ANNUAL REVIEWS

Annual Review of Pharmacology and Toxicology

Oral Anticoagulants Beyond Warfarin

Renske H. Olie,[1] Kristien Winckers,[1] Bianca Rocca,[2,3] and Hugo ten Cate[1,4]

[1]Departments of Internal Medicine (Section of Vascular Medicine) and Biochemistry, Thrombosis Expertise Center, and CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands; email: h.tencate@maastrichtuniversity.nl

[2]Section of Pharmacology, Catholic University School of Medicine, Rome, Italy

[3]Department of Neurosciences, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

[4]Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Annu. Rev. Pharmacol. Toxicol. 2024. 64:551–75

First published as a Review in Advance on September 27, 2023

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

https://doi.org/10.1146/annurev-pharmtox-032823-122811

Keywords

direct oral anticoagulants, venous thromboembolism, atrial fibrillation, cancer-associated thrombosis, bleeding, reversal agents, antiplatelet agents, chronic kidney disease, drug interactions, factor XI inhibitors

Abstract

Direct oral anticoagulants (DOACs) have largely replaced vitamin K antagonists, mostly warfarin, for the main indications for oral anticoagulation, prevention and treatment of venous thromboembolism, and prevention of embolic stroke in atrial fibrillation. While DOACs offer practical, fixed-dose anticoagulation in many patients, specific restrictions or contraindications may apply. DOACs are not sufficiently effective in high–thrombotic risk conditions such as antiphospholipid syndrome and mechanical heart valves. Patients with cancer-associated thrombosis may benefit from DOACs, but the bleeding risk, particularly in those with gastrointestinal or urogenital tumors, must be carefully weighed. In patients with frailty, excess body weight, and/or moderate-to-severe chronic kidney disease, DOACs must be cautiously administered and may require laboratory monitoring. Reversal agents have been developed and approved for life-threatening bleeding. In addition, the clinical testing of potentially safer anticoagulants such as factor XI(a) inhibitors is important to further optimize anticoagulant therapy in an increasingly elderly and frail population worldwide.

1. INTRODUCTION

Vitamin K antagonists (VKAs), mainly warfarin, were the mainstay of oral anticoagulant (OAC) therapy over the past century until, in the first decade of the present century, a new class of OACs was generated. They were initially labeled as new OACs, later renamed as nonvitamin K OACs, and then, more recently, reflecting a pharmacodynamics (PD)-based definition, reclassified as direct oral anticoagulants (DOACs). While the VKAs' PD relies on the indirect inhibition of the hepatic synthesis of mature vitamin K–dependent coagulation enzymes, particularly factors (F)II (i.e., prothrombin), VII, IX, and X, DOACs directly target the active site of either FIIa, thrombin (dabigatran), or activated factor X (FXa; rivaroxaban, apixaban, and edoxaban) to inhibit procoagulant enzymatic activity. Both VKAs and DOACs, through different mechanisms, inhibit (the formation of) thrombin and the clotting end product, fibrin.

Differences not only in the PD but also in the pharmacokinetics (PK) of DOACs (**Table 1**) led to different ways of OAC management. Due to high PK- and PD-based intra- and interindividual variability in drug response and the narrow therapeutic window, VKAs require strict monitoring of the prothrombin clotting time [standardized as international normalized ratio (INR)] and consequent dose adjustment, targeting an INR-based therapeutic range of 2–3 in most cases. Instead, DOACs are given in fixed doses (**Table 1**), differently adjusted for age, body weight, and/or renal function (**Tables 1** and **2**), without the need for routine drug monitoring.

Large Phase III randomized clinical trials (RCTs) have established the efficacy and safety of DOACs versus VKAs for the prevention and treatment of venous thromboembolism (VTE), including pulmonary embolism, and the prevention of cardioembolic stroke in nonvalvular atrial fibrillation (AF), the latter representing the largest share of OAC use worldwide (about 65%) (1). For many major indications, due to their favorable practical management and lack of monitoring requirements, DOACs have largely replaced VKAs, except for some high-thrombogenic conditions such as end-stage renal failure and hemodialysis (HD), mechanical heart valves (2), triple-positive antiphospholipid syndrome (APS) (3), and valvular AF (4) (see following sections).

The most important adverse effect of all anticoagulants is major bleeding, which for VKAs and DOACs varies between 1.6% and 3.4% per year, depending on the patient's age, renal function, and other comorbidities and comedication (5, 6). An advantage of DOACs over VKAs is a lower risk of intracranial bleeding (0.1% versus 0.3% annually, respectively) (7).

When considering VKAs and DOACs, some off-target effects may be important: VKAs increase vascular calcification through inhibition of vitamin K–dependent proteins in the vascular tissue, although the long-term clinical consequences remain unknown (8). The impact of the small DOAC molecules with high tissue-penetrating properties is yet unknown. DOACs may interfere with FXa- or thrombin-mediated protease-activated receptor (PAR) signaling in various tissues, including the vasculature, which might slow the progression of atherosclerosis, given preclinical data showing the protective effects of dabigatran and rivaroxaban in mouse models of atherosclerosis (9). However, in other experimental settings, dabigatran and rivaroxaban have differential cellular protective properties, in part because dabigatran-inhibited thrombin can still activate PAR-1 (10). Postmarketing surveillance of DOACs, as for VKA-associated calcification, may help clarify the additional clinical readouts of on- and off-target effects that may require decades to become evident (11–13).

In this review, we consider current indications for DOACs, with a major focus on their challenging management in specific, more uncertain, or complex conditions. We consider drug-drug interactions (DDIs) and indications for the drug's monitoring or measuring, and finally, we discuss new developments in OACs.

