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Very low-dose direct oral anticoagulants combined with platelet inhibitors in coronary artery disease: ready for widespread use?

Nägele Matthias P.[ab], **Beer Jürg H.**[ac]

[a] Department of Internal Medicine, Cantonal Hospital of Baden, Switzerland
[b] Department of Cardiology, University Hospital Zurich, Switzerland
[c] Center for Molecular Cardiology, University of Zurich, Switzerland

Summary

After an acute coronary syndrome (ACS), there is evidence for a hypercoagulable state even several months after the initial event. This may also hold true for patients with stable coronary artery disease (CAD) who have a high risk for ischaemic events. In two recent trials, very low-dose (VLD) anticoagulation with rivaroxaban (2.5 mg twice daily) added to baseline antiplatelet therapy reduced cardiovascular events and mortality in patients with ACS or stable CAD at high risk of ischaemic events and low risk of bleeding. This benefit came at the cost of increased major bleedings. Intracranial haemorrhage was of particular concern in patients on concomitant dual antiplatelet therapy (DAPT). Rigorous selection of patients in line with the entry criteria of both trials appears to be crucial to balance the benefits and risks of this new treatment strategy. The efficacy and safety of VLD rivaroxaban compared to prolongation of DAPT with third-generation P2Y12 inhibitors (prasugrel or ticagrelor) is unclear. Given the lack of safety data, VLD rivaroxaban should not be combined with third-generation DAPT. In patients with CAD and concomitant heart failure with reduced ejection fraction, a large randomised trial failed to show a net benefit of VLD rivaroxaban. This suggests that VLD anticoagulants are only beneficial in situations where atherothrombotic events make up the majority of cardiovascular events. This review aims to provide an overview on past and current efforts of establishing prolonged anticoagulation in coronary artery disease.

Keywords: *coronary artery disease, antiplatelet therapy, direct oral anticoagulants, very low-dose rivaroxaban*

Correspondence:
Correspondence: Dr Matthias P. Nägele, MD, Department of Internal Medicine, Cantonal Hospital of Baden, Im Ergel 1, CH-5404 Baden, matthias.naegele[at]ksb.ch

Introduction

Coronary artery disease (CAD) is a common disorder in westernised aging societies. It is characterised by the gradual development of coronary atheromatous plaques, which can impair myocardial perfusion either via progressive luminal stenosis or sudden rupture of vulnerable plaques with subsequent platelet activation and formation of occlusive coronary thrombi (also known as type-1 myocardial infarction). The mainstays of treatment include lifestyle interventions, lipid-lowering, antianginal and antihypertensive therapies, coronary revascularisation and, importantly, antiplatelet drugs.

The current treatment standard in CAD is long-term low-dose aspirin monotherapy and time-limited dual antiplatelet therapy (DAPT) with a P2Y12 inhibitor after an acute coronary syndrome (ACS) and/or coronary revascularisation via percutaneous coronary intervention or coronary artery bypass grafting [1]. In selected cases, prolongation of DAPT beyond the usual duration of 6 to 12 months may be considered [1].

The rationale for anticoagulants in CAD

Despite significant progress in prevention and treatment, the disease burden of CAD remains high. Every fifth death in 2017 was attributed to CAD, making it the single most important cause of death in European Society of Cardiology (ESC) member countries [2]. Even with the third-generation P2Y12 inhibitors ticagrelor and prasugrel, around 10% of ACS patients develop a recurrent major adverse cardiovascular event in the first year [3, 4].

Many factors are involved in the high recurrence rate of CAD patients, one of which may be chronic activation of the plasmatic coagulation system. Besides affecting fibrin generation, thrombin, the central downstream enzyme of the plasmatic coagulation cascade, is a potent platelet activator. Coagulation activation is most profound during an ACS and parenteral anticoagulation has been shown to be beneficial in the acute phase [1]. Therapeutic anticoagulation is usually discontinued after successful reperfusion, unless there are specific indications for its continuation. However, persistence of a hypercoagulable state has been observed in some CAD patients and is associated with an increase in cardiovascular events [5, 6]. With this premise, long-term oral anticoagulant therapies were hypothesised to be of benefit in CAD. First trials of vitamin K antagonists (VKAs) in CAD patients were performed in the early 1980s, before the widespread adoption of aspirin thera-

