an objectively confirmed diagnosis of DVT and an indication for anticoagulation for at least 3 months. After rivaroxaban's approval for PE treatment, enrollment of patients with concomitant DVT and PE (but not with isolated PE) was enabled. The choice of the anticoagulant regimen was left at the discretion of treating physicians. Patients receiving rivaroxaban were younger and fewer had concomitant pulmonary embolism or cancer. Major bleedings were 59% less common with rivaroxaban as compared to standard anticoagulation (which included heparin, fondaparinux and/or VKA); further, in the rivaroxaban group there were less VTE recurrences (by 33%) and less deaths (by 74%). However, after taking into account baseline features by means of propensity scoring, there were no significant differences for major

bleedings, recurrent VTE or all-cause mortality between the 2 treatment groups.
Therefore, XALIA confirmed rivaroxaban's safety profile, with low bleeding and recurrent VTE rates, similar to those observed in EINSTEIN DVT, in a real-world setting of unselected patients.
These studies supported an epochal change in the management of VTE and especially PE, giving the clinician an opportunity to treat patients with low risk VTE with a fully oral treatment and with no need for injections, thus facilitating early home discharge.

4.2 Extended therapy

The optimal duration of antithrombotic therapy after a VTE episode remains a clinical dilemma. The physician must determine the risk/benefit ratio of an extended vs. a conventional antithrombotic treatment for each patient.
In the 10th Edition of the Chest antithrombotic guidelines for VTE,[xxxii] an extended anticoagulation regimen is recommended over a 3 months course after a first unprovoked proximal DVT or PE for patients at low-moderate bleeding risk. In case the patient is stopping the anticoagulant, aspirin is recommended over no aspirin, based on the results of 2 randomized trials in which low dose aspirin reduced the risk of recurrent VTE by 1/3 when administered after a 3-18 months anticoagulation regimen.[xxxiiixxxiv]
In this context, rivaroxaban has been evaluated in the Continued Treatment Study of the EINSTEIN programme and in the EINSTEIN CHOICE (Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism) trial.[xxxv]
Both trials were double blind and included patients who had been treated for an objectively confirmed VTE for 6 to 12 months with either a VKA or a NOAC. Patients were eligible if there was equipoise for prosecution of anticoagulation according to the treating physician.
One important limitation of both studies is that they did not include only patients with unprovoked VTE events, which comprised about 70% of the study population in the Continued Treatment Study but only about 40% in EINSTEIN CHOICE.
Again, severe CKD patients (e.g., patients with an eGFR < 30 ml/min) were excluded.
The 2 trials differed for the study treatments: in the Continued Treatment Study, patients were randomized to rivaroxaban 20 mg QD at a fixed dose or placebo; in EINSTEIN CHOICE, rivaroxaban 20 mg QD was compared to rivaroxaban 10 mg QD and to aspirin 100 mg QD. The treatment period lasted for a maximum of 12 months.
The primary efficacy outcome of recurrent symptomatic VTE was reduced by 82% in the Continued Treatment Study with few major bleedings and net clinical benefit favoring rivaroxaban. Readers' doubts fostered by the comparison against a placebo were further clarified by the results of EINSTEIN CHOICE.
In this more recent trial, both rivaroxaban 20 mg QD and rivaroxaban 10 mg QD proved superior to aspirin, with a relative reduction in the risk of recurrent symptomatic fatal or nonfatal VTE by 66 and 74%, respectively. The study was not powered to detect any significant difference between the 2 rivaroxaban doses. Major bleedings were rare (0.3-0.5%) and not significantly different among the different treatment groups.
Therefore, rivaroxaban proved more effective and as safe as low dose aspirin for the prevention of recurrent VTE, albeit the duration of the extended treatment was limited at 1 year in the trials. These findings deserve a critical attention given the high case fatality rate of recurrent PE.