Table 1 Main pharmacological characteristics of OACs and DDIs

	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
PD	VKOR inhibitor Indirect reduction of vitamin K–dependent coagulation proteins (protein S; protein C; factors II, VII, IX, and X)	Direct inhibitor of IIa, prodrug	Direct inhibitor of Xa	Direct inhibitor of Xa	Direct inhibitor of Xa
Daily dosing	Adjusted based on INR monitoring	Fixed 110 or 150 mg Twice	Fixed 15 or 20 mg Once	Fixed 2.5 or 5 mg Twice	Fixed 30 or 60 mg Once
Bioavailability	>90%	3–7% (gastric pH dependent)	80%	50–60%	62%
Drug efflux transporter	None	P-gp strong substrate	P-gp weak substrate, BCRP	P-gp substrate, BCRP	P-gp strong substrate
Involvement of CYP450s	CYP3A4 CYP2C9 CYP2C19	None	20% CYP3A4 20% CYP2J2	30% CYP3A4, 1A2, 2C8, 2C9, 2C19, and 2J2 (minor)	10% CYP3A4
Kidney clearance	85% (inactive metabolites)	85–90% (active metabolite)	60% (approx. half unchanged)	30–40% (approx. half unchanged)	50% (approx. 60% unchanged)
Laboratory assessment	INR	Screening: aPTT or TT Quantification: dTT or ECT	Quantification: anti-Xa	Quantification: anti-Xa	Quantification: anti-Xa
Antidote/ reversal agents	Vitamin K PCC	Idarucizumab	Andexanet alfa	Andexanet alfa	Andexanet alfa
DDIs EMA labeling	Warfarin can interact with many other drugs*; unless a drug is known not to interact with warfarin, its introduction or deletion requires monitoring for possible changes in anticoagulant effect Drugs that compete as substrates for CYP1A2, 3A4, and 2C9 or inhibit their activity may increase warfarin plasma concentrations and INR, potentially increasing the risk of bleeding; when these drugs are coadministered, warfarin dosage may need to be reduced and the level of monitoring increased; conversely, drugs that induce these metabolic pathways may decrease warfarin plasma concentrations and INR, potentially leading to reduced efficacy, and when these drugs are coadministered, warfarin dosage may need to be increased and the level of monitoring increased	Contraindicated with strong P-gp inhibitors, including dronedarone Caution with amiodarone, quinidine, verapamil, and clarithromycin, especially in mild to moderate renal impairment Ticagrelor should not be coadministered at loading dose Strong P-gp inducers not recommended	Combined strong P-gp and CYP3A4 inhibitors not recommended* Caution for clarithromycin, erythromycin, and moderate renal impairment (<50 mL/min) Avoid strong combined inducers	Combined strong P-gp and CYP3A4 inhibitors not recommended* Caution for strong combined inducers	Dose reduction with strong P-gp inhibitors, including dronedarone and erythromycin Caution for strong P-gp inducers

(*Continued*)

Table 1 (*Continued*)

	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
DDIs FDA labeling	Inhibitors and inducers of CYP2C9, 1A2, or 3A4: monitor INR closely Antibiotics and antifungals: closely monitor INR when initiating or stopping an antibiotic or antifungal course of therapy Botanical (herbal) products: some may necessitate close INR monitoring; consult labeling of all concurrently used drugs for complete information about interactions with warfarin or increased risks for bleeding	Avoid strong P-gp inducers, e.g., rifampin Reduced dose for dronedarone in patients with moderate renal impairment (CrCl 30–50 mL/min) Not recommended for P-gp inhibitors in severe renal impairment (CrCl <30 mL/min)	Avoid combined P-gp and strong CYP3A inhibitors and inducers No precautions for clarithromycin Not to be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (e.g., erythromycin)	Reduced dose or avoid for dual inhibitors of CYP3A4 and P-gp, including clarithromycin Avoid with strong dual inhibitors or inducers of CYP3A4 and P-gp	No dose reduction recommended for concomitant P-gp inhibitors Avoid with strong P-gp inducers
Age-related drug dosing	No specific recommendations, INR-based adjustment	Reduce dose starting from 80 years old	No dose change	Reduced dose if 80+ years old and has at least one of the following: weight ≤60 kg or serum creatinine ≥1.5 mg/dL (133 μmol/L)	Age from 75 years: full dose after taking renal function and body weight into account

Asterisks denote that the effect of warfarin can be enhanced and bleeding risk increased based on PD or PK interactions with capecitabine; 5-fluorouracil; heparins/LMWHs; thyroid hormone; allopurinol; danazol; disulfiram; anabolic steroids and androgens; strong to moderate inhibitors of CYP2C9, including amiodarone; azole antimycotics; isoniazid; selective serotonin reuptake inhibitors; propafenone; and antibiotics (for many, this may be more related to the disease itself). Cotrimoxazole is to be avoided, as are sulfonylurea derivatives, statins and fibrates, valproic acid, cimetidine, omeprazole, esomeprazole, leflunomide, kinidine, and tamoxifen. The effect of warfarin can be diminished by strong inducers of CYP2C9 or CYP2C19, including carbamazepine; barbiturates; rifampicin when used for >5 days; chronic use of alcohol; bosentan; fosaprepitant; HIV protease inhibitors; oral contraceptives; and thyreostatics. In all cases careful and more frequent INR monitoring is warranted! Abbreviations: IIa, factor IIa (thrombin); anti-Xa, antifactor Xa level; aPTT, activated partial thromboplastin time; BCRP, breast cancer resistance protein; CrCl, creatinine clearance; CYP, cytochrome; DDI, drug-drug interaction; dTT, diluted thrombin time; ECT, ecarin clotting time; EMA, European Medicines Agency; FDA, US Food and Drug Administration; INR, international normalized ratio; LMWH, low–molecular weight heparin; OAC, oral anticoagulant; PCC, prothrombin complex concentrate; P-gp, P-glycoprotein; PD, pharmacodynamic; PK, pharmacokinetic; TT, thrombin time; VKOR, vitamin K epoxide reductase; Xa, factor Xa.

Table 2 Approval of DOACs across stages of CKD

GFR (mL/min)	CKD stage	Dabigatran		Apixaban		Edoxaban		Rivaroxaban	
		FDA labeling	EMA labeling	FDA labeling	EMA labeling	FDA labeling	EMA labeling	FDA labeling	EMA labeling
50–59	3a	150 mg bd	150 mg bd	5 mg bd Reduced dose of 2.5 mg bd when 2 out of 3 criteria are met: Creatinine ≥1.5 mg/dL (133 µmol/L) Age ≥80 years Body weight <60 kg	5 mg bd Reduced dose of 2.5 mg bd when 2 out of 3 criteria are met: Creatinine ≥1.5 mg/dL (133 µmol/L) Age ≥80 years Body weight <60 kg	60 mg od	60 mg od	20 mg od	20 mg od
30–44/ 45–49	3a/3b	Consider reduced dose (75 mg bd) when combined with dronedarone or systemic ketoconazole	Consider reduced dose (110 mg bd)			30 mg od	30 mg od	15 mg od	15 mg od
15–29	4	75 mg bd Avoid the use of any P-gp inhibitor	CI		2.5 mg bd				Use with caution
<15	5	CI			NR	NR	NR	NR	NR
HD				5 mg bd					

Table showing FDA and EMA approval for the different DOACs across stages of CKD. Dark green indicates that the recommended dose is the full dose, light green indicates that the recommended dose is either the full or reduced dose, yellow indicates that the recommended dose is the reduced dose, orange indicates that use is not recommended, and red indicates that use is contraindicated. CKD stage 3a is defined by a GFR >45 and ≤60 mL/min; however, for the EMA and FDA labeling, an upper range of 49 mL/min is used. Abbreviations: bd, twice daily; CI, contraindicated; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; HD, hemodialysis; NR, not recommended; od; once daily.

