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Oral anticoagulant use in cardiovascular disorders: a perspective on present and potential indications for rivaroxaban

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Abstract

Background: Four nonvitamin K antagonist oral anticoagulants (NOACs) have been approved for use in various cardiovascular indications. The direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban are now increasingly used in clinical practice. For some of these agents, available data from real-world studies support the efficacy and safety data in phase III clinical trials.
Objectives: This review aims to summarize the current status of trials and observational studies of oral anticoagulant use over the spectrum of cardiovascular disorders (excluding venous thrombosis), provide a reference source beyond stroke prevention for atrial fibrillation (AF) and examine the potential for novel applications in the cardiovascular field.
Methods: We searched the recent literature for data on completed and upcoming trials of oral anticoagulants with a particular focus on rivaroxaban.
Results: Recent data in specific patient subgroups, such as patients with AF undergoing catheter ablation or cardioversion, have led to an extended approval for rivaroxaban, whereas the other NOACs have ongoing or recently completed trials in this setting. However, there are unmet medical needs for several arterial thromboembolic-related conditions, including patients with: AF and acute coronary syndrome, AF and coronary artery disease undergoing elective percutaneous coronary intervention, coronary artery disease and peripheral artery disease, implanted cardiac devices, and embolic stroke of unknown source.
Conclusion: NOACs may provide alternative treatment options in areas of unmet need, and numerous studies are underway to assess their benefit–risk profiles in these settings.

Keywords: direct oral anticoagulant, factor Xa inhibitor, lifecycle management, rivaroxaban

Introduction

The scope for the nonvitamin K antagonist oral anticoagulants (NOACs) includes a range of cardiovascular diseases (CVDs), including coronary artery disease (CAD), cerebrovascular disease, atrial fibrillation (AF), peripheral artery disease (PAD), and venous thromboembolism (VTE). AF, the most prevalent cardiac condition with an anticoagulant indication, affects 0.7–3% of the population and prevalence increases with age [1-5]. It predisposes patients to develop left atrial (LA)/left atrial appendage (LAA) thrombus [6], and stroke risk is increased 5-fold [7]. Acute coronary syndrome (ACS) onset involves atheromatous plaque disruption or erosion complicated by platelet aggregation and thrombosis. Thrombosis may also be implicated in the consequences of myocardial infarction (MI), including left ventricular dysfunction, heart failure (HF), arrhythmia development, and VTE. For secondary prevention in ACS, guidelines recommend dual antiplatelet therapy (DAPT; acetylsalicylic acid [ASA] plus clopidogrel, prasugrel, or ticagrelor) [8-12]. However, even with antiplatelet therapy, the annual risk of cardiovascular death, nonfatal MI, or stroke remains ~10% [13], prompting a re-evaluation of the role of combined anticoagulant and antiplatelet therapy [13].

Several studies have assessed the efficacy and safety of anticoagulants in arterial disease. The SAVE (Survival and Ventricular Enlargement) trial suggested that anticoagulation therapy (warfarin or heparin) protects against stroke after MI, but this study predated modern revascularization and antiplatelet therapy [14]. A meta-analysis of observational studies concluded that warfarin was more effective for the prevention of thrombosis in patients with transmural anterior MI than antiplatelet therapy alone [15]. However, in other studies, low-dose warfarin plus ASA was not more effective than ASA alone, and high-intensity warfarin without ASA increased bleeding risk in CVD secondary prevention [12].
More recently, NOACs were developed to improve anticoagulation consistency, without routine coagulation monitoring or food–drug and drug–drug interactions of vitamin K antagonists (VKAs). Phase III studies with dabigatran [16], rivaroxaban [17], apixaban [18], and edoxaban [19] showed that NOACs were as good as or better than warfarin for the prevention of stroke and systemic embolism (SE) in patients with nonvalvular AF (NVAF). The NOACs also significantly reduced intracranial hemorrhage (ICH) and mortality, with similar major bleeding rates, but often increased gastrointestinal bleeding risk versus warfarin [20]. Subgroup analyses (e.g., by age, history of stroke, and renal impairment) suggest that some NOACs have better benefit–risk profiles than others in specific patient groups [21]. All 4 NOACs are now approved for the prevention of stroke and SE in moderate-to-high-risk patients with AF in many countries; additionally, in Europe, rivaroxaban (2.5 mg twice daily—a quarter of the AF dose) is approved in combination with antiplatelet therapy for secondary prevention after ACS in patients with elevated biomarkers (troponin or creatine kinase-MB) [22-30]. Guidelines (e.g., from the American College of Chest Physicians [ACCP] and the European Society of Cardiology [ESC]) recommend NOACs for stroke prevention in high-risk patients with AF, either as an alternative option or in preference to warfarin (Supplemental Table 1) [6,31-35]. However, guidelines differ in their definitions of 'high-risk' patients and preferred scoring system. Ultimately, treatment decisions should be made on an individual basis for each patient and based on local guidelines [36].

Real-world data support the efficacy and safety of rivaroxaban, dabigatran, and apixaban in patients with AF reported in phase III studies (real-world data with edoxaban are not yet published) [37-45]. Several ongoing large-scale prospective studies or registries are continuously assessing the use of NOACs and their effectiveness and safety outcomes in patients with NVAF (Supplemental Table 2). In general, studies have shown that, in routine clinical practice, patients are generally more persistent and adherent to NOACs than VKAs and may have better long-term clinical outcomes [46,47].

