Exploring unmet needs in venous and arterial thromboembolism with rivaroxaban

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Summary

The vast clinical research programme for the direct, oral factor Xa inhibitor rivaroxaban has generated a wealth of data since the first rivaroxaban approval in 2008 for the prevention of venous thromboembolism (VTE) in patients undergoing elective hip or knee replacement surgery. While rivaroxaban is widely used across a spectrum of seven indications, there is continuous commitment to investigating its wider benefits in new indications and attempts to refine current evidence. Key data from recently completed randomised controlled trials (RCTs) have shown that rivaroxaban is a feasible anticoagulation option for patients with non-valvular atrial fibrillation (NVAF) undergoing cardioversion or catheter ablation. Now, a number of Phase II and III RCTs are underway that seek to uncover further roles for rivaroxaban in patients at risk of thrombosis and aim to improve quality of life. This article will introduce and provide context for these RCTs in the contemporary management of arterial and venous thromboembolism in the following underserved areas: Patients with both NVAF and acute coronary syndrome (ACS) requiring percutaneous coronary intervention (PCI); patients with embolic stroke of undetermined source (ESUS); patients who require transcatheter aortic valve replacement (TAVR); patients with acute or chronic coronary artery disease (CAD; including those with heart failure [HF]); those at risk of or suffering from cancer-associated thrombosis (CAT) and those requiring long-term anticoagulation. It is hoped that this collection of studies provides clarity around the use of rivaroxaban as a fundamental component of antithrombotic therapy in an array of clinical situations.

Keywords

Rivaroxaban, acute coronary syndrome, atrial fibrillation, venous thromboembolism, transcatheter aortic valve replacement

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An extensive clinical programme for rivaroxaban

The non-vitamin K antagonist (VKA) oral anticoagulant (NOAC) rivaroxaban received its first marketing authorisations in the European Union (EU) and Canada in 2008, for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (1, 2). Since then, an extensive randomised controlled trial (RCT) programme evaluating the safety and efficacy of rivaroxaban in a wide range of patient populations (3–6) has led to the approval of rivaroxaban for a total of seven indications (1):

1. The prevention of VTE in adult patients undergoing elective hip replacement surgery
2. The prevention of VTE in adult patients undergoing elective knee replacement surgery
3. The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors
4. The treatment of deep-vein thrombosis (DVT) in adults
5. The treatment of pulmonary embolism (PE) in adults
6. The prevention of recurrent DVT and PE in adults
7. The prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine

Rivaroxaban is now the most prescribed NOAC worldwide, with more than 15 million patients being treated or having received treatment since 2008.

Despite the widespread use of rivaroxaban across a spectrum of patient groups, Bayer Pharma AG is committed to investigating the potential benefits of rivaroxaban in patients who are in need of anticoagulation, through both company-sponsored studies and investigator-initiated research (IIR). In this article, we present the rationale for and describe a number of relevant oral anticoagulant studies investigating rivaroxaban across both venous and arterial thromboembolism that are planned, ongoing, or recently completed. These studies will supplement our understanding of the role of oral anticoagulation in these areas of unmet need