4.3 VTE and cancer

VTE is a common complication of cancer and tends to recur at least twice as commonly when compared to patients with no cancer.[xxxvi]
Antithrombotic therapy in oncologic patients is further complicated by an increased bleeding risk and by multiple drug-drug interactions with

antineoplastic and support drugs.[xxxvii] For the past 15 years, the optimal treatment of VTE in cancer patients has been low-molecular-weight heparin (LMWH) for at least 6 months,[xxxviiixxxix] a therapeutic regimen which has the important limitation of requiring daily subcutaneous injections. Further, the optimal duration of anticoagulant therapy after the initial 6 months is still discussed, even though guidelines recommend that treatment continue as long as the cancer is active.[xl]

For this group of patients, for whom quality of life issues are fundamental, rivaroxaban may represent a very practical option because of its oral administration. In the EINSTEIN programme,[xli] only 5.5% of patients had active cancer at baseline and rivaroxaban's comparator was a VKA and not the gold standard of long-term LMWH. While not guidelines-recommended for cancer patients, rivaroxaban has been prescribed for this indication, and some real-world studies showed a reassuring efficacy and safety profile.

More recently, the SELECT-D (Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism) randomized open-label pilot study[xlii] was conducted in order to evaluate the role of rivaroxaban in cancer-associated VTE. The study was intended to evaluate VTE recurrence rate at 6 months in patients with active cancer after a symptomatic or incidental PE or a symptomatic lower-extremity proximal DVT. Patients were randomized to rivaroxaban (15 mg BID for 21 days and 20 mg QD for a total of 6 months) or dalteparin (200 IU/kg daily during month 1, then 150 IU/kg for month 2-6). Patients at the highest bleeding risk or with major organ disfunction were excluded, and rivaroxaban was withheld in case of a platelet count < 50,000/mm^3. Each treatment arm had 203 patients; in 52% of patients, the index VTE event was an incidental PE and colorectal cancer was the most common neoplasia (25%). 58% of subjects had metastatic disease and 69% were receiving anticancer treatment at the time of their VTE; thus, in this study cancer was "definitely active".

Patients allocated to rivaroxaban experienced 57% less VTE recurrences at 6 months but also a trend to a greater number of major bleedings. No such bleedings occurred in the central nervous system and most of them were gastrointestinal; patients with gastroesophageal or esophageal cancer had significantly more major bleedings with rivaroxaban, an effect that may be at least in part attributable to a local effect of rivaroxaban on the gastrointestinal system.

To sum up, rivaroxaban, with its practical QD oral regimen, should be considered an option for patients with active cancer after a VTE episode; nevertheless, larger studies are necessary to draw definitive conclusions on its efficacy and safety.

5. Atrial fibrillation

5.1 Stroke prevention in non-valvular atrial fibrillation

Since the beginning of the 20th century, it was recognized that atrial fibrillation (AF) is associated with a significant thromboembolic risk. Starting in the second half of that century,[xliii] VKAs have been used to reduce this risk, and a meta-analysis of warfarin trials showed that this drug is associated with a 26% reduction in all-cause mortality and a 62% reduction in the risk of stroke.[xliv]

DOACs represent a very convenient option for these patients, because of their lower risk of interactions with other drugs, their good therapeutic index and their predictable anticoagulant effect, which make monitoring of coagulation parameters unnecessary.[xlv]

Rivaroxaban was the first once daily, fixed dose regimen evaluated for stroke prevention in AF in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial.[xlvi] This was a double blind, double dummy trial which was designed to test the primary hypothesis that rivaroxaban

would be non-inferior to warfarin. The primary efficacy endpoint was the composite of stroke (ischemic and hemorrhagic) and systemic embolism, whereas the primary safety endpoint was the composite of major and non-major clinically relevant bleedings.

This study included 14,264 patients with non-valvular AF (defined in the protocol as the absence of hemodynamically significant mitral valve stenosis and prosthetic heart valve) and a moderate-to-high risk of stroke, as defined by a CHADS2 (Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, prior Stroke/TIA/thromboembolism) score of 2 or more.

These subjects were randomized to receive adjusted dose warfarin in order to achieve an INR of 2.0 to 3.0 or rivaroxaban at a fixed dose of 20 mg QD or 15 mg QD in case of an eGFR between 30 ml/min and 49 ml/min.