Despite the established effectiveness and safety of the NOACs in stroke prevention in AF, best practice in specific scenarios is uncertain, although there are several completed and ongoing studies

in those settings (See Supporting Information, Table 1, in the online version of this article). The field is evolving rapidly, but lacks a reference source of current trials beyond stroke prevention in patients with AF. This review provides such a resource and examines the potential for new applications in the cardiovascular field. Recent data and upcoming studies that assess NOACs are summarized—with a focus on rivaroxaban—in a broad range of CVD indications, including cardioversion or catheter ablation, AF and ACS, AF and CAD with percutaneous coronary intervention (PCI), CAD, and PAD.

Methods

Using a predefined search strategy, PubMed, ClinicalTrials.gov and meeting abstracts were searched through September 2017 for data on completed and upcoming trials of oral anticoagulants in patients with cardiovascular disorders. All resulting studies and clinical trials were retrieved, reviewed, and checked for related publications. The following search terms were used: atrial fibrillation, cardioversion, catheter ablation, acute coronary syndrome, coronary and peripheral artery disease, percutaneous coronary intervention, heart failure, hypertrophic cardiomyopathy, atrial tachyarrhythmia, left atrial/left atrial appendage thrombi, valve disease, valve replacement, mitral stenosis, and antiphospholipid antibody syndrome (APS).

Potential benefits of NOACs in patients with cardiovascular disorders: recent and current studies

AF and stroke risk: real-world evidence

International Medical Statistics Health data from 2014 indicate that factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have a higher usage rate than thrombin inhibitors (dabigatran), and that rivaroxaban is the most commonly used factor Xa inhibitor [48].

Effectiveness and safety

NOACs should demonstrate similar, or lower, rates of stroke/SE and major bleeding compared with warfarin in order to demonstrate clinical effectiveness. Several studies have compared the real-world effectiveness and safety of VKAs and NOACs such as rivaroxaban for stroke prevention in AF. These observational studies reflect use in clinical practice in populations without the inclusion and exclusion restrictions of phase III trials. The findings in these more inclusive populations underpin the effectiveness and safety of NOACs versus VKAs seen in phase III clinical trials [42-44,49-52]. In the prospective, international, noninterventional phase IV XANTUS (Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation) study, stroke, and major bleeding rates were low in patients given rivaroxaban (mean $CHADS_2$ score 2.0) [41]; major bleeding rate was lower than in the phase III 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); (2.1 vs 3.6%/year, mean $CHADS_2$ score in ROCKET AF 3.5) (Figure 1) [17,41,42,53,54]. Data from the Dresden NOAC Registry suggest that in a real-world setting, rates of major bleeding and outcomes with rivaroxaban may be better than or similar to those obtained with a VKA [42]. In a study assessing patients with AF from the Dresden NOAC Registry who received rivaroxaban, the rate of major bleeding was 3.0 per 100 patient-years for the on-treatment population [53]. The rate of stroke, transient ischemic attack and SE was 2.0 per 100 patient-years in the intention-to-treat population [53]. In a similar study assessing patients with AF in the Dresden NOAC Registry who remained on a VKA, the rate of major bleeding was 4.2 per 100 patient-years, and the rate of stroke, transient ischemic attack and SE was 1.3 per 100 patient-years in the intention-to-treat population [51]. Real-world studies have indicated a similar or decreased risk of ICH with rivaroxaban, apixaban, or dabigatran versus warfarin, consistent with the phase III clinical trial results [16,17,41,55-57]. Gastrointestinal bleeding risk is similar for rivaroxaban and warfarin in real-world settings [47,58,59]; findings for dabigatran versus warfarin have been inconsistent in this setting [37-39,58-61].

Most real-world effectiveness and safety outcomes data with NOACs versus VKAs are from retrospective database analyses, and outcomes are largely consistent with phase III trial results. For

example, a US Department of Defense claims database analysis indicated low rates of major bleeding with rivaroxaban (2.9%/year) [54]. Significantly lower rates of stroke with dabigatran versus warfarin (0.9%/year vs 1.3%/year; hazard ratio [HR]: 0.73, 95% confidence interval [CI]: 0.55–0.97) and similar rates of major bleeding (3.1% vs 3.7%) were also observed, consistent with results for the dabigatran 150 mg twice-daily dose in the phase III trial [16,62]. However, other studies have reported inconsistent effectiveness and safety outcomes versus other database analyses or phase III trial results [63]. These findings may be due to differences in patient characteristics and outcome definitions, and incomplete ascertainment of safety and efficacy outcomes in datasets extracted from routine records. There are also other factors that may affect data quality and limit the generalization of findings based on claims datasets. These include potential bias in drug and control group selection, coding errors, missing data, and varying or missing follow-up; therefore, retrospective datasets are insufficient, and prospective observational studies are required to support phase III study results.