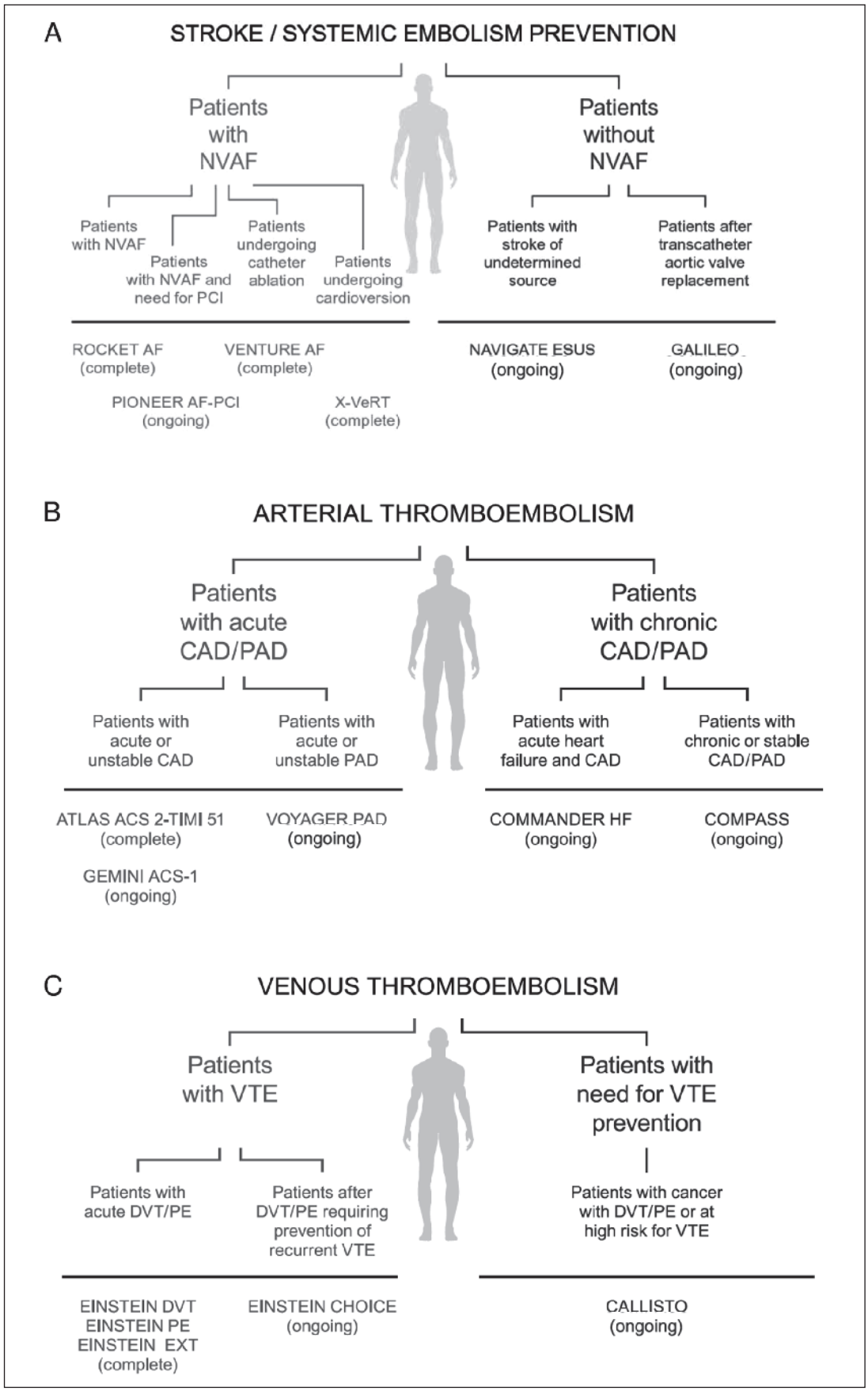

Figure 1: Unmet medical needs of different patients at risk of stroke and systemic embolism (A), arterial thromboembolism (B) and VTE (C). CAD: Coronary artery disease; DVT: Deep vein thrombosis; NVAF: Non-valvular atrial fibrillation; PAD: Peripheral arterial disease; PCI: Percutaneous coronary intervention; PE: Pulmonary embolism; VTE: Venous thromboembolism.

(►Figure 1). Further information on planned and ongoing studies specifically in the fields of VTE and stroke prevention is covered in more detail in accompanying articles *'Spotlight on advances in VTE management: CALLISTO and EINSTEIN CHOICE'* by Bach et al. and *'Spotlight on unmet needs in stroke prevention: The PIONEER AF-PCI, NAVIGATE ESUS and GALILEO trials'* by Hemmrich et al., respectively.

New perspectives in stroke prevention

Rivaroxaban is licensed for stroke prevention in patients with NVAF (1) but, until recently, there was limited information on its safety and efficacy in NVAF patients undergoing rhythm control. The 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 (X-VeRT) and 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 (VENTURE-AF) trials of rivaroxaban vs VKA in NVAF patients undergoing cardioversion and catheter ablation, respectively, are examples of how the ongoing rivaroxaban trial programme may enable improved care of specific populations for whom optimal therapy has been challenging (7, 8).

Rivaroxaban in patients with non-valvular AF undergoing cardioversion: X-VeRT

Cardioversion is used to rapidly restore sinus rhythm in symptomatic atrial fibrillation (AF). Without adequate anticoagulation, the periprocedural risk of thromboembolism with cardioversion is 5–7% (9). The European Society of Cardiology (ESC) guidelines recommend anticoagulation with dose-adjusted VKA (International normalised ratio [INR] range 2.0–3.0) for at least three weeks pre-cardioversion, continued for a minimum of four weeks post-cardioversion, for patients with AF of ≥48 hours or unknown duration scheduled for elective (electric or pharmacological) cardioversion (10). Although planned cardioversion was an exclusion criterion for the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, a small number of patients (N=285) underwent cardioversion (3, 11). In a post-hoc analysis, the incidence of electrical cardioversion, pharmacological cardioversion, or AF ablation and subsequent outcomes were compared – the yearly incidences of stroke or systemic embolism (SE) (1.88% vs 1.86%) and death (1.88% vs 3.73%) were similar in the rivaroxaban- and warfarin-treated groups (11), suggesting that rivaroxaban may be a feasible alternative to VKA in this setting. Subsequently, the Phase III trial X-VeRT was designed as the first prospective RCT to explore the efficacy and safety of rivaroxaban compared with VKA in the prevention of cardiovascular (CV) events in patients with NVAF scheduled for early and delayed cardioversion (7, 12). In this open-label, parallel group, active-controlled trial, patients (N=1504) were assigned to early (1–5 days post-randomisation) or late (3–8 weeks post-randomisation) cardioversion at investigators discretion and then randomised 2:1 to rivaroxaban 20 mg once-daily (Q.D.) or VKA (target INR 2.0–3.0) (12). All patients received study treatment for six weeks post-cardioversion (12). The rate of the primary efficacy outcome (a composite of all strokes, transient ischaemic attacks [TIAs], non-central nervous system SE, myocardial infarction [MI], and CV deaths) was low and similar between patients in the rivaroxaban arm (0.51%) and in the VKA arm (1.02%). Major bleeding rates were also low and similar (0.61% vs 0.80%) (7). Interestingly, the median time to cardioversion was significantly shorter in the delayed group with rivaroxaban vs VKA (22 vs 30 days; $p<0.001$) (7). Furthermore, of those patients assigned to delayed cardioversion, a significantly larger proportion in the rivaroxaban arm received cardioversion as scheduled vs those in the VKA arm (77% vs 36%; $p<0.001$) (7). Thus, in addition to demonstrating that rivaroxaban offers an effective alternative to VKA with a good safety profile, X-VeRT also showed that rivaroxaban may overcome a limitation of VKA by offering a significant reduction in time to cardioversion (7). Based on these positive results, the European rivaroxaban label was updated to include specific guidance on the use of rivaroxaban in patients with NVAF who require cardioversion (13). At present, rivaroxaban is the only NOAC with specific label guidance for peri-procedural thromboembolic protection in patients undergoing early or delayed cardioversion.

