When and How to Combine Antiplatelet and Anticoagulant Drugs?

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Hamostaseologie 2022;42:73–79.

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Abstract

Antiplatelet and anticoagulant drugs work at different places in the coagulation system. Antiplatelet drugs are usually indicated in patients with atherosclerosis. Anticoagulant drugs are mostly used in patients with atrial fibrillation, venous thromboembolism, or technical heart valves. In some clinical situations, combination of antiplatelet and anticoagulant therapy can be indicated. The most recent situations are a more intensive antithrombotic therapy for risk reduction in patients with atherosclerosis and temporary addition of antiplatelet drugs in patients with indication for long-term anticoagulation. Temporary combination of antiplatelet and anticoagulant drugs is usually necessary after coronary intervention in patients with atrial fibrillation. In patients with high-risk atherosclerosis, the combination of low-dose rivaroxaban and aspirin reduces major adverse cardiovascular events (myocardial infarction, stroke, cardiovascular death) and major adverse limb events. But every combination of antiplatelet and antithrombotic drugs can increase bleeding risk. Therefore, a careful assessment of thrombotic versus bleeding risk is necessary for each patient.

Keywords
- antiplatelet drugs
- anticoagulant drugs
- bleeding risk
- thrombotic risk
- prognosis

Introduction

Blood coagulation is a very complex system. Platelet activation and aggregation as well as fibrin generation are crucial in this process. Drugs such as aspirin, clopidogrel, prasugrel, and ticagrelor are inhibitors of platelet aggregation. Vitamin K antagonists (VKAs), factor X inhibitors (apixaban, edoxaban, rivaroxaban), and dabigatran inhibit fibrin generation. However, we have to keep in mind that every intervention on one side has side effects on other side (►**Fig. 1**).

Antiplatelet and anticoagulant drugs are used in different indications and dosages. Usually, anticoagulant drugs are necessary in patients with venous thromboembolism or atrial fibrillation. In these indications, therapeutic dosage of anticoagulants is necessary. When VKAs are used, dosage is assessed according to international normalized ratio (INR). Usually, a range of 2 to 3 in venous thromboembolism or atrial fibrillation is indicated. In these indications, factor Xa inhibitors (rivaroxaban: 20 mg od, apixaban: 5 mg bd, edoxaban: 60 mg od) or thrombin antagonists (dabigatran: 110 or 150 mg bd) are used in standardized dosage if there is no renal insufficiency. In patients with atherosclerosis of coronary or peripheral arteries, usually antiplatelet drugs are used.

Combination of antiplatelet and anticoagulant drugs can be indicated, for example, in high-risk patients with atherosclerosis using low-dose rivaroxaban (2.5 mg bd) and aspirin. In addition, patients with indication for an anticoagulant may need addition for several months of an antiplatelet after coronary or peripheral intervention. A combination of antiplatelet and anticoagulant drugs can also be discussed in special situations like in patients with severe antiphospholipid antibody syndrome (APS). However, we should always keep in mind that multiple antithrombotic medications lead

received
October 10, 2021
accepted after revision
December 15, 2021

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-1724-4922.
ISSN 0720-9355.