Treatment patterns

The GARFIELD-AF (Global Anticoagulant Registry in the FIELD-AF) registry is a comprehensive multinational prospective program charting the evolving use of anticoagulants in patients with newly diagnosed AF. It examines treatment patterns (including no treatment), patient characteristics, and therapy choice in sequential cohorts [64]. Both men and women aged 18 and over, with a first diagnosis of NVAF within the previous 6 weeks, and with one or more investigator-defined risk factors for stroke, were included [64]. Cohorts were divided by date of enrollment (cohort 1 between March 2010 and October 2011; cohort 2 between August 2011 and June 2013; cohort 3 between April 2013 and October 2014; cohort 4 between March 2014 and July 2015; and cohort 5 between August 2015 and July 2016) [64]. Data from 39,670 patients in cohorts 1–4 showed that, since the introduction of the NOACs, newly diagnosed at-risk patients with AF increasingly receive guideline-recommended therapy, driven by increased use of NOACs and reduced VKA use (with or without antiplatelets), and reduced use of antiplatelets alone in patients with CHA_2DS_2-VASc scores ≥2 [64]. Unpublished data from cohort 5 show a similar pattern to cohort 4 (Figure 2). However, because anticoagulant management was based on clinician decisions (rather than a risk score), the study observed use of anticoagulants and antiplatelets in patients without a risk score or other indication for anticoagulation (CHA_2DS_2-VASc score of 0) (Figure 2) [65].

Many patients given NOACs do not receive the appropriate dose [66,67], signifying a need for further education on appropriate dosing of NOACs. The extent of use of the lower dose of NOACs differs by anticoagulant, and for some agents this differs substantially from the use in the phase III trials [56,68]. Despite increasing use of anticoagulant therapy in line with guidelines, ~25% of patients with AF at risk of stroke still do not receive anticoagulation. Conversely, ≤40% of those at very low stroke risk (CHA_2DS_2-VASc score of 0) receive anticoagulation and/or antiplatelet therapy despite guideline recommendations [64].

Adherence/persistence

Adherence relates to a patient acting in accordance with the prescribed interval and dose of the drug regimen (percentage of doses taken as prescribed) [69]. Persistence measures treatment duration and excludes permissible gaps [69].

In the Dresden NOAC Registry, persistence with therapy was analyzed using prescription refill data. Persistence was defined as 'a refill within the period covered by the previous prescription or within 60 days after the end of this period' [70]. This included patients in whom treatment may have been interrupted but who received their following prescription within 60 days [70]. Persistence with therapy with rivaroxaban (66.0%) at 180 days was significantly higher than with VKA therapy (58.1%) in patients with AF [70]. Similarly, in 2 retrospective US database analyses, patients with AF were significantly more persistent at 6 months with rivaroxaban (74% and 82% persistent) than warfarin

(67% and 68% persistent) [46,47]. In 2 retrospective analyses of different US databases, rivaroxaban was associated with significantly higher persistence rates at 1-year follow-up, and significantly better adherence than dabigatran [71,72]. In a small-scale Canadian study, once-daily oral anticoagulant therapy was associated with better adherence than twice-daily therapy [73].

These observational studies indicate that patients receiving rivaroxaban were significantly less likely to discontinue treatment versus other oral anticoagulants (8% for rivaroxaban vs 18% for warfarin; 18% for dabigatran and 27% for apixaban; data for edoxaban are not yet available) [73].

Specific patient subpopulations

Despite the overall evidence for use of NOACs [6,31-35], there are specific situations for which there is a lack of clinical evidence. These include cardioversion, AF ablation, subclinical AF, dissolution of thrombi present in the LAA, concomitant AF and ACS, and patients with a high $CHADS_2$/CHA_2DS_2-VASc score and no known AF. The latest European Heart Rhythm Association (EHRA) 2015 practical guidelines, and other recent consensus documents, advise how to manage selected, specific clinical situations [74-76], although they may need revision as trial evidence emerges.

Cardioversion

In patients with AF without adequate anticoagulation, cardioversion is associated with a 5–7% risk of thromboembolic events [77]. Thrombi are usually already present in the LAA or develop there after cardioversion [77]. Adequate anticoagulation in the weeks before cardioversion, or exclusion of patients with LA thrombi before the procedure, reduces this risk [77]. Guidelines recommend anticoagulation therapy before and after cardioversion, irrespective of $CHADS_2$/CHA_2DS_2-VASc score or cardioversion method (electrical or pharmacological) [6,31]. An alternative way to reduce the risk of thromboembolic events without prior anticoagulation is to perform transesophageal echocardiogram (TEE)-guided cardioversion [77]. This procedure can establish the presence of a thrombus in the LA/LAA prior to cardioversion (incidence of LA thrombus in patients with AF pre-cardioversion is ~7–12%) [77-79]. Therefore, if patient compliance with anticoagulation therapy is doubtful, patients undergoing cardioversion or ablation (see section 2.2 below) need to be assessed for the presence of an LA/LAA thrombus [74]. Immediate anticoagulation post-cardioversion is still required for up to 4 weeks because of the risk of thrombi developing after the procedure [77]. Improved strategies are needed because cardioversion frequently has to be rescheduled because of poor international normalized ratio control, and prolonged delays reduce restoration of sinus rhythm.