Rivaroxaban in patients with non-valvular AF undergoing catheter ablation: VENTURE-AF

Catheter ablation is an alternative to antiarrhythmic drug therapy for rhythm control in patients with paroxysmal AF (10). Adequate anticoagulation during ablation plays an important role in the prevention of thromboembolic complications (10). The latest ESC guidelines recommend considering continuation of VKA (i.e. an uninterrupted anticoagulation strategy) during planned catheter ablation, maintaining an INR close to 2.0; however, the guidelines note that experience and robust data with NOACs are lacking (10). In response to this unmet need, the Phase III open-label trial VENTURE-AF (Clinicaltrials.gov identifier: NCT01729871) evaluated the safety of rivaroxaban as a periprocedural ablation strategy (14, 15). VENTURE-AF, a prospective, randomised, active-controlled, global multicentre safety trial, was conducted to determine if the use of uninterrupted rivaroxaban is associated with a safety profile that is similar to that of uninterrupted VKA in patients undergoing catheter ablation for NVAF (14, 15). Patients with a history of paroxysmal or persistent NVAF who were scheduled to undergo an elective catheter ablation procedure (N=248) were randomised to rivaroxaban 20 mg Q.D. or VKA (INR 2.0–3.0) before the ablation procedure (14). Rivaroxaban demonstrated similar efficacy and safety to uninterrupted VKA, with low and similar rates of major complications between the two treatment groups (8). There were no cases of major bleeding (the primary outcome) in the rivaroxaban group and one in the VKA

group (0.0% vs 0.4%). The overall complication rate was 20.6%, and of these 0.8% were thromboembolic complications (no events with rivaroxaban vs two events in two patients with VKA) (8). The results of VENTURE-AF confirm that uninterrupted rivaroxaban in NVAF patients undergoing ablation is feasible (8).

Further studies in stroke prevention

Additional groups of patients who have an increased risk for thromboembolic events and thus may benefit from primary and/or secondary prevention of stroke or thrombotic events with rivaroxaban include those with both AF and ACS (requiring percutaneous coronary intervention [PCI]), those with embolic stroke of undetermined source (ESUS), or those requiring transcatheter aortic valve replacement (TAVR). These unmet needs and respective studies designed to address them are introduced below and discussed in detail in the article *'Spotlight on unmet needs in stroke prevention: The PIONEER AF-PCI, NAVIGATE ESUS and GALILEO trials'* by Hemmrich et al.

Rivaroxaban therapy in patients with non-valvular AF undergoing PCI with stent placement: PIONEER AF-PCI

Patients with concomitant AF and ACS represent a major clinical challenge as the optimal management of the two conditions differ. Specifically, studies have shown that for AF, dual antiplatelet therapy (DAPT; ASA plus clopidogrel) is not as effective as warfarin (16), but for patients with coronary stents, DAPT (ASA plus ticlopidine) is more effective than warfarin (17). A dual pathway approach (i.e. targeting both the coagulation cascade and the antiplatelet pathway) may be considered a rational approach for such patients. Triple combination therapy (VKA plus ASA plus clopidogrel) is recommended in patients with AF who require PCI following an ACS event but — in patients at high risk of bleeding — must be limited to four weeks, followed by dual combination therapy (VKA plus ASA / clopidogrel) (18). The open-label RCT What Optimal antiplatElet and anticoagulant in patients with oral anticoagulation and coronary StenTing (WOEST) evaluated a double therapy strategy (VKA plus clopidogrel) vs triple therapy (VKA plus clopidogrel plus ASA) in patients requiring PCI with stenting and who had an indication for chronic oral anticoagulation (indication was AF / atrial flutter in 326/563 patients) (19). At 1 year, the overall rate of bleeding events was significantly lower with double therapy compared with triple therapy (19.4% vs 44.4%; $p<0.0001$), with no increase in thrombotic events (19). The results suggest that oral anticoagulation is at least as good as ASA in preventing thrombotic events, and that ASA may not be needed in patients undergoing PCI and receiving oral anticoagulation, but a larger, confirmatory trial is necessary (19). It has been proposed that a dual pathway approach that includes a NOAC, rather than VKA, may reduce bleeding risk without excess ischaemic hazard. The Phase III open-label randomised trial oPen-label, randomised, controlled, multicentre study explorIng twO treatmeNt stratEgiEs of Rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in patients with Atrial Fibrillation who undergo Percutaneous Coronary Intervention (PIONEER AF-PCI; Clinicaltrials.gov identifier: NCT01830543) is the first randomised comparison of VKA vs a NOAC in patients with NVAF receiving antiplatelet therapy after PCI to assess the relative risks of bleeding complications (20). It will assess the safety of two rivaroxaban regimens vs VKA, in addition to antiplatelet therapy, after PCI in patients with AF (20). Approximately 2100 subjects are being randomised in a 1:1:1 ratio to receive either rivaroxaban 15 mg Q.D. plus clopidogrel 75 mg daily for 12 months (a WOEST trial–like strategy), or rivaroxaban 2.5mg twice-daily (B.I.D.; with stratification to a prespecified duration of DAPT 1, 6, or 12 months, an ATLAS trial–like strategy), or dose-adjusted VKA once daily (with stratification to a prespecified duration of DAPT 1, 6, or 12 months, traditional triple therapy) (21). Results are expected in December 2016.

Rivaroxaban in patients with embolic stroke of undetermined source: NAVIGATE ESUS

In patients who suffer from an ischaemic stroke, the median duration of survival following the event was shown to be only 1.8 years compared with 5.7 years in matched non-stroke comparators (22). The underlying cause of an ischaemic stroke is usually identifiable, but for around a quarter of patients the cause remains unknown (23). For such patients with ESUS (previously known as 'cryptogenic stroke'), antiplatelet therapy is recommended for the prevention of subsequent thrombotic events; however, this is based upon limited data (23). It has been hypothesised that safe and predictable oral anticoagulation may be more effective than ASA in this setting, but there are no or limited supporting data (23). The Phase III RCT New Approach riVaroxoban Inhibition of Factor Xa in a Global Trial vs Aspirin to prevenT Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS; Clinicaltrials.gov identifier: NCT02313909) will explore the role of rivaroxaban for secondary prevention of ischaemic events in this high-risk population (24). Patients who are ≥50 years old and had recent ESUS (between 7 days and 6 months) will be randomised 1:1 to rivaroxaban 15 mg Q.D. or ASA 100 mg Q.D. (24). Results are expected in 2018.