py. Monotherapy with anticoagulants profoundly reduced cardiovascular events in CAD patients compared with no therapy, but they were not consistently superior to aspirin monotherapy and involved an increased bleeding risk [7]. Subsequent studies compared the addition of VKAs to aspirin with aspirin monotherapy. Likewise, these studies did not consistently demonstrate a benefit on cardiovascular events and showed a significant increase in major bleedings with the combination therapy [8]. With the advent of DAPT, which had a more favourable benefit-risk profile compared with VKAs, this treatment strategy lost support in clinical practice.

Direct oral anticoagulants in CAD: the search for an optimal dose

Interest in long-term anticoagulation in CAD was renewed when direct oral anticoagulants (DOACs) entered the market. The major approval studies in atrial fibrillation showed that these drugs had a more favourable profile of antithrombotic effect versus bleeding risk than VKAs, especially concerning the reduced incidence of intracranial haemorrhage with DOACs. Enthusiasm was dampened when the first dose-finding trials with DOACs added to antiplatelet therapy in patients with CAD without a concomitant indication for anticoagulation (such as atrial fibrillation) were published.

The phase II APPRAISE study tested apixaban at daily doses of 5 to 20 mg after ACS in patients on single antiplatelet therapy (SAPT) with aspirin or DAPT with aspirin and clopidogrel [9]. A dose-related increase in bleeding was noted, which was more pronounced in apixaban-treated patients on DAPT compared with SAPT. The daily dose of 10 mg apixaban (as 5 mg twice daily; 2.5 mg twice daily in patients with advanced kidney disease) was then investigated in the phase III APPRAISE-2 trial in ACS patients, most of whom were on concomitant DAPT [10]. These therapeutic doses of apixaban failed to reduce cardiovascular events while significantly increasing the rate of major bleeding.

Dabigatran was investigated in the phase II RE-DEEM study in ACS patients on DAPT [11]. Twice daily doses ranging between 50 and 150 mg were tested. As with apixaban, a dose dependent increase in bleeding was observed. Although the study was not powered for efficacy endpoints, a numerical decrease in ischaemic events was noted in the therapeutic dose groups (110 and 150 mg) and a numerical increase was noted in the lower dose groups (50 and 75 mg). Dabigatran was not advanced into phase III in CAD patients.

ATLAS ACS-TIMI 46 was the dose-finding phase II trial for rivaroxaban in ACS patients [12]. It compared daily doses of 5 to 20 mg given either once or twice daily in patients stratified by either concomitant SAPT (aspirin) or DAPT (aspirin with a thienopyridine). In line with the results on dabigatran and apixaban, rivaroxaban led to a dose-dependent increase in bleeding events. Numerically lower rates of cardiovascular events were noted in the very low-dose (VLD) rivaroxaban group (2.5 mg twice daily), whereas there were numerical higher rates in DAPT-treated patients on the therapeutic rivaroxaban doses of 15 and 20 mg daily.

In summary, these dose-finding studies showed that there is a very narrow optimal therapeutic window between additional antithrombotic efficacy and an increase in bleeding events in CAD patients. At therapeutic DOAC doses (equivalent to the doses used in atrial fibrillation and thereby comparable to VKAs at international normalised ratio [INR] 2.0 to 3.0), the risk-benefit profile appeared to be unfavourable, especially when adding DOAC to DAPT as compared with aspirin monotherapy.

Importantly, despite higher bleeding rates, higher doses of DOACs did not appear to reduce cardiovascular events more profoundly than lower doses, indicating a ceiling effect of our current antithrombotic therapies. This observation is in line with evidence on triple therapy in patients with an indication for both anticoagulation (e.g., atrial fibrillation) and antiplatelet therapy (e.g., coronary intervention and/or acute coronary event). Preliminary trial evidence indicates that in this constellation, dual therapy (OAC with SAPT) as compared to triple therapy (OAC with DAPT) is superior in terms of bleeding risk without sacrificing antithrombotic efficacy [13, 14]. An intriguing explanation for this counterintuitive phenomenon is that excessive antithrombotic therapy may increase microbleeds into atheromatous plaques leading to intraplaque inflammation, which can result in plaque progression, instability and eventually rupture [15]. Another explanation is that bleedings often lead to (temporary) withdrawal of antithrombotic therapies or reduced patient adherence, which may lead to increased thrombotic events at further follow-up.