Anticoagulation with warfarin or NOACs should continue for ≥4 weeks after cardioversion, based on ESC and American Heart Association (AHA)/ American College of Cardiology (ACC)/ Heart Rhythm Society (HRS) guidelines [31,80]. Post hoc analyses of phase III studies with dabigatran, rivaroxaban, and apixaban have shown the efficacy and safety of NOACs in patients with AF undergoing cardioversion [81-83]. The European approved indications for these 3 NOACs have, therefore, been extended to include continued use in cardioversion [23,25,27]. The prospective X-VeRT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in subjects with non-valvular aTrial fibrillation scheduled for cardioversion) trial with rivaroxaban supports the findings of the post hoc analysis of ROCKET AF, but the sample size only allowed for a descriptive analysis [84,85]. Rivaroxaban administered de novo, as ongoing therapy, or instead of VKAs or another anticoagulant had a low risk of thromboembolic and bleeding events, similar to VKA treatment [84]. Rivaroxaban had similar risks to VKAs in both early and delayed cardioversion strategies, with a significantly shorter time to cardioversion in the delayed strategy group [84], resulting in the European approved indication for rivaroxaban being extended to include de novo rivaroxaban use in patients potentially undergoing cardioversion. In this case, rivaroxaban should be started ≥4 hours before cardioversion to ensure adequate anticoagulation before the procedure [23]. ENSURE-AF was a recent prospective trial comparing edoxaban with enoxaparin/warfarin in patients

undergoing cardioversion for NVAF. Efficacy and safety endpoint rates were low in each group [86]. A trial assessing apixaban in cardioversion is ongoing (EMANATE [NCT02100228]).

Catheter ablation

Catheter ablations are associated with a 0.3–0.4% incidence of clinically evident thromboembolic events, as observed in studies by Gaita *et al*. and Kirchhof *et al*. Interestingly, these studies also identified a proportion of patients with asymptomatic acute small cerebral lesions following catheter ablation, 14% and 26% respectively[87,88]. In the COMPARE trial, continuous warfarin therapy in patients undergoing catheter ablation reduced thromboembolic event rates [89], and guidelines recommend thromboprophylaxis in the peri-ablation setting [6,90]. Evidence that catheter ablation reduces stroke or mortality risk is lacking, but it is effective in controlling heart rhythm disorders and their symptoms. Practical guidance recommends ≥8 weeks' post-procedure anticoagulation, depending on stroke risk [90].

Several studies have demonstrated that fewer complications occur with uninterrupted versus interrupted VKA; therefore, guidelines recommend continuous anticoagulation for patients receiving VKA during catheter ablation [6]. Nonrandomized studies using various dose–timing protocols suggest that the rate of major complications was low in patients undergoing catheter ablation with uninterrupted rivaroxaban, similar to other NOACs [91,92]. One retrospective study of uninterrupted warfarin or dabigatran versus a bridged warfarin strategy reported a higher rate of major complications with uninterrupted warfarin [93]. For continuous anticoagulation with NOACs, the lack of reversal agents in the ablation setting has initially been a barrier to use [94]. However, idarucizumab is now approved for use as a reversal agent for dabigatran, with promising ongoing studies for the reversal agents for the other NOACs, including andexanet alfa (reversal agent for apixaban, edoxaban, and rivaroxaban) and ciraparantag (reversal agent for several anticoagulants) [94].

VENTURE-AF was the first prospective trial of an uninterrupted NOAC versus a VKA in patients with AF undergoing catheter ablation; 248 patients were randomized to either uninterrupted rivaroxaban or uninterrupted VKA before catheter ablation and for 4 weeks post-ablation. There was 1 major bleeding event, 1 ischemic stroke, and 1 vascular death in the VKA group; no such events occurred in the rivaroxaban group [95]. Although small scale, this study suggests that use of uninterrupted rivaroxaban is feasible in this setting [95].

Other trials assessing the use of NOACs in the ablation setting are ongoing (See Supporting Information, Table 1, in the online version of this article). Data will become available over the coming years, and will inform treatment decisions.

Secondary prevention of future cardiovascular events after ACS

Several antithrombotic strategies have been tested for secondary prevention of coronary events, including DAPT with various antiplatelet combinations, a platelet-specific thrombin receptor antagonist (vorapaxar), and anticoagulation [96-104].

In the phase III ATLAS ACS 2 TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome) trial, rivaroxaban (2.5 mg or 5 mg twice daily) plus antiplatelet therapy (ASA alone or ASA plus clopidogrel) versus antiplatelet therapy alone reduced the risk of the composite of cardiovascular mortality, MI, and stroke in patients with a recent ACS [101]. Rivaroxaban increased major bleeding and ICH risk, but not fatal bleeding risk [101]. The most favorable benefit–risk profile was seen with rivaroxaban 2.5 mg twice daily. The phase III APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) trial assessed apixaban (full AF dose of 5 mg twice daily) plus standard antiplatelet therapy versus antiplatelet therapy alone in this setting. The study was prematurely terminated owing to increased major bleeding in the apixaban group (2.7% vs 1.1%; $p<0.001$) with no significant reduction in

cardiovascular death, MI or ischemic stroke compared with antiplatelet therapy alone (7.5% vs 7.9%, respectively; p=0.51) [103]. In a phase II, double-blind study, patients who had recently had an MI receiving dual antiplatelet therapy were randomized to dabigatran (various doses) or placebo [104]. Results showed that bleeding event rates were significantly higher with dabigatran (HR=1.77–4.27 with increasing dose) versus placebo. However, dabigatran did demonstrate a significantly reduced level of coagulation activity (45% reduction at week 4; p<0.001) [104]; no phase III dabigatran study is currently underway.