Patients enrolled had a mean age of 73 years, i.e. 1 to 3 years higher than in the other 3 trials evaluating dabigatran, apixaban or edoxaban vs. warfarin for stroke prevention in non-valvular AF. Moreover, this trial included patients at a higher risk of thromboembolic events due to the higher proportion of subjects with previous strokes, transient ischemic attacks (TIAs) or systemic embolic events (30% higher than in the trial evaluating apixaban) and the higher average CHADS2 score.

The ROCKET AF trial supported the non-inferiority of rivaroxaban for the primary efficacy endpoint, both in the per-protocol population (i.e., the patients who took at least one dose of the study drug, were compliant to the protocol and were followed for events, with HR 0.79, 95% CI 0.66-0.96) and in the intention to treat population (i.e., the patients originally allocated to one of the 2 treatments in study and that were followed for events, with HR 0.88, 95% CI 0.74-1.03). Even if the prespecified analysis conducted in the on treatment safety population (patients who took at least one dose of the study drug and were followed for events irrespective of any adherence to the protocol) did show superiority, results in the intention to treat population did not. This underlines how important it is to consider intention to treat populations, which are populations that respect more closely real world patients and provide a more "conservative" estimate of a treatment effect, instead of per-protocol populations, which are "ideal" populations of patients compliant to treatments in study, when drawing conclusions on the superiority of one treatment over another in medical literature in order to avoid potentially misleading biases. On the other hand, non-inferiority should be consistently proven in both per-protocol and intention to treat populations.

The ROCKET AF trial also supported a similar safety of rivaroxaban and warfarin, both for the primary safety outcome of major and non-major clinically relevant bleedings and for the prespecified secondary outcome of major bleedings. Rivaroxaban was associated with a significant reduction in risk of intracranial bleedings which was offset by an increase in risk of major gastrointestinal bleeds.

These data were further confirmed outside the clinical trial setting in real-world studies, which provide interesting observational data. For example, the XANTUS (Xarelto® for Prevention of Stroke in Patients with Atrial Fibrillation) study[xlvii] enrolled patients younger than the ROCKET AF study (mean age, 71 years) and with a lower stroke risk (mean CHADS2 score, 2), that is a population with baseline features similar to those enrolled in the other DOACs phase 3 trials. Not unexpectedly, risk of major adverse events was lower than in ROCKET AF, with a major bleeding rate of 2.1% at 1 year. Even though there was no comparator in this study, readers can draw important insights on how baseline features of a population can impact on studies' results.

Therefore, rivaroxaban at a fixed QD dose is an effective and safe alternative to warfarin for stroke prevention in NVAF, with the advantages of being associated with less intracranial bleedings and not requiring any laboratory monitoring.

5.2 Cardioversion

Patients experiencing symptoms due to AF have an indication for cardioversion, that is an attempt to restore sinus rhythm either by applying a current to the patient's thorax (electrical cardioversion) or by giving an antiarrhythmic drug (pharmacological cardioversion).[xlviii] Patients undergoing cardioversion suffer from an increase in post-procedural stroke risk,[xlix] which can be reduced by anticoagulation with VKAs.[l]

Rivaroxaban's efficacy and safety were established in patients undergoing cardioversion in 2 studies, a post-hoc analysis of the ROCKET AF trial[li] and a randomized controlled open label phase IIIb trial, the X-VeRT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with non-valvular aTrial fibrillation scheduled for cardioversion).[lii]

The former provided gross data on patients undergoing either cardioversion or ablation during the course of the ROCKET AF trial; patients treated with rivaroxaban had similar outcomes as compared to patients treated with warfarin.

The X-VeRT study included 1,504 patients with NVAF scheduled for a cardioversion, mainly electrical (97.6%), but also pharmacological (2.4%). These subjects were randomized to rivaroxaban 20 mg QD (or 15 mg QD in case of an eGFR of 30 to 49 ml/min) or a VKA with a target INR of 2.0 to 3.0. Only about 1 patient out of 5 had a first diagnosed atrial fibrillation; more than 40% of patients were oral anticoagulant experienced. The study design consented 2 cardioversion strategies: an early cardioversion strategy (58% of patients), in which rivaroxaban or VKA had to be given for 1 to 5 days before cardioversion and continued for 6 weeks afterwards, or a delayed cardioversion strategy (42% of patients), in which the anticoagulant regimen had to be given for 3 to 8 weeks before cardioversion; patients receiving VKA had to have an INR of 2.0 to 3.0 for 3 consecutive weeks before any cardioversion attempts. A transesophageal echocardiography (TEE) was performed in 65% of patients in the early cardioversion group and in 10% of patients in the delayed cardioversion group.