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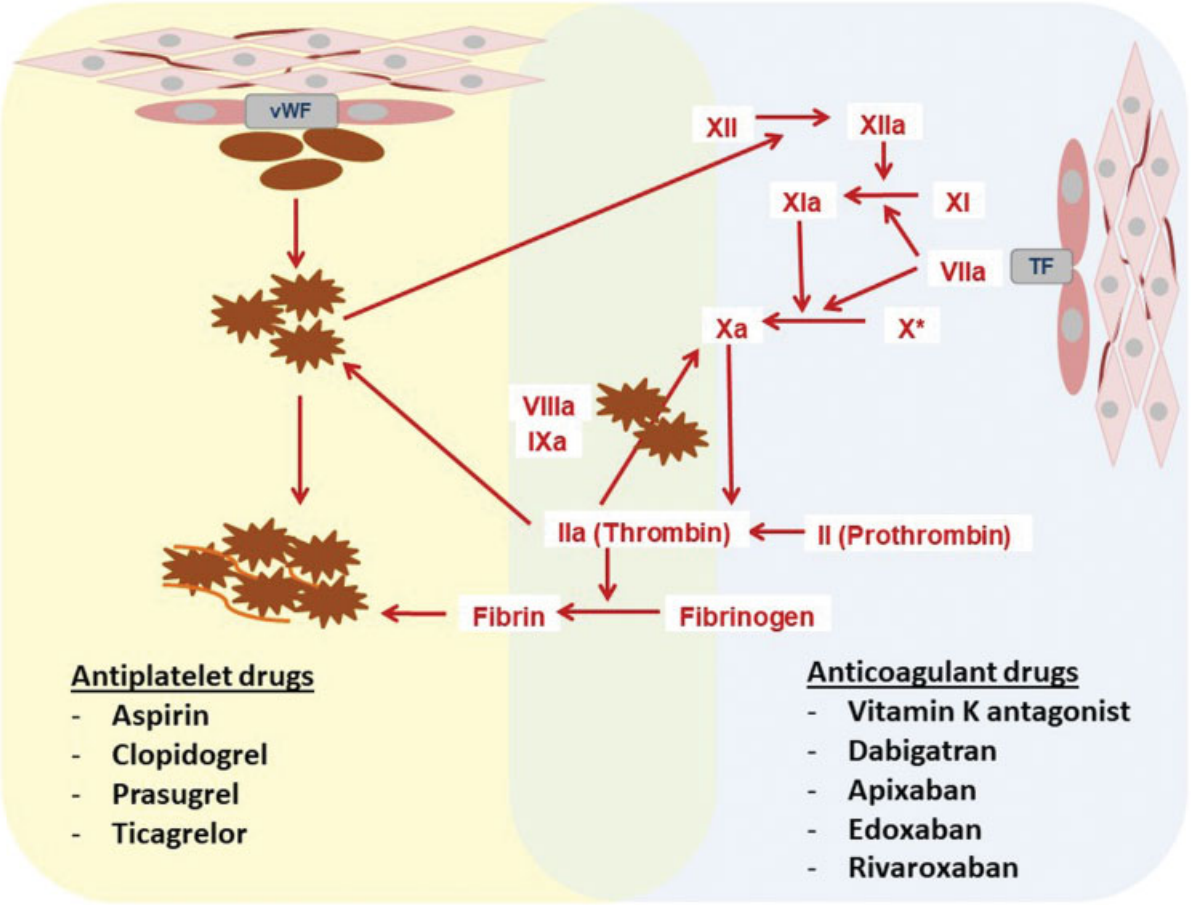

Fig. 1 Effect of antiplatelet and anticoagulant drugs in the coagulation system.

to increased bleeding risk. Therefore, the indication and duration of combined antiplatelet and anticoagulant drugs must be assessed carefully.

This review focuses on the two frequent indications: more intensive antithrombotic therapy for risk reduction in patients with atherosclerosis and temporary therapy with antiplatelet drugs in patients with indication for anticoagulation.

Temporary Therapy with Antiplatelet Drugs in Patients with Indication for Anticoagulation

Usually, after percutaneous coronary intervention (PCI), dual-antiplatelet therapy is indicated.[1,2] Duration of dual-antiplatelet therapy depends on clinical situation (acute coronary syndrome or chronic coronary artery disease) and procedure-related points (e.g., left main intervention). In particular, patients with acute coronary syndrome need prolongation of intensive antiplatelet therapy.

In some patients undergoing PCI, long-term oral anticoagulation is indicated and should be continued after the intervention because of increased risk for thromboembolic events. Most patients need long-term anticoagulation because of atrial fibrillation; therefore, major randomized trials have been performed including these patients.[3] In the following section, the main results of randomized controlled trials including patients with PCI requiring anticoagulation and antiplatelet therapy are summarized[4,5] (►**Table 1**).