More recently, the phase II GEMINI ACS 1 (NCT02293395) trial demonstrated that rivaroxaban 2.5 mg twice daily had a similar bleeding risk to ASA in patients with a recent ACS who were receiving a $P2Y_{12}$ inhibitor. Similar efficacy outcomes were observed in both treatment arms, although the trial was not powered to detect a difference in efficacy [105].

In summary, rivaroxaban 2.5 mg twice daily in addition to antiplatelet therapy may provide greater clinical benefits compared with antiplatelet therapy alone (standard of care). Rivaroxaban is indicated for secondary prevention of cardiovascular events after an ACS event in patients with elevated cardiac biomarkers (troponin or creatine kinase-MB; approved by the European Medicines Agency [EMA] but not the US Food and Drug Administration [FDA]) [23]. The role of the other NOACs is uncertain and apixaban, dabigatran and edoxaban are currently not indicated for use in the post-ACS setting.

Coronary and peripheral artery disease

Coronary artery disease and PAD often occur concomitantly; 1 study showed that 68% of patients aged >50 years with PAD also had CAD [106]. PAD affects 12–14% of the population and prevalence increases with age, affecting ≤20% of patients aged >75 years [107,108]. Patients with PAD have increased thrombogenicity and an increased relative risk of 3.1 (95% CI: 1.9–4.9) for all-cause mortality, and 5.9 (95% CI: 3.0–11.4) for cardiovascular mortality [109]. Because of the coexistence of CAD and cerebrovascular disease, PAD is associated with increased risk of cardiac and cerebrovascular events, in addition to obstructive disease of the lower extremities. Antiplatelet therapy can reduce the rate of the composite of cardiovascular death, MI, or stroke to <10% at the cost of increased minor bleeding; however, individual outcomes still occur in 2–20% of patients [110]. Revascularization strategies are also indicated to decrease the risk of limb loss, relieve symptoms, and improve quality of life [108].

In patients with PAD, the WAVE trial showed that a VKA plus ASA was no more effective than ASA alone in preventing cardiovascular complications, and increased the risk of life-threatening bleeding events [111]. Older trials support anticoagulation treatment in patients with CAD [112], and rivaroxaban is being assessed in this setting in phase III clinical trials (See Supporting Information, Table 1, in the online version of this article).

The phase III COMPASS (Cardiovascular OutcoMes for People Using Anticoagulation StrategieS) trial (NCT01776424) was stopped early after rivaroxaban 2.5 mg twice daily plus ASA clearly demonstrated efficacy in patients with CAD and/or PAD [113]. Rivaroxaban 2.5 mg twice daily plus ASA significantly reduced the composite incidence of cardiovascular death, stroke or MI, compared with ASA alone (4.1% vs 5.4%, HR: 0.76, 95% CI: 0.66–0.86, $p < 0.001$). In addition, rivaroxaban 2.5 mg twice daily plus ASA was associated with a nominally significant reduction in all-cause mortality compared with ASA alone (3.4% vs 4.1%; $p = 0.01$; threshold for significance = 0.0025). The overall incidence of major bleeding was low but significantly increased with rivaroxaban 2.5 mg twice daily plus ASA, compared with ASA alone (rivaroxaban 2.5 mg twice daily plus ASA vs ASA alone: 3.1% vs 1.9%, $p < 0.001$); there was no increase in fatal bleeding or intracranial hemorrhage. Rivaroxaban 5 mg twice daily was also evaluated in COMPASS but did not demonstrate significant benefits in

efficacy outcomes compared with ASA alone and showed similar safety outcomes to rivaroxaban 2.5 mg twice daily plus ASA [113].

A subanalysis of the COMPASS data showed that the overall study outcomes were consistent in the subgroup of patients with PAD; importantly, rivaroxaban 2.5 mg twice daily plus ASA was associated with a significant 70% reduction in the incidence of major amputation in patients with PAD compared with ASA alone [114]. Additional data on the efficacy of rivaroxaban in patients with PAD will be provided by the phase III VOYAGER PAD trial (NCT02504216) in patients with PAD who have undergone recent procedures to improve peripheral blood flow.

Patients with AF and CAD and those undergoing PCI

Acute coronary syndrome is commonly associated with prevalent or incident AF, with an incidence of AF in ACS of 2.3–21% [115]. Concomitant AF and ACS increases mortality by 40% versus ACS alone [116-118]. There are insufficient data to guide clinical practice or identify the optimal antithrombotic therapy [119].