The trial was exploratory in nature, because a sample size of more than 25,000 patients would have been needed in order to statistically prove rivaroxaban's non-inferiority. Nonetheless, the observed rate of the primary efficacy outcome (a composite of stroke, TIA, embolism, myocardial infarction) was low and similar between the 2 treatment groups in both the early and the delayed cardioversion strategies. The same applied for the primary safety outcome of major bleedings, which were very rare. One practical advantage of rivaroxaban in the delayed cardioversion group was that it enabled a shorter anticoagulation time before cardioversion, because of the difficulties in achieving and maintaining a therapeutic INR for 3 consecutive weeks with VKAs.

Thus, rivaroxaban has good quality evidence in support of its use in the common clinical scenario of cardioversion for atrial fibrillation.

5.3 Ablation

Ablation of atrial fibrillation, mainly targeted at electrical isolation of pulmonary veins from the left atrium, is a very effective measure to pursue rhythm control. This procedure carries a high risk of thrombotic complications, related to endothelial damage, trans-septal sheath placement and atrial stunning; at the same time, patients suffer an increased risk of haemorrhagic complications related to vascular accesses or pericardial effusions/tamponade.[liii]

Whereas there's a general consensus that unfractionated heparin should be administered during ablation in order to achieve and maintain an ACT of more than 300 s, there is more uncertainty on the best antithrombotic strategy in the peri-procedural period. A recent randomized controlled trial proved the safety and effectiveness of performing ablation procedures on uninterrupted warfarin.[liv]

Rivaroxaban was the first DOAC evaluated in this clinical context in the randomized phase IIIb open label VENTURE-AF (ActiVe-

controlled multi-cENTer stUdy with blind-adjudication designed to evaluate the safety of uninterrupted Rivaroxaban and uninterrupted vitamin K antagonists in subjects undergoing cathEter ablation for non-valvular Atrial Fibrillation) trial.[lv] It included 248 patients with paroxysmal, persistent or long-standing persistent non-valvular AF scheduled for an ablation procedure. An anticoagulant regimen of rivaroxaban 20 mg QD was compared to VKA with a target INR of 2.0 to 3.0. The study protocol admitted 2 strategies: a delayed ablation strategy, in which patients had to take the anticoagulant for 3 weeks before ablation, or an early ablation strategy, in which ablation could be performed after 1-7 days of anticoagulation as long as intracardiac thromboses could be ruled out by means of TEE or intracardiac echocardiography. The intraprocedural anticoagulation management was conventional, with unfractionated heparin administered in order to achieve an ACT > 300s; after the procedure, rivaroxaban could be restarted after at least 6 hours since haemostasis' achievement. The study drugs were administered for 30 ± 5 days.

Although underpowered to prove superiority or non-inferiority of rivaroxaban for the primary endpoint of major bleedings, the observed number of events was expectedly low and similar in the 2 groups.

In the end, current clinical practice guidelines suggest that ablation be performed on uninterrupted anticoagulation with rivaroxaban.[53]

6. Atherosclerotic vascular disease

6.1 Recent acute coronary syndrome

After an acute coronary syndrome (ACS), patients remain at substantial risk of death and further atherothrombotic events, despite the widespread use of dual antiplatelet therapy (DAPT) comprising low dose aspirin and a P2Y12 inhibitor. This risk is at least in part related to persistent activation of the coagulation cascade with excessive thrombin generation.[lvi] Therefore, there has been a longstanding interest in the use of oral anticoagulants in this clinical context.

Although warfarin in addition to aspirin proved very effective in reducing atherothrombotic events,[lviilviii] it was associated with a significant bleeding risk.[lix] Also, ximelgatran, an oral direct thrombin inhibitor, proved beneficial in terms of cardiovascular outcomes, but detrimental for its hepatotoxic profile.[lx]

Rivaroxaban was evaluated in patients after a recent ACS in the phase II ATLAS ACS-TIMI 46 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46)[lxi] and in the phase III ATLAS ACS-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51)[lxii] trials.