2. CANCER AND THROMBOSIS

Since early 2000, low–molecular weight heparins (LMWHs) have been used as the preferred anticoagulant therapy for cancer-associated thrombosis (CAT), mostly VTE, based on their superior protection against recurrent VTE and similar bleeding risk as compared to VKAs. However, a more recent series of RCTs comparing different DOACs with LMWHs in CAT showed that DOACs are equally effective as LMWHs in preventing recurrent VTE, and at comparable bleeding risks, at least in patients with tumors outside of the gastrointestinal (GI) and urogenital tracts (14, 15). Since DOACs have the obvious advantage of oral over parenteral administration, certainly in the case of prolonged treatment (typically ≥3–6 months or longer based on type and stage of malignant disease and its treatment), they are becoming the preferred agents over LMWHs.

However, important caveats remain, including bleeding risk–enhancing factors, DDIs (see Section 4.3), and drug absorption. Recommendations for the use of anticoagulant drugs in patients with CAT are given in the recent European Society for Medical Oncology Clinical Practice Guideline (16).

2.1. Managing Bleeding Risk–Enhancing Factors

Bleeding risk estimation is pivotal in all patients on anticoagulants but even more so in those with cancer (17–19). Risk factors for bleeding may be related to the patient (e.g., old age, extreme body weight, frailty, and severely impaired renal function; see following sections); location of the tumor; comedications, including chemotherapies; and platelet count. Risk should be assessed on an individual basis involving the patient and other stakeholders, and it should be done repeatedly as risk-enhancing factors may vary over time.

General measures include confirming the indication for anticoagulation and addressing potentially modifiable risk factors for bleeding, including hypertension, renal failure, and polypharmacy, for example, avoiding interacting medications such as nonsteroidal anti-inflammatory drugs and antiplatelet therapy (see Section 4.3 and **Table 1**) (20) as well as preventing GI bleeding by implementing gastroprotection (21, 22). The localization of the tumor matters, and GI or urogenital tract tumors are more likely to bleed in patients on DOACs compared to those on LMWHs, resulting in increased rates of major bleeding for rivaroxaban and edoxaban—less so for apixaban, although for apixaban there was a higher incidence of clinically relevant nonmajor bleeding (23–25). Since GI tract bleeding is also a major side effect of DOAC use in patients without cancer, the level of tissue penetration and relatively high local concentrations in GI and urinary tract tissues may contribute to a relatively high bleeding risk with such drugs. Primary brain tumors, in contrast to brain metastases, are associated with a higher risk of intracranial bleeding, aggravated by any anticoagulant (23, 26). Organ-specific bleeding may vary over time. For instance, while upon presentation a GI tumor may be likely to bleed on anticoagulants, antitumor treatment may diminish this risk, eventually allowing oral anticoagulation with DOACs.

When starting a DOAC in a patient with CAT, the choice of a specific drug should be personalized by considering absorption (e.g., history of resection of GI tract segments, malabsorption after surgery, or chemotherapy) (27), elimination (renal and liver clearance differ among DOACs), DDIs (20, 28–30), dosing frequency (once or twice daily), and body weight (31). In a personalized strategy, laboratory monitoring can be helpful to assess the DOAC plasma anti-Xa or anti-IIa level to avoid excess drug exposure (see Section 6).

In general, the risk of GI bleeding may be reduced by proton pump inhibitors (PPIs), and this is certainly the case in patients with thrombocytopenia, which is an important risk factor in cancer that is related either to cancer treatment or to the malignant disease itself (32). A recent European Hematology Association–European Society of Cardiology guideline gives specific recommendations on the management of antithrombotic therapy in thrombocytopenic patients with a clear indication, including those with CAT (33).

2.2. Duration of Anticoagulation and Recurrent Thromboembolism

The evidence for optimal duration of anticoagulant therapy in CAT beyond the first three to six months is weak and depends on the individual risk of recurrent thrombosis versus bleeding assessment (34–36). Factors that influence recurrence risk include type of cancer, presence of distant metastasis, and residual thrombotic obstruction (30). In the setting of highest thrombosis risk, anticoagulant therapy is usually continued, whereas for DOACs the question is whether dose reduction, while reducing the risk of major bleeding, is sufficiently effective. Recurrent

thromboembolism while on anticoagulant therapy is common in CAT, posing new challenges to its management (35, 37, 38). While obvious explanations for anticoagulant failure such as poor drug compliance or major DDIs should be ruled out, dose escalation is a next step in anticoagulant management, and this usually implies switching to parenteral LMWHs (39). For LMWHs, dose increases of 20–25% are considered in progressive or recurrent thrombotic disease during anticoagulation, eventually guided by anti-Xa monitoring. Upon stabilization of thrombosis management, resuming OACs can be considered again on an individual basis, especially considering factors such as quality of life.

3. SPECIAL POPULATIONS

3.1. Extremes of Body Weight

Although body composition may affect the PK of several drugs, including DOACs, these are prescribed at fixed doses over a wide range of body weights. High-degree obesity, that is, body mass index (BMI) >35 kg/m^2, might be associated with low drug exposure and decreased efficacy for fixed-dose drugs (40–44). Analysis from the DOAC Phase III RCTs showed no difference in clinical outcomes in both VTE and AF in obese versus nonobese patient subgroups, although subjects with a high degree of obesity were largely underrepresented (45). Current guidelines [European Heart Rhythm Association/International Society on Thrombosis and Haemostasis (ISTH) and European Society of Cardiology (ESC) consensus document (44)] recommend VKAs over DOACs in patients with severe obesity, that is, BMI >40 kg/m^2 or a weight >120 kg, because VKA monitoring by INR may ensure the proper drug dosage within the therapeutic range (44, 46). A recent meta-analysis that included morbidly obese nonvalvular AF patients showed no significant difference in stroke or systemic embolism between DOACs and VKAs, but DOACs were associated with a lower risk of major bleeding (47–49). Also, in morbidly obese patients with VTE, no differences were found in efficacy and safety between warfarin and DOACs. Altogether, DOACs, particularly apixaban and rivaroxaban, seem safe and effective in patients with a BMI up to 40 kg/m^2, with the limitation of a lack of high-quality evidence. Above 40 kg/m^2, VKAs may be preferable; alternatively, direct FXa inhibitors with monitoring of anti-FXa activity may be helpful in identifying the best individualized OAC treatment (44).

Patients undergoing bariatric surgery are of special pharmacological concern. A drug's bioavailability depends on coadministration of food (mainly for rivaroxaban), stomach pH (mainly dabigatran), intestine transit time, surface, and site of absorption, which may all be variably modified by bariatric surgery. RCTs comparing DOACs with VKAs in patients after bariatric surgery are lacking. A small retrospective study in 41 patients who underwent gastric bypass surgery showed a trend toward subtherapeutic levels of rivaroxaban, but not of apixaban (48). Consistently, for dabigatran, a case series after gastric bypass surgery showed lower-than-expected dabigatran levels (50). VKAs are likely safe and effective following bariatric surgery due to the possibility of INR monitoring and adjusting therapy. For DOACs, measuring peak and trough drug levels has been recommended, at least initially, to test the feasibility of using these drugs (44).