VLD rivaroxaban in CAD: a delicate balance of benefits and risks

Based on the evidence from dose-finding studies, the two lower doses of rivaroxaban were tested in two phase III trials. The ATLAS ACS 2-TIMI 51 trial investigated rivaroxaban 2.5 and 5 mg twice daily in patients with a recent ACS, the majority of whom were on DAPT with a thienopyridine (clopidogrel or ticlopidine) [16]. After a mean of 13 months of follow-up, both doses significantly reduced the composite of cardiovascular death, myocardial infarction and stroke. This benefit was bought with an increased rate of major bleeding in both groups, in particular in the 5 mg twice daily group. Of note, despite exclusion of DAPT patients with a history of stroke or transient ischaemic attack (TIA) and other risk factors for bleeding in the entry criteria of the trial, a more than threefold increase in intracranial haemorrhage was noted in both rivaroxaban groups. Although no subgroup analyses were statistically significant, there was a signal of harm from rivaroxaban concerning the efficacy endpoint in the smaller sample of SAPT-treated patients with previous stroke or TIA. Fatal bleedings were not significantly increased in either group. Interestingly, when the efficacy of the two doses was compared, only VLD rivaroxaban (2.5 mg twice daily) significantly reduced cardiovascular and all-cause mortality as well as stent thrombosis compared with the 5-mg group, again suggesting a ceiling effect of antithrombotic efficacy.

The majority of the DOAC trials focused on the 6- to 12-month-long phase after an ACS, when hypercoagulability is believed to be most pronounced. The concept of anti-

coagulation in CAD was advanced when focus was shifted to patients with stable cardiovascular disease. The COMPASS trial was a large trial programme that investigated the value of rivaroxaban, either 2.5 mg twice daily combined with aspirin or 5 mg twice daily as monotherapy compared with aspirin alone in patients with stable CAD or peripheral artery disease (only the results of the CAD arm are discussed in this review) [17]. Patients on concomitant DAPT were excluded and the entry criteria of the trial were constructed to select CAD patients with a higher ischaemic but lower haemorrhagic risk. Patients with a history of myocardial infarction were enrolled a mean of 7.1 years after the acute event and received the study treatment for a mean of 23 months. VLD rivaroxaban (2.5 mg twice daily) combined with aspirin, but not rivaroxaban 5 mg twice daily alone, significantly reduced the primary composite outcome of cardiovascular death, stroke and myocardial infarction. A significant reduction in cardiovascular and all-cause mortality was noted in the VLD rivaroxaban but not the 5 mg group. Interestingly, the majority of benefit with VLD rivaroxaban was achieved by reducing the incidence of ischaemic stroke, whereas there was no significant decrease in myocardial infarction. In line with previous evidence, a significant increase in major and minor bleeding was observed in both groups, with a numerically higher rate in the VLD rivaroxaban-aspirin group than in the rivaroxaban monotherapy group. The majority of bleedings were of gastrointestinal origin. Interestingly, in the combination group fatal bleedings or intracranial haemorrhages were not significantly increased compared with aspirin monotherapy. In contrast, compared with aspirin there was a significant increase in total intracranial haemorrhages and haemorrhagic stroke in the rivaroxaban monotherapy group.