The former was a double blind dose-escalation study, in which different rivaroxaban regimens were compared with placebo. In particular, patients could receive rivaroxaban at a 5 to 20 mg daily dose, either in a QD or in a BID regimen. The trial showed a dose-related increase in clinically significant bleedings and also a significant reduction in the main secondary efficacy endpoint of stroke, myocardial infarction or death when rivaroxaban was compared to placebo. After this study, the 2.5 mg BID and the 5 mg BID regimens were chosen to be evaluated in a phase III trial because at these doses, rivaroxaban proved already effective at the expense of a moderate increase in bleeding risk. Further, rivaroxaban's pharmacokinetics suggested higher trough and lower peak levels when given twice daily.

The ATLAS ACS-TIMI 51 trial included 15,526 patients within 7 days after hospital admission for an ACS; in the end, the index ACS was a ST-segment elevation myocardial infarction (STEMI) in 50% of patients, a non-ST-elevation myocardial infarction (NSTEMI) in 26% and unstable angina in 24%. Patients who were under 55 years of age had either

diabetes mellitus or a previous myocardial infarction in addition to the index event. Interestingly, patients with a previous ischemic stroke or TIA and who were taking both aspirin and a P2Y12 inhibitor were excluded.

Patients were randomized in a 1:1:1 fashion to rivaroxaban 2.5 mg BID, 5 mg BID or placebo, with a maximum follow up of 31 months. All patients had to take low dose aspirin, whereas the administration of a P2Y12 inhibitor varied according to existing guidelines. The randomization process, which was stratified on the basis of P2Y12 inhibitors administration, was performed after clinical stabilization, including revascularization. The primary endpoint of death, myocardial infarction or stroke was reduced by 16% with rivaroxaban after a mean duration of treatment of 13.1 months; also, risk of stent thrombosis was 31% less with the study drug. When the 2.5 mg BID and the 5 mg BID regimens were evaluated individually, they equally and significantly reduced the primary endpoint, but only the 2.5 mg BID regimen significantly reduced the risk of both death from any cause and from cardiovascular causes.

Risk of TIMI major bleedings was approximately 4 times greater and risk of intracranial haemorrhage higher in patients taking rivaroxaban, although the number of fatal bleedings was not significantly different from placebo. In the comparison of the 2 rivaroxaban regimens, there was a trend towards less TIMI major bleedings and a significant reduction in minor bleedings with the lower dose.

Thus, this study established the role of rivaroxaban as a possible beneficial add-on treatment for patients with coronary artery disease, in whom persistent activation of the coagulation cascade plays a detrimental role. In particular, the low dose (2.5 mg BID, a quarter the daily dose commonly used for stroke prevention in non-valvular AF) appeared to balance the risk of greater number of bleedings with a 1.4% absolute reduction in the rate of death from cardiovascular causes.

6.2 Atrial fibrillation and PCI

Atrial fibrillation and coronary artery disease (CAD) are two common comorbidities and the appropriate management of antithrombotic strategies when these two conditions coexist is largely based on outdated data. In fact, after percutaneous coronary intervention (PCI) with a first generation stent, DAPT proved superior to anticoagulation to prevent thrombotic events,[lxiii] whereas the reverse was true for ischemic stroke prevention in AF.[lxiv] In current clinical practice, patients often receive a combination of DAPT plus an oral anticoagulant for a certain amount of time (usually 1 to 6 months). Although effective in preventing atherothrombotic events, this strategy is burdened by a high bleeding risk of 4-12% in the first year of treatment.[lxv]

The PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) clinical trial[lxvi] was conducted to better inform clinicians' decisions regarding the best combination of antiplatelet and anticoagulant agents in patients with both atrial fibrillation and CAD requiring stenting. The trial included 2,124 patients who had just undergone PCI with stenting. Also, patients had a history of AF within 1 year before screening or more than 1 year before screening but had been taking anticoagulants for AF for the 3 months preceding the PCI. The clinical indication for PCI and stenting was either stable ischemic heart disease or an ACS; approximately 18% of patients had a STEMI as the index event. Subjects with a high bleeding risk (e.g., patients with a haemoglobin concentration < 10 g/dl, with a recent significant gastrointestinal bleeding, with a previous stroke or TIA) were excluded from the trial. Participants were first stratified according to the intended duration of DAPT of 1, 6 or 12 months and also according to the preferred P2Y12 inhibitor; then, patients

were randomized in a 1:1:1 fashion to 1 of 3 treatment groups.