On the other side of the body size spectrum, dabigatran and apixaban show relatively high drug concentrations in patients with low body weight (<60 kg) (40, 42). A positive correlation between drug level and bleeding was found for dabigatran (40, 51). In the landmark trials, only 2% [Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) for dabigatran] and 11% [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) for apixaban] of patients had a low body weight (e.g., <60 kg), and subgroup (52) and post hoc (53) analyses showed similar efficacy in DOACs as compared to warfarin. Reduced-dose apixaban was associated with less bleeding even in patients with a body weight <50 kg. In

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), only 4.6% of the population was <70 kg, and subgroup analysis revealed no differences in study outcomes in patients above or below this threshold (54). Observational data in AF patients with low body weight (<50 kg) show similar or better efficacy and safety for DOACs as compared to warfarin (55). Thus, in addition to the approved and recommended reduced dose for dabigatran, apixaban, and edoxaban, DOAC monitoring or switching to VKAs could be advised in low-weight patients (<60 kg).

3.2. Advanced Age and Frailty

Aging and frailty are independent risk factors for bleeding; thus, although antithrombotic therapy in elderly patients yields net clinical benefit when indicated, systematic bleeding risk assessment is recommended by several guidelines to enhance safety (46, 56). Scores that have been developed to predict the benefits and risks of antithrombotic therapies, that is, CHA2DS2-VASc (57), HAS-BLED (58), ABC (59), PRECISE-DAPT (60), and the ARC-HBR criteria (61) all incorporate age as a risk factor. Thus, advanced age alone should not be a reason to avoid OACs (56). However, general preventive measures against bleeding are advisable, such as PPIs to prevent GI bleeding, optimal blood pressure control, and tailoring drug dosing to age, body weight, and renal function according to approved indications and current guidelines (56) (**Table 1**). In an AF observational cohort of over 15,000 patients aged ≥90 years old, warfarin was associated with a favorable benefit/risk ratio when compared to antiplatelet or no antithrombotic therapy but with a higher risk of intracranial hemorrhage (ICH) compared to DOACs (62). In meta-analyses of randomized or observational studies of AF patients aged ≥75 years old, VKAs appear to be less effective than DOACs in preventing thromboembolism, with higher rates of ICH, higher or comparable rates of major bleeding, and lower or comparable rates of GI bleeding (63, 64).

When using VKAs in elderly patients on polypharmacy, DDIs need to be considered (see Section 4.3). For some DOACs, age-related adjusted doses are recommended (**Table 1**). Age is an independent predictor of increased dabigatran plasma concentrations based on the RE-LY PK study. Therefore, dabigatran at a reduced dose (110 mg) is indicated in patients ≥80 years old. Apixaban doses should be halved in the presence of two or more of the following factors: age ≥80 years old, body weight ≤60 kg, or serum creatinine ≥1.5 ml/dL. Edoxaban and rivaroxaban do not need adjustment for age.

Frailty is associated with weight loss and is more common in the chronic kidney disease (CKD) population (65). To ensure safe DOAC dosing, these factors should be considered. Elderly frail patients are more likely to fall (66). Although falling increases the risk for both intracranial and extracranial bleeding, risk of falling per se is not a contraindication to OACs. However, modifiable risk factors should be assessed, and individualized treatment should be implemented to minimize bleeding due to falls. A study estimated that a patient would have to fall 295 times to tip the benefit/risk balance toward subdural hemorrhage outweighing the benefit of VKAs (67). Given the lower risk of ICH with DOACs compared to VKAs, the number needed to fall would be even higher.

3.3. Chronic Kidney Disease

AF and VTE are more common in CKD and end-stage renal disease (ESRD) than in the general population. CKD is associated with an approximate 1.5-fold increase in VTE (68) and a two- to threefold increase in AF (69, 70). Moreover, AF and CKD synergistically increase thromboembolic risk. In a Danish nationwide study, patients with concurrent AF and CKD experienced higher rates

of stroke, systemic thromboembolism, and death than did those with AF alone (71). Paradoxically, the risk of major bleeding, including ICH, is also significantly increased by CKD (71). As a result, the risk/benefit ratio of OACs in AF patients with (severe) CKD remains uncertain. Studies on warfarin in CKD and ESRD have produced conflicting results (71, 72). A large systematic review and meta-analysis of 13 observational studies, including more than 48,000 patients with AF and CKD, showed reduced ischemic stroke and mortality without an effect on bleeding in patients with non-ESRD treated with warfarin (73). However, in patients with ESRD, there was no protective effect of warfarin on stroke and mortality, and major bleeding increased (73). A poor time within therapeutic range, often observed in HD patients on VKAs, might in part explain the diminished efficacy and safety of VKAs (74). Some DOACs could be beneficial in these patients, taking into account the degree of renal excretion (52, 54, 75, 76) (**Table 2**). Evidence on the use of DOACs for different stages of CKD is limited and consists of post hoc analyses of Phase III trials for CKD stage 3 (77–80), data from observational studies for CKD stage 3 (81) and stage 4 (82, 83) and for HD patients (84), and a few RCTs comparing apixaban with VKAs in HD patients (85, 86). Nonetheless, the use of DOACs is approved by the US Food and Drug Administration and European Medicines Agency in most CKD patients (**Table 2**).

3.4. Antiphospholipid Syndrome

APS is characterized by (venous or arterial) thrombosis and/or pregnancy complications in the presence of persistent antiphospholipid antibodies. The most commonly used laboratory tests determine the presence of lupus anticoagulants, anticardiolipin antibodies (IgG/IgM), and anti-B2 glycoprotein I antibodies (IgG/IgM). Deep vein thrombosis and ischemic stroke are the most common thrombotic manifestations of APS, but all vascular beds can be involved. After the first thrombotic event, the risk of recurrence is high (10–29% per year) (87), and long-term antithrombotic treatment is required. The ESC and ISTH guideline recommends against the use of DOACs in APS patients (88) based on the results of the Trial of Rivaroxaban in AntiPhospholipid Syndrome (TRAPS) study in which rivaroxaban was associated with an increased risk of recurrent thrombotic events, compared to warfarin, in triple-positive (high-risk) APS patients, particularly those with previous arterial thrombosis (89). The thrombotic risk in DOAC- versus VKA-treated patients is unknown for venous thrombosis in non-triple-positive APS patients. As a result, the ISTH guideline considers continuation of DOACs in a low-risk APS patient who is stable on DOAC treatment a justifiable option (90).