Two studies included patients treated with VKA. The WOEST (What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) study was the first randomized trial to address the optimal antiplatelet therapy in patients on oral anticoagulation undergoing coronary stenting.[4] In total, 573 patients have been included in the trial. Triple antithrombotic therapy (TAT) with VKA, clopidogrel, and aspirin was compared with dual antithrombotic therapy (DAT) with VKA and clopidogrel. Triple therapy resulted in significant higher bleeding risk compared with dual therapy without aspirin. The ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen-Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients with Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting) trial randomized 614 patients to 6 weeks of triple therapy with VKA, aspirin, and clopidogrel followed by VKA and aspirin compared with 6 months of triple therapy with VKA, clopidogrel, and aspirin.[5] At 9 months, there was no significant difference between the groups with regard to thrombotic or bleeding events. The WOEST and ISAR-TRIPLE study showed in a quite small number of patients that after PCI and stenting, the combination of VKA with only one antithrombotic drug is not associated with an increase of thrombotic events.

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Table 1 Summary of randomized controlled trials including patients with acute coronary syndrome requiring anticoagulation and antiplatelet therapy according to some studies[3–10]

RCT	Patient groups	Primary endpoint
WOEST[4] $N = 573$	DAT (VKA + clopidogrel) versus TAT (VKA + aspirin + clopidogrel) for 12 mo	TIMI bleeding at 1 y lower with DAT vs. TAT
ISAR-TRIPLE[5] $N = 614$	TAT (VKA + aspirin + clopidogrel) for 6 wk followed by DAT (VKA + aspirin) versus TAT (VKA + aspirin + clopidogrel) for 6 mo	Cardiac death + infarction + stent thrombosis + stroke or TIMI major bleeding at 9 mo no difference
POINEER AF-PCI[6] $N = 2{,}124$	DAT (rivaroxaban 15 mg + clopidogrel) for 12 mo versus Modified TAT (rivaroxaban 2 × 2.5 mg + aspirin + clopidogrel) for 1, 6, or 12 mo versus TAT (VKA + aspirin + clopidogrel) for 1, 6, or 12 mo	Clinically significant bleeding lower with DAT or modified TAT vs. TAT
RE-DUAL PCI[7] $N = 2{,}725$	TAT (VKA + aspirin + clopidogrel) for up to 3 mo versus DAT (dabigatran 2 × 110 or 150 mg + clopidogrel or ticagrelor)	Major or clinically relevant non-major bleeding lower in DAT 110 mg or DAT 150 mg vs. TAT
AUGUSTUS[8] $N = 4{,}614$	DAT1 (apixaban 2 × 5 mg + clopidogrel or ticagrelor or prasugrel) versus DAT2 (VKA + clopidogrel or ticagrelor or prasugrel) versus TAT1 (apixaban 2 × 5 mg + aspirin + clopidogrel or ticagrelor or prasugrel) versus TAT2 (VKA + aspirin + clopidogrel or ticagrelor or prasugrel)	Major or clinically relevant non-major bleeding lower with DAT1 compared with DAT2, TAT1, or TAT2
ENTRUST-AF PCI[10] $N = 1{,}506$	DAT (edoxaban 60 mg + clopidogrel or ticagrelor or prasugrel) versus TAT (VKA + aspirin + clopidogrel or ticagrelor or prasugrel)	Major or clinically relevant non-major bleeding non-inferior between DAT or TAT

Abbreviations: DAT, dual-antithrombotic therapy; RCT, randomized controlled trial; TAT, triple antithrombotic therapy; VKA, vitamin K antagonists.

Currently, most patients with atrial fibrillation are treated with direct oral anticoagulants. The POINEER AF-PCI study (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) tested the use of DAT with rivaroxaban 15 mg once daily and clopidogrel versus TAT with rivaroxaban 2.5 mg twice daily and aspirin and clopidogrel versus TAT with VKA and aspirin and clopidogrel.[6] The primary endpoint TIMI bleeding at 1 year was significantly lower in DAT compared with TAT.

The RE-DUAL PCI study (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) compared TAT (VKA + aspirin + clopidogrel) for up to 3 months with DAT (dabigatran 2 × 110 or 150 mg + clopidogrel or ticagrelor).[7] Major or clinically relevant non-major bleeding was significantly lower in DAT 110 mg or DAT 150 mg versus TAT.