In group 1, patients were to receive rivaroxaban 15 mg QD (or 10 mg QD in case of an eGFR of 30-50 ml/min) plus a P2Y12 inhibitor for 12 months. This regimen was chosen based on the results of the WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial, which included 573 patients undergoing PCI and in need of an oral anticoagulant (because of AF in 69% of patients).[lxvii] The WOEST trial showed a reduction in total bleedings with warfarin and clopidogrel as compared to low-dose aspirin, clopidogrel and warfarin (triple therapy) up to 12 months after PCI.

In group 2, treatment strategy included low dose aspirin (75-100 mg QD), a P2Y12 inhibitor and rivaroxaban 2.5 mg BID. For patients with an intended DAPT duration of 1 or 6 months, after this first period treatment was continued with rivaroxaban 15 mg QD (or 10 mg QD for an eGFR of 30-50 ml/min) and low dose aspirin until 12 months. As such, this regimen was similar to that evaluated in the ATLAS ACS-TIMI 51 trial.

In group 3, patients received warfarin (target INR 2.0-3.0) plus DAPT. For those patients whose intended DAPT duration was 1 or 6 months, warfarin and low-dose aspirin were maintained until month 12. This was the "standard therapy" group.

In the end, only 4% of patients received ticagrelor and 1% prasugrel as P2Y12 inhibitors; the vast majority of patients were prescribed clopidogrel.

The trial showed a marked reduction in the primary safety endpoint of clinically significant bleedings in group 1 vs. group 3 by 41% and in group 2 vs. group 3 by 37%; thus, regimens including rivaroxaban proved significantly safer than standard triple therapy.

An important limitation is that this trial was underpowered to show any significant differences in efficacy endpoints; nonetheless, the number of stent thromboses was very low. Furthermore, the rivaroxaban 15 mg QD dose (reduced to 10 mg QD in case of an eGFR of 30-50 ml/min) is not currently approved for clinical use.

Therefore, even though the PIONEER AF-PCI trial shaded light on the use of rivaroxaban in patients with AF undergoing PCI, its applicability to clinical practice is limited by these and other important issues and further research in this field is highly needed.

6.3 Stable atherosclerotic vascular disease

Until 2017, the universal antithrombotic treatment prescribed to patients with stable atherosclerotic vascular disease was low-dose aspirin, because of its longstanding proven efficacy of 19% reduction in the risk of major cardiovascular events when given for secondary prevention.[lxviii] Also, in recent years the background of secondary preventive strategies has been enriched by an almost universal prescription of statins and inhibitors of the renin-angiotensin system (RAS).

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial[lxix] was designed in order to evaluate the safety and effectiveness of rivaroxaban added to aspirin in 27,395 patients with CAD (91% of patients) or peripheral artery disease (PAD, 27%). Patients with CAD younger than 65 years of age also had to have documentation of atherosclerosis involving 2 or more vascular beds or additional risk factors. Patients at a high risk of bleeding were excluded, as were subjects with an indication for DAPT or anticoagulation.

Patients were randomized in a 1:1:1 fashion to aspirin 100 mg QD, aspirin 100 mg QD plus rivaroxaban 2.5 mg BID or rivaroxaban 5 mg BID. The trial was terminated by the independent data and safety monitoring board after the first interim analysis conducted when 50% of primary efficacy endpoint events of death, myocardial infarction or stroke had occurred because of an overwhelming evidence of benefit with rivaroxaban plus aspirin than with aspirin alone. In the end, rivaroxaban plus aspirin reduced the primary endpoint by 24% when compared to aspirin alone, at the expense

of a 70% increase in major bleedings, the majority of which were in the gastrointestinal tract, with no difference in intracranial haemorrhage. Further, patients taking rivaroxaban plus aspirin had an 18% reduction in risk of death as compared to those taking aspirin alone. On the other hand, rivaroxaban alone did not confer any statistically significant benefits over aspirin alone but was associated with more major bleedings. Finally, there was a net clinical benefit of cardiovascular death, stroke, myocardial infarction, fatal bleeding or bleeding in a critical organ in favour of rivaroxaban plus aspirin as compared to aspirin alone, with no such benefit in the comparison between rivaroxaban alone and aspirin alone.