Rivaroxaban in patients who have undergone successful transcatheter aortic valve replacement: GALILEO

TAVR is a minimally invasive treatment alternative established in patients with severe aortic stenosis with prohibitive, high and intermediate risk for surgical aortic valve replacement (SAVR) (25). TAVR offers a significant reduction in all-cause mortality in high-risk patients compared with surgical valve replacement (26), but is still associated with a risk of ischaemic events. A large meta-analysis revealed that, following TAVR, 3.3% of patients experience a stroke or TIA within 30 days (27). It is currently unknown whether an antiplatelet or anticoagulation strategy is more appropriate for

the prevention of thromboembolic events after TAVR; however, there is growing evidence of the benefits of anticoagulation in groups including those undergoing bioprosthetic aortic valve replacement (28), with transcatheter heart valve thrombosis (29) and subclinical leaflet thrombosis (30). The need for more robust data around optimal therapeutic options in this setting supports the rationale of the Phase III open-label Global study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement to Optimize clinical outcomes (GALILEO; Clinicaltrials.gov identifier: NCT02556203) (31). GALILEO will assess the safety and efficacy of rivaroxaban 10 mg Q.D. plus ASA (followed by rivaroxaban 10 mg Q.D. alone) vs ASA plus clopidogrel (followed by ASA alone) following successful TAVR (31). Results are expected in 2018.

Unmet needs in arterial thromboembolism

A number of conditions place patients at an increased risk of arterial thromboembolism — these include acute and chronic (or stable) coronary artery disease (CAD), especially when associated with concomitant heart failure (HF) and peripheral arterial disease (PAD). Below we present the planned or ongoing studies designed to explore the potential of rivaroxaban in managing a range of different patient groups with these disorders.

A dual antithrombotic therapy including rivaroxaban vs conventional DAPT in an ACS population: GEMINI ACS-1

ACS (encompassing unstable angina, ST-segment elevation MI [STEMI] and non-ST-segment elevation MI [NSTEMI]) is responsible for an estimated 2.5 million hospitalisations worldwide (32). Results from the Global Registry of Acute Coronary Events (GRACE) prospective long-term study (N=3721) revealed that 19% of STEMI patients and 22% of NSTEMI patients died within 5 years demonstrating a profound residual risk of recurrent events in a contemporary era (33). With the majority of deaths (68% of STEMI and 86% of NSTEMI) occurring after hospital discharge, the need for sustained secondary prevention is clear (33). The risk of recurrent ischaemic events is also high, with 12.7% of ACS patients experiencing at least one MI, 7.7% experiencing at least one stroke, and 53.6% readmitted to hospital at least once within 5 years (33). DAPT with ASA and an adenosine diphosphate (ADP) receptor antagonist (clopidogrel, prasugrel or ticagrelor) is the standard of care after an ACS event, used for up to 1 year regardless of the initial treatment strategy (including PCI) (34, 35). However, while offering efficacy benefits, DAPT may be associated with increased risk of major bleeding events vs ASA alone (36). The use of the novel antiplatelet agent ticagrelor has been shown to improve outcomes over clopidogrel, but nevertheless the outcome of death from vascular causes, MI or stroke still occurred in 9.8% of patients within a year, and 11.7% experienced major bleeding (37).

While rivaroxaban is approved for prevention of atherothrombotic events in adult patients after an ACS (in combination with ASA alone or ASA plus clopidogrel or ticlopidine), this is limited to patients with elevated cardiac biomarkers (1). The benefits of rivaroxaban could be offered to a wider group of ACS patients if a low dose could offer protection against recurrent ischaemic events in combination with a single, rather than dual, antiplatelet strategy with an anticipated enhanced safety profile. The Phase II randomised, double-blind, double-dummy, active-controlled, parallel group multicentre trial to compare the safety of rivaroxaban vs ASA in addition to either clopidogrel or ticagrelor therapy in subjects with ACS (GEMINI ACS-1; Clinicaltrials.gov identifier: NCT02293395) was designed to evaluate the benefits of a dual pathway strategy of rivaroxaban in combination with single antiplatelet treatment (38, 39). The design is based on the findings of the WOEST trial, which suggest that removing ASA from a triple therapy regimen (oral anticoagulant [OAC] plus ASA plus clopidogrel) may lead to a reduction in bleeding events while sustaining efficacy (19). GEMINI ACS-1 will determine the safety of rivaroxaban 2.5 mg B.I.D. vs ASA 100mg Q.D., both in addition to a single antiplatelet agent (clopidogrel [75 mg Q.D.] or ticagrelor [90 mg B.I.D.]) in patients with ACS (38, 39). The trial began recruiting early in 2015 with a target enrolment of 3000 patients across 370 sites in 22 countries (38, 39). It will include patients with recent (<10 days) unstable angina, NSTEMI, and STEMI treated with medical therapy alone, PCI or coronary artery bypass graft (CABG) surgery (38). Full details of the trial design are published (38) and also summarised in ►Figure 2. Results are expected in late 2016 or early 2017.

Rivaroxaban for the prevention of major cardiovascular events in CAD or PAD: COMPASS

A high proportion of patients with apparently stable CAD and PAD (4.5% and 5.4%, respectively) have been shown to experience CV death, MI or stroke in the course of a year (40), underlining the need to improve secondary prevention and clinical outcomes. For the prevention of CV events in patients with chronic CAD, the ESC guidelines recommend ASA (or clopidogrel for ASA-intolerant patients), while DAPT is not routinely recommended (41). For patients with symptomatic PAD, the ESC guidelines recommend ASA, but not DAPT (42). Limited benefits and an unjustified bleeding risk are cited as reasons for not recommending a DAPT strategy in patients with CAD or PAD (41, 42). Trials investigating long-term secondary prevention of ACS events have failed to generate favourable results owing to significant increases in bleeding with both ticagrelor and vorapaxar (44, 45). Furthermore, the Dual Antiplatelet Therapy (DAPT) trial of patients who had received a drug-eluting stent showed that 18 months of treatment with ASA plus clopidogrel or prasugrel (following an initial 12 months of the same regimen) reduced the rates of stent thrombosis, major adverse cardiovascular and cerebrovascular events and MI compared with ASA plus placebo, although the rate of moderate or severe bleeding was significantly higher (43). Similarly, patients with a history of MI who had received ticagrelor on a back-