4. COMBINATION WITH OTHER ANTITHROMBOTIC DRUGS AND DRUG INTERACTION

4.1. Combination with Antiplatelet Drug(s)

A significant number (about 10%) of AF patients develop acute or chronic coronary syndromes and need percutaneous coronary intervention (PCI) with stent implantation (91). Conversely, it is estimated that AF develops in up to 20% of patients following acute coronary syndrome (ACS). Thus, patients with AF undergoing PCI may require both OACs for AF and antiplatelet therapy for their coronary disease, usually dual antiplatelet therapy (DAPT) with low-dose aspirin and a $P2Y_{12}$ inhibitor post-ACS or PCI. The combination of DAPT with an OAC, the so-called triple therapy, substantially increases the risk of bleeding due to the combined blockade of primary and secondary hemostasis. The What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial was the first small study to compare the strategy of dropping one antiplatelet drug from DAPT, in that case, aspirin, versus the triple therapy with VKAs and DAPT and use safety, rather than efficacy, as the primary end

point, and it found a significant reduction in mostly minor-to-moderate bleeding (92). All four DOACs have been tested in dedicated but medium-sized RCTs, shown in **Table 3**, that mostly compared a triple antithrombotic strategy that included a VKA with double therapy that included a DOAC (93–96). These trials, and their meta-analyses (97, 98), support the use of a DOAC rather than VKA in these patients. Furthermore, data from these RCTs suggest that the combination of a DOAC and a single antiplatelet agent (clopidogrel has been the most studied) may be preferable in terms of safety over triple therapy. This combination of an OAC with single antiplatelet therapy is known as double antithrombotic therapy (DAT). DAT is associated with a large reduction in minor-to-moderate bleeding compared with triple therapy. However, none of the RCTs was powered to assess efficacy, that is, major adverse ischemic events, and available meta-analyses suggest a potential increase in myocardial infarction and stent thrombosis, especially in the months soon after PCI (97, 99) (**Table 3**). Therefore, most guidelines nowadays recommend triple therapy for up to one to three months after the ACS or PCI in high–ischemic risk patients, whereas in other patients, DAT (DOAC plus $P2Y_{12}$ inhibitor or aspirin) should be the default strategy (100, 101). The $P2Y_{12}$ inhibitor in these patients should be discontinued at one year (or at six months in high–bleeding risk AF patients), whereas OACs should be maintained indefinitely (101). Important knowledge gaps in treating these patients include the safety and efficacy of combining the more effective $P2Y_{12}$ inhibitors prasugrel and ticagrelor with DOACs, a direct comparison of $P2Y_{12}$ inhibitor discontinuation versus aspirin discontinuation in a DAT strategy, and the option of dropping OACs in the first month after PCI (i.e., DAPT followed by dual pathway inhibition).

4.2. Dual Pathway Inhibition

Atherothrombosis is the result of inflammatory processes involved in atherogenesis and the interplay between thrombin and platelets. Thrombin plays a crucial role in both coagulation and platelet activation, and therefore, adding OACs next to antiplatelet therapy could further modify the risk in patients with atherothrombosis. The addition of a very low dose of a direct FXa inhibitor on top of aspirin, the so-called dual pathway inhibition (DPI), may also have the potential to exert an anti-inflammatory, off-target effect through vessel wall cell PAR inhibition, although the clinical evidence remains weak (102, 103). The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) and Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS-ACS 2–TIMI 51) trials showed that very-low-dose rivaroxaban (2.5 mg twice daily) on top of single (aspirin) or dual (aspirin and clopidogrel) antiplatelet therapy reduced cardiovascular death, myocardial infarction, or stroke in patients with chronic or acute coronary disease, respectively, at the price of more major (but not fatal) bleeding events. However, the net clinical benefit was in favor of the combined antiplatelet/anti-FXa treatment (104, 105). Current guidelines recommend that DPI should be considered for long-term secondary prevention in stable patients with high ischemic risk and low bleeding risk (106).

4.3. Pharmacokinetic-Based Drug-Drug Interactions

The progressive aging of the population worldwide is leading to increases in comorbidities, including cardiovascular disease, and associated polypharmacy (defined as five or more coprescribed drugs) (107). Polypharmacy increases the potential for DDIs that can substantially modify the response expected of each agent when given alone, reducing efficacy or safety. Importantly, cardiovascular drugs are commonly involved in DDIs (107). In the ARISTOTLE and ROCKET-AF trials recruiting nonvalvular AF patients with an indication for OACs, the median number of drugs per patient at study entry was 6 [interquartile range (IQR) 5–9] and 5 (IQR 4–8), respectively

Table 3 Trials in and meta-analyses of subjects with AF and ACS or post-PCI

Study (Reference)	Characteristics, sample size	Design	Primary end points	Secondary end point(s)	Primary outcomes	Secondary outcomes
PIONEER-AF-PCI (93)	2,124 patients with AF and PCI with stenting	Group 1: rivaroxaban 15 mg od + $P2Y_{12}$ inhibitor for 12 months Group 2: rivaroxaban 2.5 mg bd + DAPT for 1, 6, or 12 months, receiving ASA + rivaroxaban 15 mg for the remainder of the 12 months Group 3: VKA + DAPT for 1, 6, or 12 months, receiving ASA + VKA for the remainder of the 12 months 94% clopidogrel	Major and minor TIMI bleeding or bleeding requiring medical attention Follow-up: 12 months	Composite of CV death, MI, and stroke (MACE)	Group 1: 16.8% Group 2: 18.0% Group 3: 26.7% HR (group 1 versus 3) = 0.59, 95% CI 0.47–0.76 HR (group 2 versus 3) = 0.63, 95% CI 0.50–0.80	MACE: Group 1: 41 (6.5%) Group 2: 36 (5.6%) Group 3: 36 (6.0%) HR (group 1 versus 3) = 1.08, 95% CI 0.69–1.68 HR (group 2 versus 3) = 0.93, 95% CI 0.59–1.48
RE-DUAL PCI (94)	2,725 patients with AF and PCI	Randomization to: VKA + $P2Y_{12}$ inhibitor + ASA (3 months for DES) (TAT), then continue with VKA + $P2Y_{12}$ inhibitor, or Dabigatran (2 doses) + $P2Y_{12}$ inhibitor (DAT) for 12 months 88% clopidogrel	Major or clinically relevant nonmajor bleeding according to the ISTH definition Noninferiority comparison Follow-up: 14 months	Composite of MI, stroke, systemic embolism, death, and unplanned revascularization Noninferiority comparison	15.4% in the 110-mg DAT group versus 26.9% in the TAT group (HR = 0.52, 95% CI 0.42–0.63, $p < 0.001$ for noninferiority and superiority) 20.2% in the 150-mg DAT group versus 25.7% in the TAT group (HR = 0.72, 95% CI 0.58–0.88, $p < 0.001$ for noninferiority only)	239 (13.7%) DAT versus 131 (13.4%) TAT (HR = 1.04, 95% CI 0.84–1.29, $p = 0.005$ for noninferiority) Thromboembolic events: 168 (9.6%) DAT versus 83 (8.5%) TAT (HR = 1.17, 95% CI 0.9–1.53, $p = 0.11$ for noninferiority)
ENTRUST (96)	1,506 patients with AF after PCI for stable CAD or ACS	Edoxaban (60 mg od) + $P2Y_{12}$ inhibitor for 12 months, or VKA + $P2Y_{12}$ inhibitor + ASA for min. 1 month and max. 12 months 93% clopidogrel	Major or clinically relevant nonmajor bleeding according to the ISTH definition Follow-up: 12 months	CV death, stroke, systemic embolic event, MI, or definite stent thrombosis	128 (17%) in the DAT-edoxaban group versus 152 (20%) in the TAT group (HR = 0.83; 95% CI 0.65–1.05; $p = 0.0010$ for noninferiority only, p = NS for superiority) Median TAT: 2 months	49 (7%) DAT 46 (6%) TAT HR = 1.06, 95% CI 0.71–1.69