Thus, the addition of a low dose of rivaroxaban to a background therapy of low-dose aspirin conferred a significant clinical benefit, even on a background of optimal use of secondary prevention therapies such as statins (90% of patients), RAS inhibitors (71%) and beta-blockers (70%) and with mean blood pressure readings of 136/78 mmHg. Moreover, the death advantage already observed in ATLAS ACS-TIMI 51 with the combination of aspirin and rivaroxaban 2.5 mg BID was confirmed in a different population (in COMPASS, patients with a history of myocardial infarction had a mean interval of 7.1 years between the acute event and trial enrollment) and was additive to that of other fundamental therapies.

As Eugene Braunwald brilliantly pointed out,[lxx] the COMPASS trial was an important step for thrombocardiology; nonetheless, research in the field will need to continue in order to provide deeper insights in the personalization of antithrombotic regimens.

Table 2: rivaroxaban's selected phase III clinical trials

Trial name	N of patients	Rivaroxaban regimen(s)	Comparator	Primary efficacy outcome (R vs. comparator)	Primary safety outcome (R vs. comparator)
Acute DVT Study[27]	3,449	R 15 mg BID for 3 weeks, R 20 mg QD for 3, 6 or 12 months thereafter	Enoxaparin 1.0 mg/kg BID bridged with warfarin/acenocoumarol (target INR 2.0-3.0) for 3, 6 or 12 months	2.1% vs. 3.0% (HR 0,68; 95% CI, 0.44-1-04)	8.1% vs. 8.1% (HR 0.97; 95% CI, 0.76-1.22)
Acute PE Study[28]	4,832	R 15 mg BID for 3 weeks, R 20 mg QD for 3, 6 or 12 months thereafter	Enoxaparin 1.0 mg/kg BID bridged with warfarin/acenocoumarol (target INR 2.0-3.0) for 3, 6 or 12 months	2.1% vs. 1.8% (HR 1.12; 95% CI, 0.75-1.68)	10.3% vs. 11.4% (HR 0.9; 95% CI, 0.76-1.07)
Continued Treatment study[27]	1,197	R 20 mg QD for 6 or 12 months	Matching placebo for 6 or 12 months	1.3% vs. 7.1% (HR, 0.18; 95% CI, 0.09-0.039)	0.7% vs. 0 (p=0.11)
EINSTEIN CHOICE[35]	3,396	R 20 mg QD OR R 10 mg QD for 12 months	Aspirin 100 mg QD for 12 months	1.5% (R20) vs. 1.2% (R10) vs. 4.4% (ASA 100)	0.5% (R20) vs. 0.4% (R10) vs. 0.3% (ASA 100)