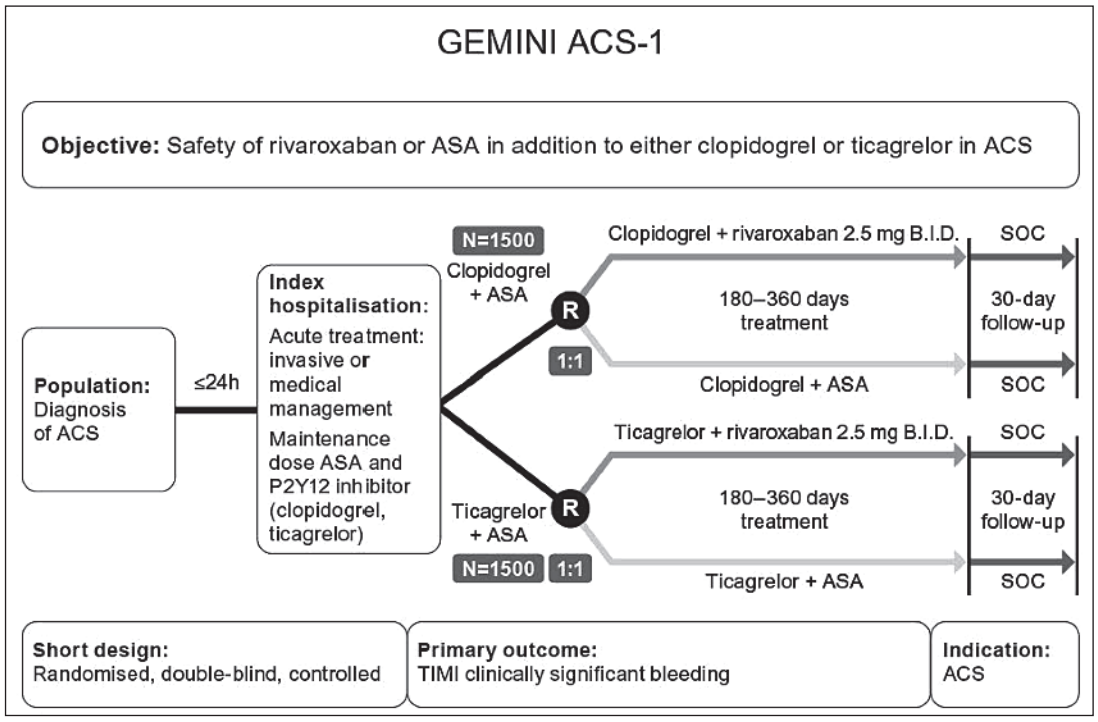

Figure 2: GEMINI ACS-1 trial design (38). ACS: Acute coronary syndrome; ASA: Acetylsalicylic acid; B.I.D.: Twice-daily; R: Randomised; SOC: Standard of care; TIMI: Thrombolysis In Myocardial Infarction.

ground of low-dose ASA and who were followed for a median duration of 33 months in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial showed a significant reduction in CV death, MI or stroke but an increased risk of major bleeding (44).

It has been shown that around 55–80% of those with PAD also have CAD (46, 47). In patients with chronic CAD and/or PAD, there is a clear unmet need for a treatment that is more effective than but with similar safety to ASA. A low level antithrombotic or a dual pathway approach, including a single antiplatelet agent and a low-dose NOAC, may offer a more favourable benefit-risk profile. Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome –Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) provided evidence that rivaroxaban 2.5 mg B.I.D. plus standard antiplatelet therapy protects patients with CAD who recently experienced an ACS event against recurrence (6).

The Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS; Clinicaltrials.gov identifier: NCT01776424) trial was designed to evaluate the potential of a dual pathway strategy in a large population of stable CAD and/or PAD patients (48). COMPASS is a Phase III, randomised, double-blind, placebo-controlled trial that will determine the efficacy and safety of low-dose rivaroxaban (2.5 mg B.I.D.) plus ASA or rivaroxaban 5 mg B.I.D. vs ASA alone in the prevention of ischaemic events in patients with CAD and/or PAD (48). The primary efficacy outcome is the composite of MI, stroke and CV death; the primary safety outcome is International Society on Thrombosis and Haemostasis (ISTH) major bleeding. The trial will include participants aged ≥18 years with documented CAD or PAD. Those with CAD must be at least 65 years old or have documented atherosclerosis or revascularisation involving at least two vascular beds, or at least two additional risk factors (48). Recruitment began in early 2013, with a target enrolment of approximately 27,500 patients and completion is scheduled for 2018. The trial design is summarised in ▶Figure 3. COMPASS is the single largest randomised trial of a NOAC and has the potential to redefine standard of care for a large number of patients with established atherothrombotic disease.

Rivaroxaban in PAD patients undergoing peripheral revascularisation procedures: VOYAGER PAD

For patients with symptomatic lower extremity PAD (LEAD), revascularisation procedures may be used to both relieve symptoms and reduce the risk of CV events in patients with acute or critical limb ischaemia, and in those with lifestyle-limiting intermittent claudication who do not respond favourably to conservative management (42). Revascularisation options include surgical revascularisation with graft bypass or endovascular revascularisation with or without stenting (42). Antiplatelet therapy is recommended after revascularisation to reduce the risk of CV events and to improve patency rates (42). A dual antithrombotic approach is thought to be more appropriate; however, an unjustified increased bleeding risk has been noted in both PAD patients undergoing revascularisation who received ASA and warfarin (49) and who received DAPT plus warfarin (50). Cochrane authors leading a meta-analysis of antiplatelet agents and/or anticoagulants in PAD patients undergoing infra-inguinal arterial bypass surgery concluded that VKA was more likely to confer benefit than antiplatelet