(*Continued*)

Table 3 (*Continued*)

Study (Reference)	Characteristics, sample size	Design	Primary end points	Secondary end point(s)	Primary outcomes	Secondary outcomes
AUGUSTUS (95)	4,614 patients with persistent, permanent, paroxysmal AF and recent ACS or PCI with planned use of $P2Y_{12}$ inhibitor	Two-by-two factorial design: Apixaban or VKA ASA 81 mg or placebo All for 6 months, and on a background of 93% clopidogrel	Major or clinically relevant nonmajor bleeding according to the ISTH definition Noninferiority and superiority comparisons Follow-up: 6 months	Death; hospitalization; and composite of stroke, MI, and stent thrombosis (definite or probable); or Urgent revascularization	10.5% apixaban 14.7% VKA (HR = 0.69, 95% CI 0.58–0.81, $p < 0.001$ for noninferiority and superiority) 16.1% ASA 9.0% placebo (HR = 1.89, 95% CI 1.59–2.24, $p < 0.001$)	154 patients (6.7%) on apixaban versus 163 (7.1%) on VKA 149 patients (6.5%) on ASA versus 168 (7.3%) on placebo p = NS
Meta-analysis (97)	10,234 AF patients undergoing PCI from four trials: PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST (DAT = 5,496 versus TAT = 4,738)	DAT versus TAT	ISTH major or clinically relevant nonmajor bleeding at longest available follow-up (between 6 and 14 months)	All-cause death, CV death, trial-defined MACE, MI, stroke, and ST	13.4% DAT 20.8% TAT RR = 0.66, 95% CI 0.56–0.78, $p < 0.0001$	DAT versus TAT: CV death 2.6% versus 2.4% (RR = 1.10, 95% CI 0.86–1.41) MACE 8.6% versus 8.0% (RR = 1.08, 95% CI 0.95–1.23, $p = 0.26$) MI 3.6% versus 3.0% (RR = 1.22, 95% CI 0.99–1.52, $p = 0.07$) ST 1.0% versus 0.6% (RR = 1.59, 95% CI 1.01–2.50, $p = 0.04$) Similar results in ACS and stable CAD patients
Meta-analysis (98)	9,463 AF patients undergoing PCI from three trials: PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS	DAT versus TAT	Major bleeding according to ISTH definition and TIMI-refined, or clinically relevant nonmajor bleeding	All-cause and CV death, stroke, MI, and ST	DAT versus TAT (ISTH-defined major bleeding) (OR = 0.59, 95% CI 0.49–0.72, $p < 0.001$)	All ischemic events: 4.1% DAT 3.2% TAT MI (OR = 1.2, 95% CI 0.96–1.5, $p = 0.1$) ST (OR = 1.67, 95% CI 1.02–2.73, $p = 0.04$)

Studies are ordered according to the year of publication. Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; bd, twice daily; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; DES, drug-eluting stent; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular event; MI, myocardial infarction; NS, not significant; od, once daily; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; ST, stent thrombosis; TAT, triple antithrombotic therapy; TIMI, thrombolysis in myocardial infraction; VKA, vitamin K antagonist.

(108, 109). Interestingly, the greater safety of apixaban versus warfarin in the ARISTOTLE trial was blunted as a function of the number of coprescribed drugs (108).

VKAs, especially warfarin, are particularly exposed to DDIs due to multiple mechanisms (**Table 1**): PK-related biotransformation changes due to the inhibition or induction of several CYP450s (3A4, 2C9, 2C19), pharmacogenomics due to loss of function alleles (CYP2C9 and vitamin K epoxide reductase), antibiotics affecting gut microbiota and thereby reducing the endogenous daily vitamin K production, and drugs affecting the intestinal mobility. However, since VKA dosing is monitored and adjusted with the INR, clinically relevant DDIs can usually be identified and prevented and drug dosing adjusted accordingly.

DOACs can also be exposed to specific, clinically relevant DDIs (**Table 1**). The P-glycoprotein (P-gp) efflux transporter has high affinity for the prodrug dabigatran etexilate, and this drug is highly dependent on P-gp for its cell clearance (110, 111). It has been estimated that nearly 50% of patients on OACs are prescribed drugs that interact with P-gp (112). Clinically relevant DDIs with dabigatran occur with strong inhibitors or inducers of P-gp such as verapamil, digoxin, quinidine, dronedarone, and amiodarone as they may significantly modify dabigatran's area under the curve (AUC), and regulatory recommendations reflect this drug disposition. Apixaban and rivaroxaban have a mixed PK that involves many CYP450s, including CYP3A4, and different efflux transporters, not only the P-gp. Thus, only drugs that combine strong inhibition or induction of both CYP3A4 and P-gp can generate relevant DDIs. Edoxaban has a higher affinity for P-gp than do the other two anti-FXa DOACs (110), and therefore DDIs and recommendations reflect this drug disposition. Recent postmarketing data clearly show the clinical relevance and impact of DDIs for DOACs (113) and have added new evidence for valproic acid, levetiracetam (CYP3A4 and P-gp inducers), and bisoprolol (CYP3A4 inhibitor) as drugs that interact with DOACs and are associated with decreased efficacy and safety, respectively (114). Based on DDIs, azithromycin should be preferred to clarithromycin, especially in elderly patients on DOACs (115).

Recent population PK derived from in silico models and simulations instructed by data from RCT, PK, or large cohort studies appear to be able to identify the covariates significantly affecting DOACs and to predict the changes in AUC. Relevant covariates for dabigatran's changes in AUC, even at a reduced dose (110 mg), are age, kidney function, and P-gp inhibition (116). For rivaroxaban and edoxaban, relevant covariates significantly affecting the AUC are kidney function and combined P-gp/CYP3A4 inhibition, but not age, for both full and reduced dosing; for apixaban, the genotype of the ABCG2 transporter also seems relevant in affecting the AUC (116).

In conclusion, DDIs with other cardiovascular drugs are possible and likely specific for each DOAC. Large postmarketing surveillance studies and drug modelling are adding new information not only on the clinical impact of DDIs but also on the different impacts of DDIs as a function of age, kidney function, and pharmacogenomics. Major features and regulatory recommendations are summarized in **Table 1**.