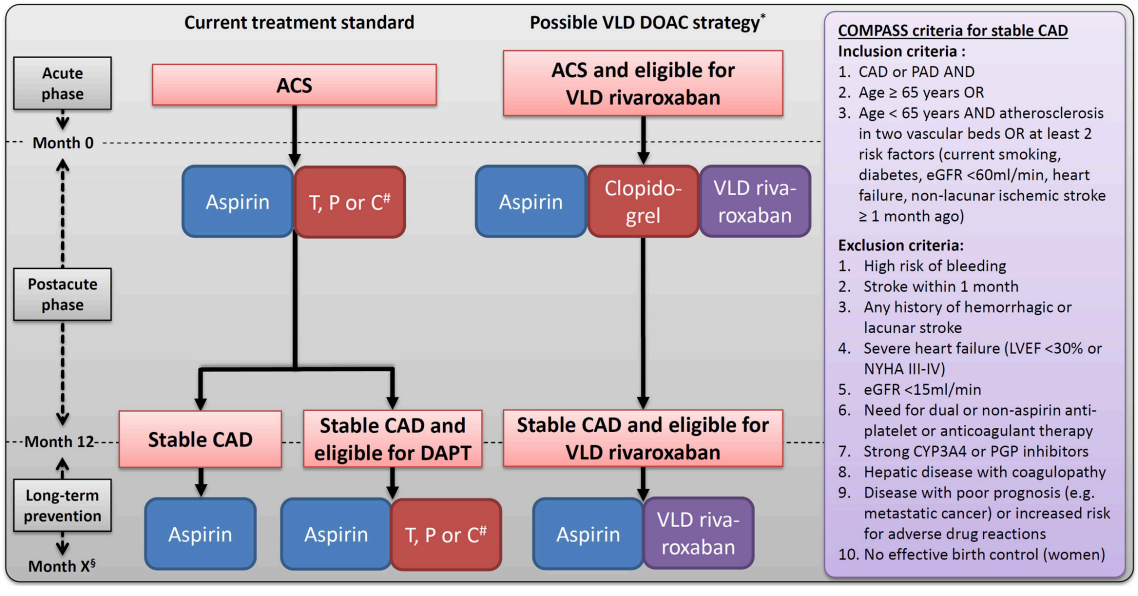
It should be noted that the COMPASS trial was terminated prematurely after the interim efficacy analysis by the data and safety monitoring board, which may overestimate the efficacy outcomes. Taken together, these two trials could establish a possible net benefit of adding VLD rivaroxaban to clopidogrel/ticlopidine-based DAPT after a recent ACS or to aspirin SAPT in stable CAD (fig. 1).

In the summer of 2018, both the US Food and Drugs Administration (FDA) and the European commission approved VLD rivaroxaban combined with aspirin for the prevention of atherothrombotic events in patients with CAD or peripheral artery disease and a high ischaemic risk. In Switzerland, VLD rivaroxaban was approved in June 2019. Its use has been limited to patients that match the inclusion criteria of the COMPASS trial (see figure 1). For stable CAD, recommendations by major clinical guidelines are still pending. After an acute coronary event, the ESC guidelines recommend that rivaroxaban may be considered in selected patients with no prior stroke/TIA who are receiving aspirin and clopidogrel, have a high ischaemic risk and a low bleeding risk, after the discontinuation of parenteral anticoagulation and for approximately one year (class IIb recommendation, level of evidence B) [1].

The critical question of optimal patient selection

Although the data from ATLAS ACS 2 and COMPASS opened up the avenue for prolonged VLD anticoagulation

Figure 1: Antithrombotic therapy in ACS and CAD patients. Comparison of the established DAPT strategies with a suggested DOAC-based strategy using VLD rivaroxaban (2.5 mg twice daily). Eligibility for VLD rivaroxaban depends on the concomitant ischaemic and bleeding risk as defined by the ATLAS ACS 2[16] and COMPASS [17] trials (eligibility criteria of the COMPASS trial are shown in the figure). Both charts only apply to patients without a concomitant indication for anticoagulation (e.g. not applicable to patients with atrial fibrillation). Several exceptions apply (such as shorter DAPT regimens in patients with higher bleeding risks). The readers are referred to the appropriate ESC guidelines [1].* The VLD rivaroxaban chart shown here does not represent guideline recommendation.# Clopidogrel is recommended when ticagrelor or prasugrel are not indicated or available.§ Whereas secondary prevention with aspirin is usually recommended without a time limitation in CAD, less efficacy and safety data exist for DAPT or VLD rivaroxaban beyond 2 ½ to 3 years of follow-up.ACS = acute coronary syndrome; b.i.d. = twice daily; C = clopidogrel; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration fraction; ESC = European Society of Cardiology; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PAD = peripheral artery disease; P = prasugrel; PGP = p-glykoprotein; T = ticagrelor; VLD = very low-dose