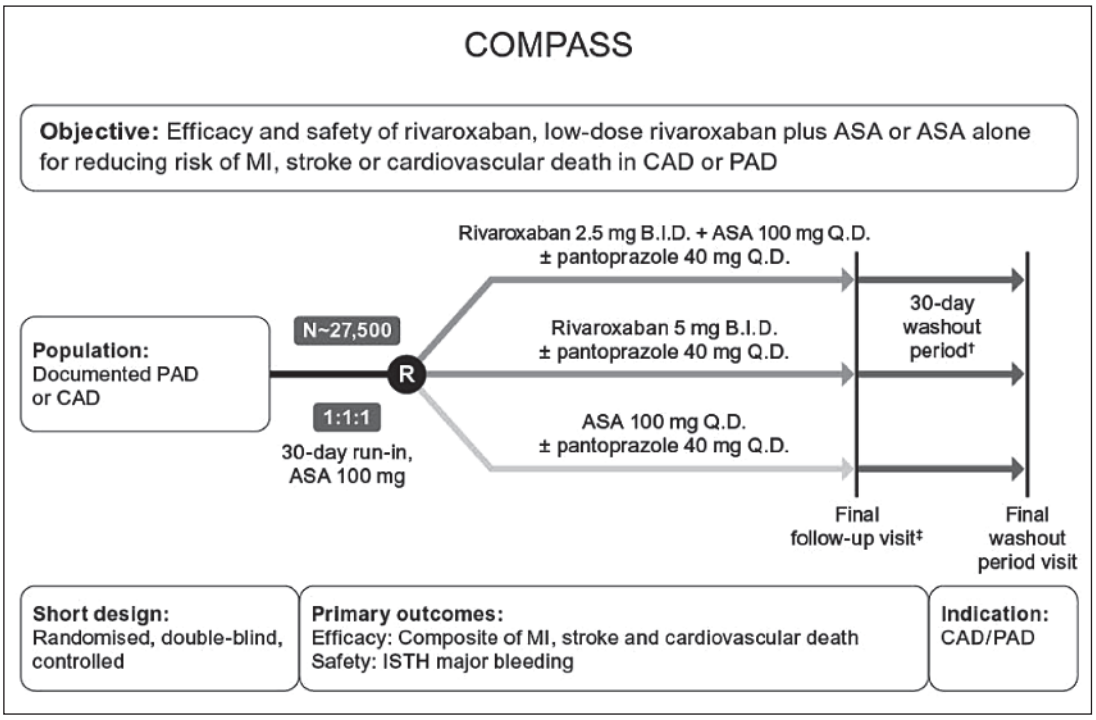

Figure 3: COMPASS trial design (48). † Patients treated according to local standard of care; ‡ ≤30 days of the required pre-specified number of events having occurred. ASA: Acetylsalicylic acid; B.I.D.: Twice-daily; CAD: Coronary artery disease; ISTH: International Society on Thrombosis and Haemostasis; MI: Myocardial infarction; Q.D.: Once-daily; PAD: Peripheral arterial disease.

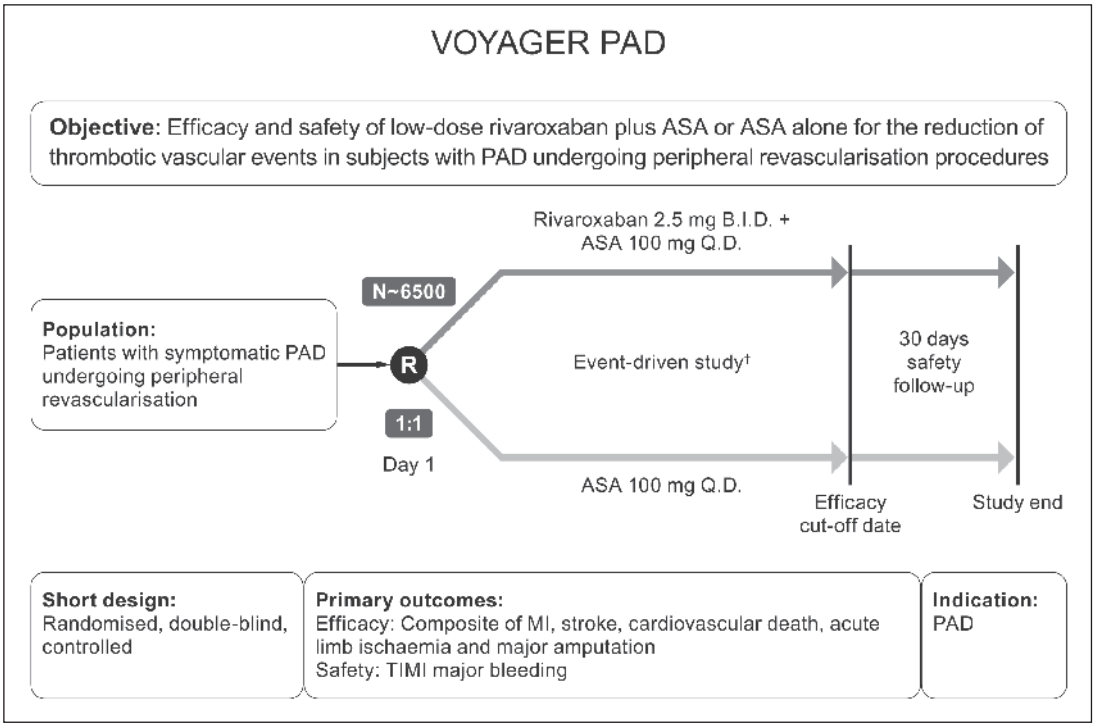

Figure 4: VOYAGER PAD trial design (52). † Mean treatment duration ~30 months. ASA: Acetylsalicylic acid; BID: Twice-daily; MI: Myocardial infarction; Q.D.: Once-daily; PAD: Peripheral arterial disease; TIMI: Thrombolysis In Myocardial Infarction.

agents, and noted that trials investigating the safety and efficacy of NOACs in this setting are needed (51).