Patients with concomitant AF and ACS are challenging, because the combination of antiplatelet (ASA and/or a $P2Y_{12}$ inhibitor) and anticoagulation therapy, especially at doses indicated for AF, increases annual risk of fatal and nonfatal bleeding episodes [120-122]. The WOEST (What is the Optimal antiplatElet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) trial was the first randomized trial comparing single versus DAPT in VKA-treated patients undergoing PCI (~280 patients in each arm); ~70% of enrolled patients had AF as the indication for oral anticoagulation [123]. Treatment with clopidogrel and a VKA significantly lowered the risk of bleeding complications versus triple therapy with ASA, clopidogrel, and a VKA. Although the trial was small, there was no increased risk of thrombotic events with VKA plus single antiplatelet therapy [123]. Similar results were reported in a Danish registry study [124]. Based on the WOEST findings, the AHA/ACC/HRS guidelines recommend dual therapy with a VKA and clopidogrel [31]. By contrast, the 2016 ESC guidelines recommend initial triple therapy (VKA or NOAC, plus both clopidogrel and ASA), followed by dual therapy (VKA or NOAC, plus either clopidogrel or ASA) [80]. Because of the increased bleeding risk, triple therapy duration should be as short as possible [74].

Combined antiplatelet and anticoagulant therapies for the initial phase after PCI in patients with AF are recommended [6,31,74,75,125], but observational data suggest that combination therapies increase the risk of bleeding [124]. Several ongoing trials are assessing NOACs in this setting (See Supporting Information, Table 1, in the online version of this article); 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) demonstrated improved safety versus VKA in rivaroxaban-treated patients with ACS undergoing PCI [126]. As a consequence of PIONEER AF-PCI, rivaroxaban 15 mg once daily in combination with a $P2Y_{12}$ inhibitor was approved for the treatment of patients with NVAF who require oral anticoagulation and undergo PCI with stent placement [23]. RE-DUAL PCI (Randomized Evaluation of DUAL antithrombotic therapy with dabigatran versus triple therapy with warfarin in patients with nonvalvular atrial fibrillation undergoing Percutaneous Coronary Intervention) demonstrated that two different regimens of full-dose anticoagulation therapy with dabigatran (either 110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) resulted in a significantly lower risk of major or clinically relevant nonmajor bleeding events when compared with triple therapy with warfarin; in addition, dual therapy with dabigatran was noninferior to triple therapy with warfarin with respect to the composite efficacy endpoint of thromboembolic events, death, or unplanned revascularization.[127]

Heart failure

Heart failure constitutes a prothrombotic state, but evidence that an oral anticoagulant reduces mortality/morbidity in HF versus placebo or ASA is lacking [128]. However, phase III subanalyses

suggest that anticoagulation may benefit patients with HF and CAD. In a subgroup analysis of ATLAS ACS 2 TIMI 51, rivaroxaban 2.5 mg twice daily was associated with a lower rate of the composite of death from cardiovascular causes, MI, and stroke (primary efficacy outcome) versus placebo (11.6 vs 18.6%) in patients with HF and ACS.

Only one ongoing trial is assessing NOACs in patients with HF–COMMANDER-HF (NCT01877915) [129]. It will assess the effectiveness and safety of rivaroxaban compared with placebo (both in addition to standard therapy for HF and CAD) in reducing the risk of death, MI, and stroke in patients with HF and significant CAD (see Supporting Information, Table 1, in the online version of this article).

Related fields of research

"Cryptogenic" stroke: Embolic Stroke of Undetermined Source (ESUS)

Ischemic stroke accounts for 80% of all strokes [130]. Of these, 25% are 'embolic stroke of undetermined source' (ESUS), previously designated as cryptogenic stroke [131], which is defined as a nonlacunar brain infarct (subcortical infarct >1.5 cm on computed tomography or >2.0 cm on magnetic resonance imaging) without proximal arterial stenosis or an identified source of cardioembolism (including AF). Recurrent stroke in patients with ESUS is reported inconsistently, because of differing diagnostic and prognostic criteria and lack of standardization, but ranges from 3% to 6% per year [131]. Treatment options to prevent recurrent stroke after ESUS are limited, and the mechanisms of stroke generation may be heterogeneous. A high proportion of older patients (≥55 years) who have an ESUS may have underlying paroxysmal AF [132]. Several studies observed paroxysmal AF in around 10–20% of patients with cryptogenic ischemic stroke [131]. The duration of paroxysmal AF can be short, lasting only minutes or seconds; therefore, anticoagulation therapy may not be justified [131]. Evaluating patients for AF after an ESUS is important because of the treatment implications (Supplemental Table 3).

The CRYSTAL AF study evaluated AF incidence and time to AF detection in patients with ESUS using an insertable cardiac monitor [133]. Continuous monitoring detected AF in 30% of these patients versus 3% with standard medical care at 36-month follow-up [134]. Of patients with detected AF, 97% were prescribed anticoagulation therapy [134]. Another study, EMBRACE, confirmed that paroxysmal AF was common among patients aged ≥55 years with recent ESUS or transient ischemic attack [132]. In summary, prolonged electrocardiogram monitoring substantially improved AF detection and increased the rate of anticoagulant treatment [132].

The efficacy and safety of dabigatran (RE-SPECT ESUS; NCT02239120) and apixaban (ATTICUS; NCT02427126) in patients with prior ESUS is currently being investigated. The hypothesis that a NOAC could be superior to aspirin in reducing the risk of recurrent stroke and SE was not confirmed in the NAVIGATE ESUS study. This finding has opened the field for new studies to determine the underlying mechanism of these strokes, including the complications of atherothrombotic disease in sinus rhythm [113,114,135].

Future potential applications for NOACs?