in CAD patients, several unresolved issues remain. Both trials included only patients with a higher ischaemic but lower haemorrhagic risk through specific entry criteria. A recent registry study suggested that a significant proportion of CAD patients could fit the COMPASS eligibility criteria [18], but there is still a significant proportion of patients in clinical practice who have a higher haemorrhagic or lower ischaemic risk than desired. Indiscriminate treatment of these patients could negatively affect the fine balance of benefits and risks with VLD rivaroxaban. Even though no significant interactions regarding efficacy and safety could be identified in the subgroup analyses of ATLAS ACS-2 and COMPASS [16, 17], some consistent trends may help with patient selection. In both trials, female patients (compared with males) and patients with a body weight under 60 kg (compared with higher body weight) exhibited numerically increased bleeding rates while having a comparable benefit on efficacy endpoints. Another important factor may be the age of eligible patients. In the COMPASS trial, there was a trend of reduced efficacy in patients aged 75 years and older (21% of the study sample) compared with younger patients. At the same time, these elderly patients had the highest risk for major bleeding (low-dose rivaroxaban plus aspirin vs aspirin monotherapy: 5.2 vs 2.5% in patients ≥75 years compared with 1.4 vs 1.2% in patients <65 years of age). Subgroup analyses from ATLAS ACS 2 for patients ≥75 years are not available, but it is noteworthy that only 9% of patients in the trial were in this age range. As a significant proportion of CAD patients are over the age of 75 years in current clinical practice, more safety data on VLD rivaroxaban in the elderly are certainly needed.

VLD rivaroxaban in patients with CAD and heart failure

A common comorbidity of CAD patients is chronic heart failure. CAD patients with heart failure exhibit among the highest rates of mortality and repeat hospitalisations. A hypercoagulable state was hypothesised to contribute to events in heart failure patients. Indeed, subgroup analyses of ATLAS ACS 2 and COMPASS suggested that CAD patients with heart failure derive a greater relative benefit from VLD rivaroxaban than patients without heart failure [19, 20].

Recently, the results of the COMMANDER-HF trial were reported. This trial compared VLD rivaroxaban in heart failure patients with reduced ejection fraction, sinus rhythm and a recent decompensation. Eligible patients were required to have evidence of CAD and be treated with antiplatelet therapy (58% aspirin SAPT, 5% P2Y12 inhibitor SAPT, 35% DAPT). Despite a significant baseline risk for ischaemic events, VLD rivaroxaban failed to reduce the composite endpoint of death, myocardial infarction and stroke. A 1% absolute reduction in stroke was noted, but no decrease in all-cause mortality. In contrast, there was a 1.3% absolute increase in major bleeding events. Fatal bleedings or bleeding into critical spaces were not increased. Subgroup analyses could not identify a benefit in patients on less intensive concomitant antiplatelet therapy.

The reason for the divergent results of COMMANDER-HF are unclear. One possible explanation is that VLD rivaroxaban is only of benefit in patients in whom ischaemic events contribute to the majority of cardiovascular events, whereas in advanced heart failure most events are due worsening of heart failure itself, which is not modified by anticoagulation. Another explanation may be that there was a different incidence of patients with undetected paroxysmal atrial fibrillation in the trials. In patients with undetected atrial fibrillation, VLD rivaroxaban may be of particular benefit. Indeed, with the exception of the ATLAS ACS 2 trial, a majority of the benefit from low-dose rivaroxaban appears to be derived from the reduction in ischaemic stroke. Yet, in the recent NAVIGATE-ESUS trial [21], near-therapeutic doses of rivaroxaban (15 mg daily) failed to provide cardiovascular benefit in patients with cryptogenic stroke, a population in which undetected paroxysmal atrial fibrillation is common [22]. More targeted approaches using VLD DOACs in patients at high risk of both stroke and undetected atrial fibrillation may yield different results in the future.