The AUGUSTUS (Antithrombotic Therapy After Acute Coronary Syndrome or PCI in Atrial Fibrillation) study tested two different regimens of DAT with apixaban 2 × 5 mg or VKA combined with clopidogrel or ticagrelor or prasugrel and two different regimens of TAT with apixaban 2 × 5 mg or VKA combined with aspirin and clopidogrel or ticagrelor or prasugrel.[8] In summary, major or clinically relevant non-major bleeding was lowest in the group with apixaban-DAT compared with VKA-DAT or the two TAT groups. Combination with aspirin was associated with higher bleeding risk in particular if treatment was longer than 30 days.[9]

In the ENTRUST AF PCI (Edoxaban-based Dual Antithrombotic Therapy Noninferior to VKA-based Triple Therapy After PCI) trial, DAT including edoxaban with clopidogrel or ticagrelor or prasugrel was compared with TAT with VKA, aspirin, and clopidogrel or ticagrelor or prasugrel.[10] Major or clinically relevant non-major bleeding was noninferior in the DAT group compared with the TAT group.

These studies have changed recommendation for patients with indication for anticoagulation after coronary and peripheral revascularization.[1,11] In addition, recent studies tested shorter duration of antiplatelet therapy after coronary intervention compared with longer duration.[12]

Evidence is limited to support a specific antithrombotic regimen for patients with an indication for oral anticoagulation and endovascular revascularization (EV) for peripheral arterial disease (PAD). There is no randomized trial available including patients after peripheral EV for PAD with indication for oral anticoagulation. Therefore, current guidelines recommend therapy according to PCI studies such as the previously discussed PIONEER, Re-DUAL, ENTRUST-AF, and AUGUSTUS trial.[6–10,13] As there are also limited data available for dual-antiplatelet therapy after peripheral EV in general, duration of combined therapy should be as short as possible, depending on the clinical indication and bleeding risk. With the exception of below-the-knee stenting or complex lesions at very high risk of thrombosis, triple therapy should be discouraged.[13]

Management should be carefully assessed according to thrombotic risk versus bleeding risk.[11] ►**Fig. 2** summarizes treatment duration for different clinical situations. In addition, gastric protection with a proton pump inhibitor is recommended and the dose intensity of oral anticoagulants should be carefully monitored.[2,13]

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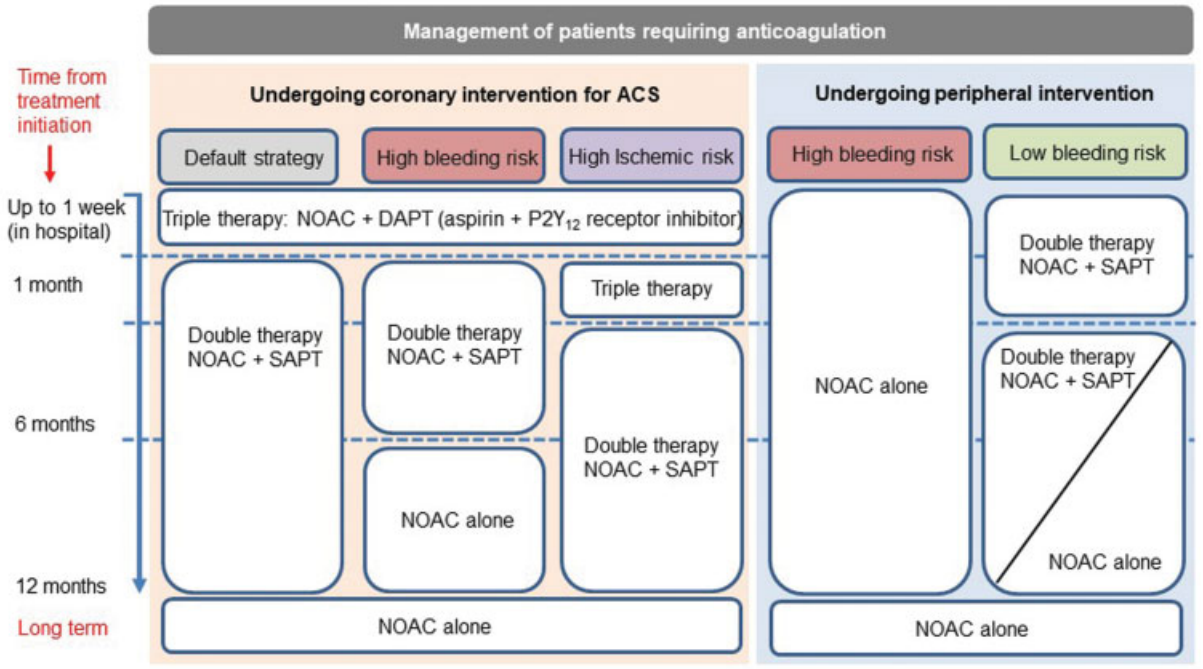