Vascular Outcomes studY of ASA alonG with rivaroxaban in Endovascular or surgical limb Revascularization for PAD (VOYAGER PAD; Clinicaltrials.gov identifier: NCT02504216), a Phase III, randomised, double-blind, placebo-controlled trial, was designed to determine the safety and efficacy of a dual pathway approach vs standard of care (ASA alone) for the reduction of thrombotic vascular events in subjects undergoing peripheral revascularisation procedures (►Figure 4) (52). Patients (N=~6500) with documented moderate or severe symptomatic LEAD and recent (≤7 days) successful peripheral infra-inguinal revascularisation, of at least 50 years of age, will receive low-dose rivaroxaban (2.5 mg B.I.D.) plus ASA or ASA alone (52). The primary efficacy

outcome is the composite of major thrombotic vascular events (MI, ischaemic stroke and CV death), acute limb ischaemia and major amputation. Thrombolysis In Myocardial Infarction (TIMI) major bleeding is the primary safety outcome (52). VOYAGER PAD, which began enrolling in Q3 2015, complements the COMPASS trial; both are exploring new ways to avoid complications in the overlapping conditions PAD and CAD. COMPASS includes those with stable PAD (including asymptomatic carotid artery stenosis of mild-to-moderate severity) (48), whereas VOYAGER PAD includes those with highly symptomatic LEAD who have recently undergone peripheral revascularisation procedures, thus with unstable or acute PAD (52). Results from VOYAGER PAD are anticipated in 2019.

Rivaroxaban in patients with heart failure and significant CAD following an exacerbation of heart failure: COMMANDER HF

The ESC guidelines do not recommend anticoagulation in patients with HF and a reduced ejection fraction (HF-rEF; also known as systolic HF) unless there is concomitant AF (53). HF is typically not considered a thrombotic disease and thus it is not surprising that anticoagulants are not the standard of care. Yet, there is a wealth of evidence supporting a central role of thrombosis in the pathophysiology of HF and a hypercoagulable state in patients with HF (54). It is reasonable to hypothesise that anticoagulants may have a role in preventing CV events in HF with sinus rhythm; however, trials to date with VKA in the setting have been inconclusive (55–57).

Interestingly, an analysis of patients with concomitant HF in ATLAS ACS 2-TIMI 51 showed that rivaroxaban 2.5 mg B.I.D. significantly reduced the primary efficacy outcome of CV death, MI or stroke compared with placebo (10.1% vs 16.8%), while exhibiting similar rates of major bleeding (0.4% vs 0.6%) (58). Following this suggestion of a role of rivaroxaban in the prevention of ischaemic events in patients with HF with sinus rhythm and concomitant acute CAD, the RCT COMMANDER HF (Clinicaltrials.gov identifier: NCT01877915) was designed to provide more robust data in the setting (59, 60).

COMMANDER HF is a Phase III, randomised, double-blind, event-driven, multicentre study comparing the efficacy and safety of low-dose rivaroxaban (2.5 mg B.I.D.) with placebo (in addition to guideline-recommended standard of care) for reducing the risk of death, MI or stroke in subjects with chronic HF and significant CAD following a hospitalisation for exacerbation of HF (59). This multicentre, international trial is currently ongoing (recruitment began in Q3 2013) and aims to enrol approximately 5000 patients to achieve 984 primary efficacy events (a composite of MI, stroke or death) (59). Patients will take their study drug until the targeted number of events has been predicted to have occurred and will be followed for approximately 7–31 months (59). The primary safety outcome is the composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability (59). COMMANDER HF will include HF patients (N-terminal of the prohormone brain natriuretic peptide [NT-proBNP] ≥800 pg/ml or B-type natriuretic peptide ≥200 pg/nl) who are clinically stable up to 30 days after a symptomatic index event (an exacerbation of HF symptoms), with left ventricular ejection fraction ≤40%, and documented significant CAD (59). Full details of the trial design are published (59) and also summarised in ►Figure 5; results are expected in 2018.

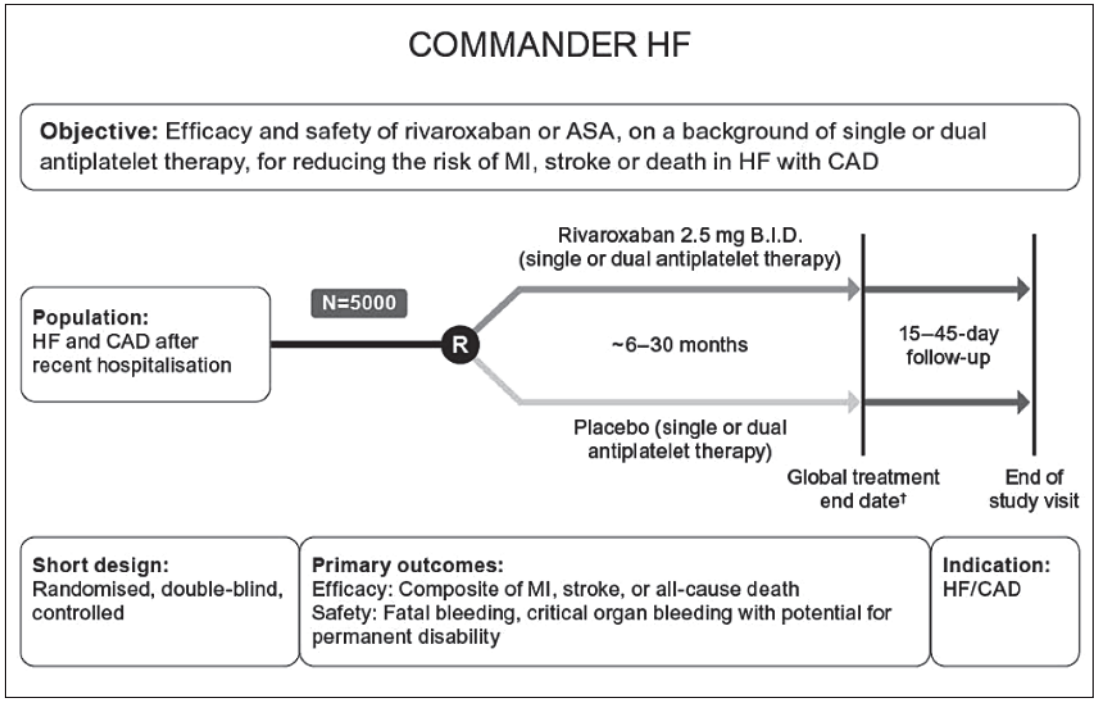

Figure 5: COMMANDER HF trial design (59). † Date when 984 primary efficacy outcome events have occurred. ASA: Acetylsalicylic acid; B.I.D.: Twice-daily; CAD: Coronary artery disease; HF: Heart failure; MI: Myocardial infarction; R: Randomised.