Beyond the unmet needs in defined patient subgroups with vascular disease, other patient groups could benefit from NOAC treatment.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetically determined heart muscle disease associated with hemodynamic abnormalities. It occurs in ~0.2% of the general population [136]. Stroke incidence in patients with HCM and AF is ~21–23% [136] and, therefore, anticoagulation therapy is recommended independent of CHA_2DS_2-VASc score [31]. Specific data for NOACs in patients with HCM are not available, but these agents may be considered [136].

Anticoagulation based on monitoring atrial tachyarrhythmia

Implanted cardiac devices can detect atrial tachyarrhythmias, allowing assessment of the correlation between AF or atrial flutter and stroke risk, and the feasibility of 'pill-in-the-pocket' anticoagulation based on daily remote transmissions from an implanted cardiac device. The IMPACT (In-hospital Mortality for PulmonAry embolism using Claims daTa) study assessed whether the initiation and withdrawal of oral anticoagulant therapy (VKAs, rivaroxaban, dabigatran, or apixaban) guided by continuous ambulatory monitoring of an atrial electrogram improves clinical outcomes versus conventional clinical management in patients with implanted dual-chamber cardiac resynchronization therapy defibrillator devices [137]. This study was terminated early (2 years' median follow-up) based on no difference in primary endpoints (stroke, SE, and major bleeding) between groups, suggesting that early initiation and withdrawal of anticoagulation based on remotely detected atrial tachyarrhythmias did not prevent thromboembolism and bleeding [137]. The REACT.COM pilot study (NCT01706146) concluded that intermittent anticoagulation with dabigatran, rivaroxaban, or apixaban guided by a continuous AF-sensing implantable cardiac monitor (Reveal XT) with remote data transmission capabilities is feasible [138]. This allows remote and continuous evaluation of patients for arrhythmias including AF recurrences, even for brief asymptomatic episodes. Whether brief episodes of AF (e.g., <6 minutes) are prognostically important is uncertain, and a role for NOACs in such patients is undetermined.

REVEAL AF (NCT01727297) uses the Reveal implantable cardiac monitor and aims to determine the incidence of AF in patients suspected to be at high risk of AF, and to understand how physicians manage these patients after AF has been detected [139]. This study aimed to identify which patient characteristics are most predictive of developing AF. A total of 385 patients with a $CHADS_2$ score of ≥3, or a $CHADS_2$ score of 2 plus at least one additional AF risk factor (to include CAD, renal impairment, sleep apnea or chronic obstructive pulmonary disease), were followed up for a mean of 22.5 months and showed an AF detection rate of 6.2% at 30 days [140]. The detection rate increased throughout the monitoring period. A high incidence of AF (lasting ≥6 minutes) was detected by cardiac monitoring in ~30% of high-risk patients at 18 months, increasing to 40% at 30 months [140]. Undetected subclinical AF may present in a substantial proportion of patients with risk factors for AF and stroke. Prophylactic therapies may be beneficial in these patients, and further research is required [140].

Other ongoing studies (e.g., ARTESiA [NCT01938248] and NOAH-AFNET 6 [NCT02618577]) are assessing oral anticoagulation versus standard therapy for ischemic stroke and SE risk reduction in patients with device-detected subclinical AF and additional stroke risk factors.

Device interventions for stroke prevention in patients with AF (LA/LAA thrombi)

Permanent treatment options, such as surgery to remove or close the LAA or percutaneous closure devices, have been explored to circumvent the risk of bleeding associated with long-term anticoagulation therapy. Although surgical closures are often incomplete, the WATCHMAN, AMPLATZER, and LARIAT devices are the 3 closure devices that are currently being studied for percutaneous LAA closure [141]. The WATCHMAN device is the most studied and is noninferior to warfarin for preventing the combined outcomes of stroke, SE, and cardiovascular death, and superior for preventing cardiovascular and all-cause mortality [142]. A meta-analysis of PROTECT-AF and PREVAIL randomized trials, and 2 nonrandomized studies, consisting of 2406 patients with 5931 patient-years of follow-up, found significantly fewer hemorrhagic strokes, cardiovascular/unexplained deaths and nonprocedural bleeding events in patients receiving LAA closure with the WATCHMAN device compared with patients treated with warfarin, with similar rates of all-cause stroke or SE between the 2 groups [143].

Valve disease and valve replacement

Antithrombotic therapy is recommended after valve replacement with mechanical prostheses, bioprostheses or transcatheter aortic valve replacement (TAVR) and should be adapted according to the type and site of prosthesis, the period considered and patient characteristics [144]. Combination therapies of both anticoagulation and antiplatelet agents have not been robustly studied in these patients. The RE-ALIGN phase II study assessed dabigatran versus warfarin in patients who had undergone aortic or mitral valve replacement with mechanical valves. The trial was terminated prematurely owing to increased rates of thromboembolic and bleeding complications in the dabigatran group, despite the use of higher doses of dabigatran than used in patients with AF [146]. Although not known, it has been assumed that as dabigatran was not suitable in the prevention of thromboembolic events in patients with mechanical heart valves, this finding can be applied to all NOACs. GALILEO (NCT02556203) is an ongoing phase III study in patients after TAVR, assessing rivaroxaban plus ASA followed by rivaroxaban alone versus ASA plus clopidogrel followed by ASA alone for superiority in reducing death or first thromboembolic events and noninferiority in the occurrence of primary bleeding events. Results are expected in 2018. Ongoing studies assessing the benefit–risk of NOACs in patients with bioprosthetic or rheumatic valves include the RIVER (NCT02303795) and INVICTUS studies (NCT02832544/NCT02832531).