Fig. 2 Management of patients requiring anticoagulation undergoing coronary and peripheral anticoagulation.[2,13] ACS, acute coronary syndrome; DAPT, dual-antiplatelet therapy; NOAC, non–vitamin K antagonist oral anticoagulant; SAPT, single-antiplatelet therapy.

Combination of Antiplatelet and Anticoagulant Drugs for Risk Reduction in Patients with Atherosclerosis

Patients with atherosclerosis in coronary or peripheral arteries are at increased risk of cardiovascular events.[1,13] Antithrombotic medication is recommended in these patients because the risk of major adverse cardiovascular events (MACE; stroke, myocardial infarction, cardiovascular death) and major adverse limb events (MALE; major amputation, acute limb ischemia) is significantly reduced.[1,13,14]

The impact of more intensive antithrombotic therapy has been evaluated in different studies. For example, in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, dual-antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg showed slight reduction of MACE in patients with symptomatic atherosclerotic diseases.[15] The PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin) study showed beneficial effect of long-term use of ticagrelor and aspirin more than 12 months after acute myocardial infarction.[16] In this trial, there was also beneficial effect for the subgroup of patients with PAD for MACE and MALE.[17] The TRA 2°P (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis) study tested the effect of vorapaxar on top of single- or dual-antiplatelet therapy in patients after myocardial infarction, stroke, or PAD.[18,19] The stroke arm was stopped early because of adverse effects. There was a reduction in MACE (secondary endpoint) for patients after myocardial infarction or with PAD, but there was a major increase in bleeding risk. In conclusion, more intensive antithrombotic therapy using multiple antiplatelet drugs reduces MACE and MALE events in patients with atherosclerosis, but the benefit is reduced by bleeding complications.[15–20]

Several years ago, the hypothesis that combination of antiplatelet and anticoagulant drugs may be beneficial in secondary prevention was tested with the combination of aspirin and the VKA warfarin. But studies such as the WAVE (Warfarin Antiplatelet Vascular Evaluation Trial) in PAD patients failed because they could not show reduction of events by major increase of bleeding risk.[21]

In patients with acute coronary syndrome, fondaparinux reduced major bleeding and mortality compared with enoxaparin on top of antiplatelet therapy (The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes study).[22] The combination of low-dose rivaroxaban and aspirin was first evaluated in the ATLAS ACS (Anti-Xa Therapy to Lower CV Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome) TIMI 51 trial.[23] In this study, more than 15,000 patients after acute coronary syndrome were treated with either placebo or rivaroxaban 2.5 mg or rivaroxaban 5 mg twice daily in combination with aspirin 100 mg. Rivaroxaban reduced risk for MACE by 16% and reduced stent thrombosis by 31%. Major bleeding was significantly higher in the rivaroxaban groups, but no increase in fatal bleeding occurred, especially in the very low dose group.

This concept was tested for patients with stable atherosclerosis in the COMPASS (Cardiovascular OutcoMes for People Using Anticoagulation StrategieS) study. COMPASS tested the combination of aspirin and low-dose rivaroxaban

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Table 2 Recommendations of current guidelines for dual-pathway anticoagulation[1,28–30]

Recommendations	Class	Level of evidence
2019 ESVM guidelines on the management of PAD[28]		
The combined therapy of aspirin 100 mg od and rivaroxaban 2.5 mg bid should be considered in PAD patients without a high risk of bleeding, or other contraindications	IIa	B
2019 ESC–EASD guidelines on diabetes, pre-diabetes, and cardiovascular diseases[30]		
In patients with diabetes and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg bid) and aspirin (100 mg od) should be considered	IIa	B
2019 ESC guidelines on the management of chronic coronary syndromes[1]		
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischemic events[a] and without high bleeding risk	IIa	A
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk	IIb	A

[a]Diffuse multivessel coronary artery disease with at least one of the following: diabetes mellitus requiring medication, recurrent myocardial infarction, peripheral arterial disease, or chronic kidney disease with estimated glomerular filtration rate of 15 to 59 mL/min/1.73 m^3.