In the end, a careful meta-analysis of individual patient data from all available trials may provide answers on who benefits most from VLD rivaroxaban. Data from such analyses may help to create risk scores similar to the CHA_2DS_2-VASc or HAS-BLED score used in atrial fibrillation to select the optimal patients for VLD anticoagulation. Biomarkers of hypercoagulability may also be helpful. Unfortunately, baseline D-dimer levels were not predictive for the response to VLD rivaroxaban in the COMMANDER-HF trial [23].

VLD rivaroxaban compared with DAPT with prasugrel or ticagrelor

An important point is that the efficacy and safety of VLD rivaroxaban either compared with or added to third-generation DAPT with prasugrel and ticagrelor is still unknown. Prasugrel and ticagrelor were not allowed within DAPT of the ATLAS 2 trial and DAPT was forbidden in the COMPASS trial. As prolonged DAPT may already be considered in selected patients according to current guidelines, physicians now need to choose between prolonged third-generation DAPT and the addition of VLD rivaroxaban to aspirin monotherapy in high-risk stable CAD patients or to clopidogrel-based DAPT in ACS patients (see fig. 1). When the efficacy and safety of third-generation DAPT is compared with VLD rivaroxaban by indirect measures (table 1), DAPT with ticagrelor or prasugrel appears to be more efficient in preventing ischaemic events at a lower risk of major bleeding in the first year after ACS. In the context of stable CAD, VLD rivaroxaban combined with aspirin SAPT appears to provide more ischaemic benefit than the prolongation of DAPT, albeit at a higher risk of bleeding. These two comparisons should be interpreted very cautiously, as they are indirect, and limited by the lack of direct comparative trials and differences in study populations, study design and time frames. It is also worth noting that the effect on all-cause and cardiovascular mortality with third-generation P2Y12 inhibitors was less pronounced compared with the benefits seen with VLD rivaroxaban in the recent trials. Ultimately, only randomised trials comparing third-generation DAPT with VLD rivaroxaban added to aspirin monotherapy or clopidogrel-based DAPT would help to resolve that question.

Table 1: Benefits vs harms of VLD rivaroxaban (2.5 mg twice daily) in the context of established antithrombotic therapies in patients with CAD.

Antithrombotic therapy	NNT for reduction of all-cause death	NNT for reduction of CV event	NNH for additional bleeding event	Ref.
Aspirin given acutely and in the first month after STEMI	36	42 for CV death	167 for minor bleeding (major bleeding not increased)	[24]
Aspirin for long-term secondary prevention after MI	91	29 for composite of CV death, MI and stroke	333 for major extracranial bleeding	[25]
Clopidogrel added to aspirin for one year after ACS or PCI (DAPT)	NS	27 for composite of non-fatal MI and stroke	114 for major bleeding	[26]
Ticagrelor added instead of clopidogrel to aspirin for one year after ACS (DAPT)	71	53 for composite of CV death, MI and stroke	143 for major bleeding not related to CABG	[3]
Prasugrel added instead of clopidogrel to aspirin for one year after ACS (DAPT)	NS	46 for composite of CV death, non-fatal MI and stroke	167 for major bleeding not related to CABG	[4]
Prolongation of DAPT beyond one year in post-MI patients over a mean of 31 months	NS	91 for composite of CV death, non-fatal MI and stroke	132 for major bleeding	[27]
VLD rivaroxaban added to DAPT (aspirin ± clopidogrel or ticlopidine) in ACS patients for a mean of 13 months (ATLAS ACS 2)	63	63 for composite of CV death, non-fatal MI and stroke	83 for major bleeding not related to CABG	[16]
VLD rivaroxaban added to SAPT (aspirin) in stable CAD for a mean of 23 months (COMPASS)	143	77 for composite of CV death, non-fatal MI and stroke	83 for major bleeding	[17]
VLD rivaroxaban added to patients with CAD and symptomatic HF with reduced ejection fraction (COMMANDER-HF)	NS	NS for composite of all-cause death, MI and stroke, 100 for stroke	77 for major bleeding	[23]

ACS = acute coronary syndrome; CAD = coronary artery disease; CABG = coronary artery bypass grafting; CV = cardiovascular; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PCI = percutaneous coronary intervention; Ref. = reference; SAPT = single antiplatelet therapy; STEMI = ST-segment elevation myocardial infarction; VLD = very low-dose NNT and NNH were extracted or calculated from the cited publications.