Mitral stenosis

Patients with hemodynamically significant mitral stenosis were excluded from the trials of stroke prevention with the NOACs, despite being at increased thrombotic, embolic, and stroke risks. Optimal anticoagulation control with VKAs is challenging, especially in regions where rheumatic heart disease is most prevalent. NOACs may have an important role in such patients [147]. Launched in June 2016, INVICTUS is a worldwide program consisting of a registry of 20,000 patients and 2 clinical trials that will examine if rivaroxaban can safely reduce strokes in patients with rheumatic heart disease [148].

Bioprosthetic mitral valves

Guidelines currently recommend VKAs as the first-line oral anticoagulation therapy in patients with AF and bioprosthetic mitral valves owing to lack of evidence with NOACs in this setting [149]. The phase II RIVER trial (NCT02303795) will assess rivaroxaban versus VKAs for the prevention of disabling strokes, major bleeding events, all-cause death, valve thrombosis, and noncentral nervous system SE in patients with AF and bioprosthetic mitral valves. Results are expected in late 2018/early 2019.

Phospholipid syndrome

The current mainstay for the prevention of VTE in patients with thrombotic APS is long-term anticoagulation with VKAs such as warfarin [150]. Several ongoing phase II/III studies are assessing rivaroxaban versus warfarin in patients with thrombotic APS with or without systemic lupus erythematosus, such as RAPS (NCT02116036) [150], and in high-risk patients with triple APS (NCT02157272) [151].

End-stage renal dysfunction and hemodialysis

Patients with severe renal dysfunction and those requiring hemodialysis were excluded from stroke prevention trials with the NOACs [16-19]. However, such patients are at increased risk of thrombotic and bleeding events. Trials with apixaban and edoxaban suggest that the factor Xa inhibitors may have a favorable benefit–risk balance compared with warfarin in such patients [152,153]. A small phase I study with apixaban has led to its FDA approval in patients with AF and end-stage renal disease (ESRD) [154,155]. A further small-scale phase I study with rivaroxaban in individuals with ESRD (but otherwise healthy) showed that deterioration of renal filtration function from severe to ESRD did not have a significant impact on rivaroxaban pharmacokinetics and pharmacodynamics

beyond changes observed with moderate or severe renal impairment [156]. Trials with patients indicated for anticoagulation have yet to be conducted.

Cognitive decline

Debate exists over the association between AF and cognitive decline, even beyond the association with recurrent embolic stroke. A recent review concludes that AF is independently associated with cognitive decline, even among patients with no clinical history of stroke [157]. Cognitive decline is associated with stroke and silent cerebral infarcts, and patients with AF have higher rates of silent cerebral infarcts than patients without AF. Among patients with AF, low scores on the Mini Mental State Examination have been associated with out-of-range international normalized ratio values and an increased risk of vascular events and bleeding. However, the impact of anticoagulation on silent cerebral infarcts remains unknown; therefore, clinical trials evaluating the effect of NOACs on cognitive decline in patients with AF would be of value [157].

Conclusions

There are significant unmet medical needs for several arterial thromboembolic-related conditions. The NOACs may provide new treatment options in these areas and studies to address these unmet clinical needs are currently ongoing. Observational studies with NOACs enable assessment of patient management, safety, and observed outcomes in an extended range of patients, including many excluded from clinical trials. Beyond the currently approved NOAC indications, there are cardiovascular and cerebrovascular conditions where further clinical studies are needed to assess the benefit–risk profile of the NOACs and the potential for practical management advantages. In this review, the emphasis has been placed on rivaroxaban as the NOAC with the broadest range of indications. This agent is also being investigated in further indications across several patient groups, for example, indications in the post-ACS setting. NOACs should be assessed at an individual level when considering future indications and use in patient subgroups that have not been investigated previously.

Figure legends

Figure 1. Rates of major bleeding with rivaroxaban in ROCKET AF, the Dresden NOAC Registry, the US Department of Defense postmarketing surveillance study, and XANTUS. Results are not intended for direct comparison. Abbreviations: NOAC, nonvitamin K antagonist oral anticoagulant; 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; XANTUS, Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation.

Figure 2. Distribution of CHA_2DS_2-VASc and pattern of anticoagulant treatment. Increase in use of NOACs from Cohort 1 to Cohort 5; overuse in patients with CHA_2DS_2-VASc = 0. 53,053 prospective patients were enrolled in 5 sequential cohorts from 2010 to 2016. Cohort 1 (2010–2011), *n* = 5,499; Cohort 2 (2011–2013), *n* = 11,662; Cohort 3 (2013–2014), *n* = 11,462; Cohort 4 (2014–2015), *n* = 11,296; Cohort 5 (2015–2016), *n* = 12,134.
AP: antiplatelet; DTI: direct thrombin inhibitor; FXa factor Xa inhibitor; VKA: vitamin K antagonist.

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