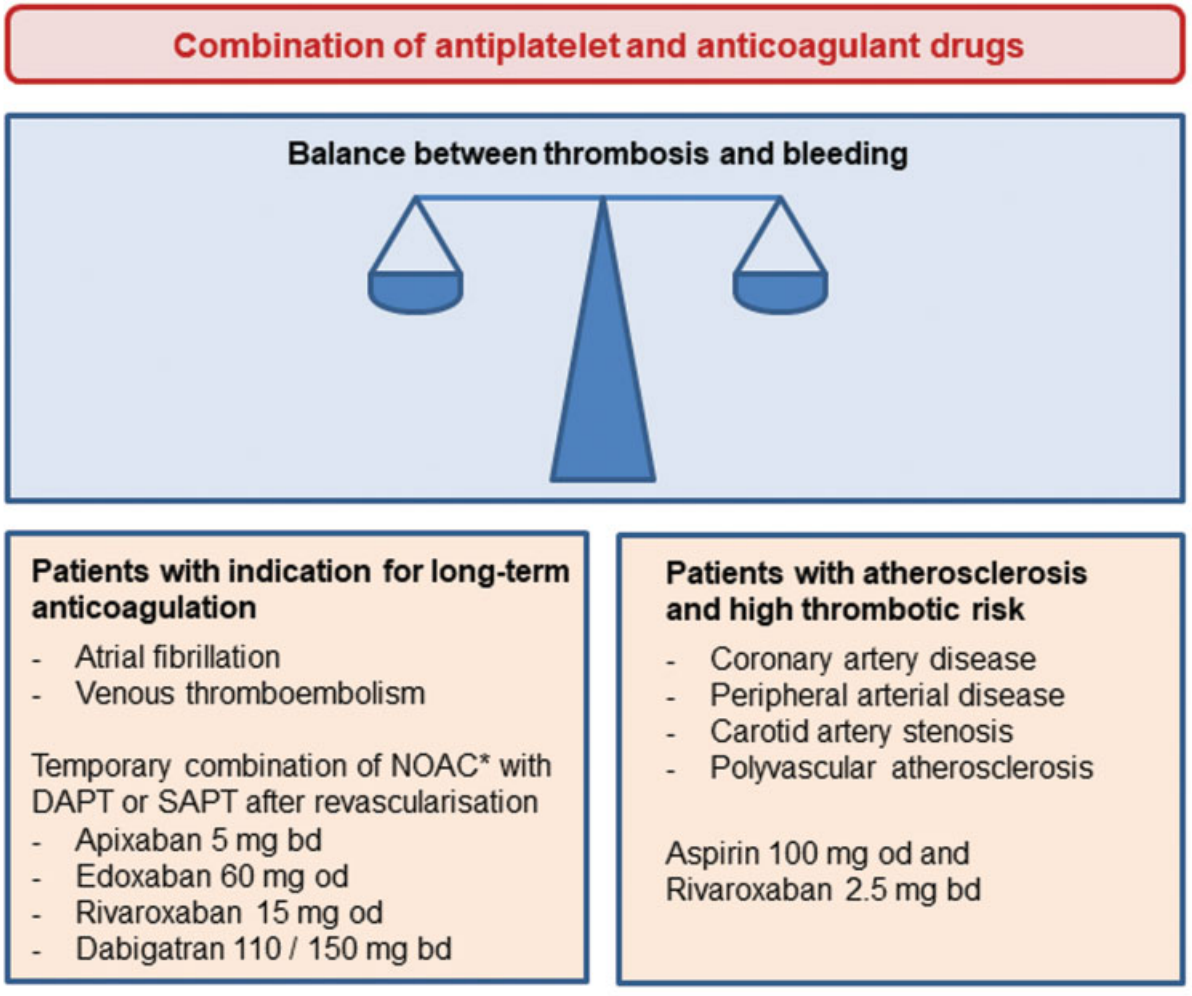

Fig. 3 Summary slide about combination of antiplatelet and anticoagulant drugs. *Dosage according to drug admission. DAPT, dual-antiplatelet therapy; NOAC, non–vitamin K antagonist oral anticoagulant; SAPT, single-antiplatelet therapy.