5. VALVES

VKAs remain the reference treatment for patients with mechanical heart valves based on the negative outcome of one Phase II RCT on dabigatran versus warfarin, which was terminated for major safety drawbacks with dabigatran (117). The harmful results of this trial hampered the development of anti-Xa compounds in this setting. Furthermore, the Prospective Randomized On-X Anticoagulation Clinical Trial Xa (PROACT Xa) trial that was designed to test the efficacy of apixaban versus warfarin in patients with aortic mechanical valves replaced at least 3 months ago (118) was also stopped in September 2022 by the Data and Safety Monitoring Board (119), but details are currently unpublished.

Large superiority RCTs comparing VKAs and DOACs soon after bioprosthetic valve replacement are also missing; thus in AF patients, DOACs are recommended with a low degree of class and level of evidence starting only 3 months or longer after bioprosthetic valve implantation (120).

Transcatheter aortic valve implantation patients with no other indications for DOACs should be treated with low-dose aspirin based on current evidence, while for patients with a clear indication for OACs, there is no convincing evidence that DOACs are superior to VKAs (121).

6. MONITORING: HOW AND WHEN

DOACs are given in a fixed dose without the need for laboratory testing based on reduced intra- and interindividual variability as compared to VKAs. Dose adjustments are made based on clinical features rather than on plasma levels of coagulation biomarker (e.g., INR). Indeed, Phase III landmark trials have shown that nonmonitored, fixed-dose regimes are safe and effective. However, patients on DOACs are still at risk of developing thrombotic recurrence or major bleeding. In RE-LY, ischemic strokes and bleeding outcomes were correlated with dabigatran plasma concentration (40). Similarly, a correlation was found between edoxaban plasma concentration and clinical outcome (122). For apixaban and rivaroxaban, data on plasma concentration in relation to clinical outcomes have not been published. For all DOACs, however, there is high variability in plasma levels between individuals, and as a result, some patients might be over- or underexposed.

Thus, it is plausible that tailoring DOAC therapy might improve its efficacy and safety. However, therapeutic ranges for DOACs have not yet been determined in prospective studies, and currently, only expected on-therapy trough and peak ranges are known. Besides, DOAC monitoring is challenging as DOACs have a short half-life, and in contrast to the INR in VKAs, DOAC (activity) levels rapidly change over hours. Therefore, for interpretation, knowledge of the exact times of drug intake and blood drawing is mandatory. Awaiting studies on the effect of DOAC tailoring with respect to clinical outcomes and safety, there are patient populations for whom laboratory monitoring should already be considered: patients with increased or decreased estimated glomerular filtration rate, extremes of body weight, extremes of age, liver dysfunction, frailty and suspected impaired GI absorption, and (multiple) DDIs. Those populations are underrepresented in the large Phase III trials, and it is reasonable to assess DOAC levels in patients with such conditions, at least once at the beginning of the treatment, since significant variations in drug concentrations are plausible based on major PK changes. Off-range DOAC levels might guide physicians to switch to a different DOAC or even different class of anticoagulant drugs. DOAC dosage adjustments based on DOAC plasma levels are still off-label, but they might be justifiable and useful in some cases.

In addition to the individualization of anticoagulant therapy, laboratory assessment of DOAC plasma levels is desirable in several other clinical situations, such as in the case of an urgent surgery, a major bleeding event, a (recurrent) thrombotic event, or suspected noncompliance. In some circumstances (e.g., major life-threatening bleeding or urgent major surgery), plasma levels might guide reversal strategies, timing of the operation/thrombolysis, and future anticoagulant therapy.

7. REVERSAL STRATEGIES

Despite improved safety of DOACs compared with VKAs, major bleedings are still the most concerning adverse events, as for all anticoagulant drugs. General measures in all DOAC-related major bleeding include stopping the DOAC, supportive care ensuring hemodynamic stability, and local hemostasis (46). DOACs have a reversible mode of action and a short half-life—some are given once, others twice daily (**Table 1**)—so a conservative approach might suffice, even in cases of major (GI) bleeding. Notably, all DOAC RCTs showing improved safety with less

major fatal bleeding were performed before the development of specific antidotes. Nonetheless, once approved, millions of patients became exposed to DOACs, and specific antidotes became needed for major, uncontrolled bleeding or for rapid reversal of hemostasis before urgent invasive interventions.

Currently, there are two approved reversal agents (idarucizumab and andexanet alfa) and one under advanced development (ciraparantag) (123). Idarucizumab is a humanized monoclonal antibody that binds dabigatran with a higher affinity than thrombin and rapidly reverses its anticoagulant properties by correcting the diluted thrombin time (dTT) and ecarin clotting time (ECT). It exerts no procoagulant effects in healthy volunteers (124) and has been studied in a single-arm multicenter trial that included 503 patients on dabigatran with uncontrolled, life-threatening bleeding or needing urgent surgery, with a soft, biomarker-based primary end point defined as the correction of ECT or dTT after bolus infusion (125). Idarucizumab resulted in a rapid and complete reversal of the anticoagulant effect of dabigatran in 98% of patients, and the effects remained for 24 h. Major limitations of this trial included the lack of clinical end point, the single-arm and open label design, the short follow-up, and the small sample size. Notably, 90-day mortality was very high (nearly 20%). Andexanet is a modified recombinant inactive form of FXa that binds and scavenges FXa inhibitors restoring FXa activity. Andexanet was developed to reverse the anticoagulant properties of all FXa inhibitors, both direct and indirect, such as enoxaparin (126). Andexanet was also studied in a single-arm multicenter trial that included 352 patients with life-threatening bleeding and had two major end points: the measure of anti-FXa activity and the clinical/laboratory/imaging evaluation of hemostasis recovery (127). Andexanet resulted in a 71% (edoxaban), 75% (enoxaparin), 93% (apixaban), and 94% (rivaroxaban) reduction of the anti-FXa activity (128). Because of faster inclusion, data on apixaban and rivaroxaban were published in 2019, whereas data on edoxaban and enoxaparin were published only very recently. Based on the design of the Phase III RCT, andexanet has been neither tested in nor approved for urgent surgery, and special caution should be taken with the off-label use of andexanet during procedures in which heparin (which is also inhibited by andexanet) is required (129). The administration of andexanet might exert some procoagulant effects since at least in vitro it inhibits tissue factor pathway inhibitor, the natural inhibitor of FXa (130). In healthy volunteers, andexanet administration is associated with increased prothrombin fragments (F1+2), thrombin-antithrombin complexes, and D-dimer levels (131); the clinical importance of this finding is uncertain.

Idarucizumab and andexanet were both approved based on small, single-arm, biomarker–end point–based trials. None of the trials included a control arm such as with four-factor prothrombin complex concentrate (PCC). Although we are awaiting results from the Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor (ANNEXA-I) trial, a RCT comparing andexanet with PCC in patients with intracranial bleeding while on a FXa inhibitor, the results of two propensity score–matched comparisons of two independent data sets were recently published and favored the use of andexanet (132, 133). The data revealed 57–64% lower 30-day mortality in patients treated with andexanet compared to matched PCC-treated patients (132).