Is it time to drop aspirin in favour of VLD rivaroxaban or P2Y12 inhibitors?

Some authors have suggested replacing aspirin as a long-term secondary preventive therapy in patients with CAD with third-generation P2Y12 inhibitors and/or VLD anticoagulants [28]. Others are more radical and suggest generally limiting aspirin therapy to the first weeks after a cardiac event [29]. The rationale is to achieve a better balance between ischaemic protection and bleeding risks as well as other side effects associated with cyclooxygenase inhibition [29]. However, the data from COMPASS strengthen the role of long-term aspirin in CAD as they suggest a synergistic effect of low-dose aspirin combined with VLD anticoagulation. This can be seen in the higher rate of intracranial bleeding and haemorrhagic stroke in the rivaroxaban monotherapy group, which at the same time showed less benefit on thrombotic endpoints such as ischaemic stroke or venous thromboembolism than the combination therapy [17]. Similarly, the GEMINI-ACS-1 trial showed that the combination of VLD rivaroxaban with a P2Y12 inhibitor compared with regular aspirin-containing DAPT in ACS patients resulted in a higher rate of International Society on Thrombosis and Haemostasis (ISTH) major bleeding without a benefit on cardiovascular events in exploratory analyses [30]. The recent GLOBAL-LEADERS trial showed that 1 month of DAPT with ticagrelor and subsequent continuation of ticagrelor monotherapy is not superior to the current standard of 12 months DAPT with continuation of aspirin monotherapy [31]. Finally, the recent TiCAB trial failed to show a benefit of replacing aspirin with ticagrelor in the first year after coronary artery bypass grafting [32].

Given its low-cost, available long-term safety data and wide range of beneficial pleiotropic effects (e.g., on low-density lipoprotein oxidation [33], plaque stability [34] as well as cancer [35]), aspirin will likely remain an integral component of modern antithrombotic combination therapies.

Conclusions and future directions

VLD anticoagulation in the form of rivaroxaban 2.5 mg twice daily is a welcome addition to the current antithrombotic arsenal in high-risk patients with ACS or stable CAD. Adequate patient selection in line with the entry criteria of the approval trials appears to be critical to avoid excessive bleeding. Risk scores similar to the CHA_2DS_2-VASc or HAS-BLED scores may be needed to decide who benefits most from the treatment. The comparative efficacy and safety with third-generation P2Y12 inhibitors needs to be studied in more detail. In patients with CAD and concomitant heart failure with reduced ejection fraction, it may not produce a net-benefit. Several ongoing trials may add more information on the safety of DOACs in CAD patients (table 2). So far, no other DOACs at very low doses are currently studied in larger trials to our knowledge.

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Table 2: Selected ongoing trials of DOACs in patients with CAD.

Trial acronym and identifier	Target population	Intervention	Estimated enrolment
APPROACH-ACS-AF (NCT02789917)	ACS with AFib	Apixaban plus clopidogrel vs VKA, clopidogrel and aspirin	400
COACH-AF-PCI (NCT03536611)	CAD after PCI/Stenting with AFib	Dabigatran plus DAPT vs VKA plus DAPT	1120
ENTRUST-AF-PCI (NCT02866175)	CAD after PCI/Stenting with AFib	Edoxaban plus SAPT vs VKA plus SAPT/DAPT	1500
EPIC-CAD (NCT03718559)	Stable CAD with AFib	Edoxaban vs edoxaban plus SAPT	1000
H-REPLACE (NCT03363035)	ACS in the acute phase	Low-dose rivaroxaban vs enoxaparin	3390
RT-AF (NCT02334254)	CAD after PCI and indication for OAC	Low-dose rivaroxaban plus ticagrelor vs VKA plus DAPT	420

ACS = acute coronary syndrome; AFib = atrial fibrillation; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; OAC = oral anticoagulant; SAPT = single antiplatelet therapy; VKA = vitamin K antagonist

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