Trial name	N of patients	Rivaroxaban regimen(s)	Comparator	Primary efficacy outcome (R vs. comparator)	Primary safety outcome (R vs. comparator)
ROCKET AF[46]	14,264	R 20 mg QD (or 15 mg QD for an eGFR of 30 to 49 ml/min)	Warfarin (target INR 2.0-3.0)	1.7% per year vs. 2.2% per year (HR 0.79; 95% CI, 0.66-0.96)	14.9% per year vs. 14.5% per year (HR 1.03; 95% CI, 0.96-1.11)
X-VeRT[52]	1,504	R 20 mg QD (or 15 mg QD for an eGFR of 30 to 49 ml/min)	VKA (target INR 2.0-3.0)	0.51% vs. 1.02% (RR 0.5; 95% CI, 0.15-1.73)	0.61% vs. 0.8% (RR 0.76; 95% CI, 0.21-2.67)
ATLAS ACS-TIMI 51[62]	15,526	R 2.5 mg BID OR R 5 mg BID	placebo	8.9% (R composite) vs. 10.7% (HR 0.84; 95% CI, 0.74-0.96)	2.1% (R composite) vs. 0.6% (HR 3.96, 95% CI, 2.46-6.38)
PIONEER AF-PCI[66]	2,124	R 15 mg QD (or 10 mg QD for an eGFR of 30 to 50 ml/min) plus P2Y12 inhibitor for 12 months OR R 2.5 mg BID plus DAPT for 1, 6 or 12 months	VKA (target INR 2.0-3.0) plus DAPT for 1,6 or 12 months	6.5% (R plus P2Y12 inhibitor) vs. 5.6% (R plus DAPT) vs. 6.0% (VKA plus DAPT)	16.8% (R plus P2Y12 inhibitor) vs. 18% (R plus DAPT) vs. 26.7% (VKA plus DAPT)
COMPASS[69]	27,395	R 2.5 mg BID plus ASA 100 mg QD OR R 5 mg BID	ASA 100 mg QD	4.1% (R plus ASA) vs. 4.9% (R alone) vs. 5.4% (ASA alone)	3.1% (R plus ASA) vs. 2.8% (R alone) vs. 1.9% (ASA alone)

ASA: acetylsalicylic acid; R: rivaroxaban; RR: risk ratio; see text for details

7. Other applications

Regardless of rivaroxaban's proven efficacy in many clinical contexts, we should recognize that in some fields it has proven unsatisfactory.

For example, the NAVIGATE ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source) trial[lxxi] of rivaroxaban 15 mg QD vs. aspirin 100 mg QD for stroke prevention in 7,213 patients after embolic stroke of undetermined source, was prematurely interrupted because of lack of benefit for the primary efficacy composite outcome of all strokes (ischemic and hemorrhagic) or systemic embolism and a concomitant increase in major bleedings with rivaroxaban.

Also, the TRAPS (Trial on Rivaroxaban in AntiPhospholipid Syndrome) trial,[lxxii] which compared rivaroxaban 20 mg QD (or 15 mg QD in case of an eGFR between 30 and 50 ml/min) with warfarin (target INR 2.5) in patients with high risk (triple positive) antiphospholipid syndrome, was precociously stopped after enrolment of 120 patients because of an excess in the primary composite outcome of thromboembolic events, major bleedings and vascular death with rivaroxaban. These results were mainly driven by a greater number of thromboembolic events, all in the arterial circulation. The findings might be explained by insufficient rivaroxaban's levels to prevent arterial thrombotic events. Alternatively, rivaroxaban's action on the sole FXa may be insufficient in a high thromboembolic risk population, in which warfarin, acting on multiple coagulation factors, might be the most appropriate treatment.

Finally, the COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trial[lxxiii] was recently conducted to test the hypothesis that the addition of rivaroxaban 2.5 mg BID to standard care would reduce the composite outcome of all cause death, myocardial infarction or stroke in 5,022 patients with heart failure (HF), reduced left ventricular ejection fraction (≤45%), recent (within 21 days) HF worsening, elevated natriuretic peptide levels, coronary artery disease and sinus rhythm. The trial showed no significant advantage for the primary efficacy endpoint with rivaroxaban and no significant increase in the number of fatal bleedings or bleedings in a critical organ. These neutral findings were attributed to the loose pathophysiological relationship between inhibition of thrombin generation by rivaroxaban and all cause deaths (which represented approximately 75% of the primary outcome events in the trial) in patients with worsening HF and no AF.[lxxiv]

Therefore, even though rivaroxaban is useful in many conditions, this drug is not a "magic bullet" and its clinical indications should always be evaluated with criticism.

8. Conclusive remarks

After 10 years of clinical experience with rivaroxaban across multiple clinical contexts, we must recognize that this molecule has revolutionized the management of many cardiovascular disorders. Nonetheless, given the great advances in antiplatelet, anticoagulant and antithrombotic agents in recent years, we still have many unanswered questions when it comes to selecting the most appropriate therapy or combination of therapies for each single patient. It is likely that in future years the field of thrombocardiology will travel in the direction of therapeutic personalization. But for now, we should be grateful for the huge amount of clinical data we have on rivaroxaban because, when read with criticism, it can help us improving patients' lives.

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