Exploring additional needs in VTE

Despite the availability of effective anticoagulant strategies, VTE continues to pose a substantial clinical risk. There are still specific patient groups for whom treatment is challenging, and even the optimal duration of therapy is not clear in many situations. Below is an introduction to studies that will aim to answer important questions around the use of long-term rivaroxaban therapy, as well as the use of rivaroxaban in patients with cancer who are at risk of or receiving treatment for VTE. These topics are described in more detail in the article *'Spotlight on advances in VTE management: CALLISTO and EINSTEIN CHOICE'* by Bach et al.

Rivaroxaban for long-term secondary prevention of VTE: EINSTEIN CHOICE

VTE is a chronic disease with up to 40% recurrence after 10 years in those who discontinue anticoagulation (61), and therefore long-term anticoagulation is warranted. On the contrary, long-term anticoagulation may place patients at an unnecessary increased bleeding risk. There is a clear unmet need for an anticoagulation strategy with a benefit-risk profile suitable for long-term use. The use of long-term ASA (≥2 years) following an initial anticoagulation period has shown potential where ASA (following completion of an initial anticoagulation period) significantly reduced the incidence of recurrent VTE without increasing bleeding in the Warfarin and Aspirin (WARFASA) trial (62). While there was no significant reduction in recurrent VTE with ASA vs placebo in the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial, a significant reduction in vascular events was noted with no increase in bleeding (63).

Rivaroxaban is licensed for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (1). Approval for its long-term use for secondary VTE prevention stemmed from the RCT EINSTEIN Extension (EINSTEIN EXT), where rivaroxaban 20 mg Q.D. (up to 2 years) was compared with placebo (4). Rivaroxaban demonstrated a significant reduction in the primary efficacy outcome of symptomatic recurrent VTE and while there was no difference in the primary safety outcome of major bleeding (p=0.11), a significant increase in the composite of major and clinically relevant non-major bleeding vs placebo was noted (p<0.001) (4). The Phase III RCT EINSTEIN CHOICE (Clinicaltrials.gov identifier: NCT02064439) was designed to determine if an alternative rivaroxaban dose could offer a favourable benefit-risk profile for secondary prevention of VTE vs ASA (64, 65). Patients ≥ 18 years old and with confirmed symptomatic PE and/or DVT who have been treated for 6 to 12 months (who did not experience a symptomatic recurrence during this period) and did not interrupt anticoagulation for longer than 1 week will be randomised 1:1:1 to rivaroxaban 20 mg Q.D., rivaroxaban 10 mg Q.D. or ASA 100 mg Q.D. and will be treated for least 12 months, with a 1-month follow-up period (64). Primary results are anticipated in 2017.

Rivaroxaban for the prevention and treatment of cancer-associated thrombosis: CALLISTO

Patients with cancer represent another group with an unmet need for appropriate thromboprophylaxis, with VTE being a leading cause of death in cancer patients (66). Thromboprophylaxis with low-molecular-weight heparin (LMWH) is a traditional choice for hospitalised patients with cancer (67–70), and may be considered in selected high-risk ambulatory patients with cancer who are receiving chemotherapy (68–71). LMWH is also a proven treatment option for acute and extended treatment of cancer-associated thrombosis (CAT; 3–6 months) (68–72) despite the need for parenteral administration and a small risk of heparin-induced thrombocytopenia (HIT) (73, 74). NOACs are now becoming recognised as an alternative option to LMWH for the treatment of CAT by the American College of Chest Physicians (ACCP), The British Committee for Standards in Haematology (BCSH) and the Association of the Scientific Medical Societies of Germany (69, 72, 75). However, long-term data and head-to-head trials between NOACs and LMWH are lacking. A pooled subanalysis of patients with active cancer (N=655) in the Phase III RCTs EINSTEIN DVT and EINSTEIN PE provided robust data suggesting that rivaroxaban was associated with a net clinical benefit (recurrent VTE and major bleeding) over LMWH / VKA (p=0.018) (76). The natural next step is to directly compare rivaroxaban with LMWH in a larger population of patients with cancer. Cancer Associated thrombosis – expLoring soLutions for patients through Treatment and Prevention with RivarOxaban (CALLISTO) is an international clinical research programme comprising clinical studies (both IIR and company-led) and registries; additionally a survey will evaluate how clinicians perceive the risk of CAT and expert guidance on management of CAT will be collated as part of the programme (77). The programme will involve more than 4000 patients worldwide and will explore the potential of rivaroxaban compared with placebo (for the prevention of CAT) or LMWH (for the treatment of CAT). CALLISTO will also assess quality of life, treatment satisfaction and patient preference with regards to their anticoagulation treatment for VTE treatment. CALLISTO furthermore aims to collect information from a range of clinical scenarios for which current knowledge on the optimal use of anticoagulation is limited (77).

Summary and conclusion

Clear areas of unmet medical need remain across a number of patient groups who suffer from thromboembolic disorders. Complex pathophysiological processes present further barriers to achieving optimal therapeutic strategies for patients. Oral anticoagulation may play an important role in wider groups of patients who have not yet been investigated as part of the pivotal RCTs that have been undertaken to date and for whom there is a lack of robust supporting data.

A comprehensive programme of Phase II and Phase III studies – undertaken by Bayer or IIR – is underway to assess the safety

and efficacy of rivaroxaban in new clinical scenarios and patient populations, such as those with chronic or acute CAD (including those with ACS and HF), chronic or acute PAD, NVAF patients requiring PCI, patients with or at risk of CAT, those requiring long-term secondary prevention of VTE, and those with ESUS or who have undergone TAVR. It is anticipated that future data may uncover novel roles for NOACs, such as rivaroxaban, in providing effective antithrombotic strategies. This extensive number of ongoing rivaroxaban RCTs will contribute a wealth of valuable information regarding the management of specific populations for whom antithrombotic therapy has been suboptimal.

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Conflicts of interest

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