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(2×2.5 mg) in patients with coronary artery disease, PAD, and carotid artery stenosis (CAS).[24] There was a significant reduction of MACE in the hole group of 27,395 study patients. A subgroup analysis including the 4,129 patients with peripheral atherosclerosis (PAD or CAS) showed a significant reduction of both MACE and MALE events.[25] As expected, the combination therapy results in a significant increase in major bleeding compared with placebo, but the positive effects outweigh these side effects.

In the COMPASS study, patients with peripheral and polyvascular atherosclerosis could be identified as high-risk population. The VOYAGER PAD (Vascular Outcomes Study of ASA Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease) study included only PAD patients after peripheral revascularization. This study is a randomized trial including 6,564 patients after successful surgical or endovascular lower extremity revascularization.[26] All patients received aspirin 100 mg and were randomized to rivaroxaban 2.5 mg twice daily or placebo. After a follow-up period of 3 years, the primary efficacy endpoint (MACE or MALE) was significantly decreased using low-dose rivaroxaban compared with placebo mostly triggered by reduction of acute limb ischemia. There was no significant difference in the primary safety outcome (TIMI major bleeding) which occurred in 2.7% in the rivaroxaban group and in 1.9% in the placebo group ($p = 0.07$). Additional treatment with clopidogrel 75 mg was allowed for up to 6 months. There was no significant difference between treatment groups in the subgroup of patients using clopidogrel 75 mg.[27] Patients who received clopidogrel on top of aspirin and low-dose rivaroxaban for more than 30 days had major increase of bleeding complications.[27]

In conclusion, the COMPASS study showed a significant reduction of cardiovascular and limb events with the combination of low-dose rivaroxaban and aspirin in patients with atherosclerosis in different vascular territories. In the VOYAGER PAD study, MACE and MALE events were significantly reduced by the combination of these antiplatelet and antithrombotic medications in patients after peripheral revascularization. Bleeding risk must be kept in mind especially gastrointestinal bleeding in the first months of treatment, but for the long term, beneficial effects overweigh the initial risk in most patients. Therefore, recent guidelines recommend the combination of aspirin and low rivaroxaban especially for patients with high risk for cardiovascular events and low bleeding risk[1,28–30] (►**Table 2**).

Combination of Antiplatelet and Anticoagulant Drugs for Rare Indications

A combination of antiplatelet and anticoagulant drugs can be used in patients with severe APS by individual decision. Usually, VKAs at therapeutic intensity (INR range of 2–3) are the standard treatment for thrombotic APS.[31] In patients with recurrent arterial thrombosis despite adequate treatment, after evaluating for other potential causes, an increase of INR target to 3 to 4 or addition of low-dose aspirin can be discussed.[31]

Conclusions

Combination of antiplatelet and anticoagulant drugs is useful in different indications (►**Fig. 3**). In patients with indication for anticoagulation, addition of an antiplatelet can be necessary for several months after coronary or peripheral intervention. In high-risk patients with atherosclerosis, low-dose rivaroxaban and aspirin improved prognosis by reduction of MACE and MALE events. Each combination of antiplatelet and anticoagulant drugs increases bleeding risk. Therefore, indication and duration of combined antiplatelet and anticoagulant drugs must be assessed carefully under weighing of thrombotic and bleeding risk.

Conflict of Interest

Honoraria for lectures or advisory boards from Amarin Germany GmbH, Amgen GmbH, Bayer Health Care, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, MSD Sharp & Dohme, Novartis Pharma, Pfizer Pharma GmbH, Sanofi-Aventis GmbH.

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