Although indirect evidence based on the correction of coagulation tests ex vivo suggests a better clinical outcome with these agents, direct evidence is lacking, especially for idarucizumab. Also, long-term and reexposure effects to the same agents are currently unknown. Meanwhile, additional reversal agents are under development and being tested in clinical studies (123). Furthest in development is ciraparantag, a small synthetic molecule that acts as a universal reversing agent. Via noncovalent hydrogen binding and charge-charge interactions, it blocks the binding of heparins and DOACs to their target sites. Ciraparantag does not bind plasma proteins or other drugs such as cardiac, antiepileptic, and diabetic drugs (134). According to the Phase I and II trials,

ciraparantag appears to be safe and easy to administer and has been shown to be effective in reversing the in vitro anticoagulant effects of enoxaparin, edoxaban, apixaban, and rivaroxaban (134).

8. NEW AVENUES IN ORAL ANTICOAGULATION

Although DOACs have markedly improved anticoagulant management by providing drugs that are more user friendly and less variable in most patients with VTE and AF, a substantial risk of major bleeding, between 2% and 3% per year in trials and up to 7% in real-life registries, poses an ongoing concern, particularly for subjects with a high bleeding risk. Therefore, investigators are exploring new, possibly safer strategies, including anticoagulants that target the upstream proteins of the coagulation cascade. The interest in FXI, and to a lesser extent in FXII, comes from observational and experimental studies showing that subjects with congenital deficiency do not have an impairment in hemostasis (FXII) or a lack of unprovoked bleeding (FXI) (135). Thus, targeting one of these factors has been hypothesized to inhibit coagulation, with less impact on hemostasis and thus a lower bleeding potential as compared to inhibition of FXa or thrombin (136, 137). Preclinical studies confirmed the antithrombotic potential of blocking either FXII or FXI; however, concerns about off-target consequences of FXIIa inhibition (on the prekallikrein/high-molecular-weight kininogen inflammatory pathways), as well as the potential of escape intrinsic pathway stimulation by thrombin feedback activation of FXI, make FXII(a) a less-attractive target (138).

Various strategies and molecules have been tested for FXI(a) (139). The first Phase II, dose-finding RCT used a small interfering RNA–silencing molecule for the FXI gene in the liver, lowering plasma concentrations to levels comparable to those of severe congenital FXI deficiency (140). This strategy proved to be safe in subjects undergoing elective knee replacement surgery, a common model of testing the thrombosis-prevention potency of anticoagulant agents, as compared with LMWHs. In addition, there were signs of similar efficacy to that of enoxaparin; however, these data await confirmation in Phase III trials.

Next, other strategies, including a monoclonal antibody and two oral small-molecule compounds, were tested against LMWHs in this surgical model in Phase II trials. For all strategies, based on small numbers, the antithrombotic efficacy seemed at least comparable to that of enoxaparin, and the risk of postoperative bleeding—mostly minor bleeds—was lower than for LMWHs, but again, Phase II trials are not powered to prove efficacy (141).

Following these promising studies, other Phase II studies were initiated to test different doses of the oral compounds asundexian and milvexian as add-ons to antiplatelet drugs in different conditions such as ACS and (prevention of) ischemic stroke.

Three different doses of asundexian on top of DAPT in ACS did not significantly increase the risk of bleeding and had a neutral impact on vascular events in dose-finding Phase II trials (142).

In patients with AF, two doses of asundexian were compared with apixaban for safety, for example, in bleeding. While there was no clear effect on thrombotic end points in an exploratory analysis, the rate of mostly minor bleeding complications was lower for asundexian than for apixaban (143). In patients who suffered an acute ischemic stroke and were treated with initial DAPT, the addition of increasing doses of asundexian showed a trend of fewer recurrent ischemic events (144). Milvexian in patients with ischemic stroke on top of DAPT showed a trend of dose-dependent increases in bleeding complications with possibly some signal of efficacy, but this was only based on a very low number of events (145).

Overall, these Phase II trials were not powered for efficacy but rather for identifying the best dosing for Phase III RCTs to test the hypothesis that these agents would have minimal impact on physiological hemostasis and would cause less bleeding.

Other ongoing studies are testing these agents in severe renal failure and CAT (139). Off-target effects of FXI(a) inhibition cannot be ruled out; these include effects on fibrinolysis, interactions with tissue factor pathway inhibitor (TFPI) (146), and perhaps also effects on the FXI protective effect on the BMP-SMAD1/SMAD5 axis in the heart (147).

9. CONCLUSIONS AND PERSPECTIVES

Oral anticoagulation beyond warfarin, the starting point of this narrative review, has been overwhelmingly fruitful in the development and large-scale clinical testing of the first generation of DOACs for major indications, including AF and the prevention and treatment of VTE. Overall, the practical benefits of fixed dosing, adjusted based on a limited number of criteria, has made oral anticoagulation much easier than INR-tailored VKA dosing. A class advantage of DOACs is a reduced risk of ICH, which in the long run is a clear benefit over VKAs. However, we identified several caveats that somewhat temper the initial optimism regarding DOACs and that justify more attention. First, the use of DOACs in specific populations, where frailty, comorbidities, and polypharmacy introduce considerable uncertainties regarding both the efficacy and safety of DOACs and DDIs, should proceed with caution. Combined anticoagulant and antiplatelet agents, often applied in patients with coronary artery disease and AF, pose substantial challenges in choosing optimal drug combinations and duration of therapy. We also identified several situations where laboratory monitoring of the DOAC plasma level may be warranted on top of regular assessment of renal and liver function and compliance. This testing may be helpful in determining the suitability of a given DOAC for an individual patient or in assessing the impact of specific DDIs; switching to another DOAC or VKA is always an option. Second, DOACs are not yet suitable for all patients with an indication for OACs—we briefly discussed indications such as mechanical heart valves—and for certain indications such as triple-positive APS, the currently limited data do not yet support the use of DOACs. In the latter situations where there is a high risk for thrombosis, a VKA is more effective than a DOAC, and while the reasons for DOACs' lack of efficacy remain unknown, it also implies that VKAs remain a highly relevant mode of oral anticoagulation for the time being.

A new generation of mostly FXIa-targeted drugs is being tested in clinical trials; Phase II studies in VTE prevention are promising, but data are highly uncertain in arterial indications, including AF, ACS, and ischemic stroke. Whether improvements in safety, and maintaining efficacy, can be achieved by inhibiting upstream proteases such as FXIa remains to be proven in Phase III studies.

DISCLOSURE STATEMENT

R.H.O. reports speaker fees from AstraZeneca and Novartis. B.R. reports a research grant to the Department of Pharmacology, Catholic University School of Medicine, from Bayer AG for a study on rivaroxaban and a consultancy fee from Aboca. H.t.C. reports consultancy fees from Bayer AG, Galapagos NV, AstraZeneca, Alveron Pharma, and Novostia SA; speaker fees from AstraZeneca; and former research support from Bayer AG. H.t.C. is a shareholder of Coagulation Profile; all benefits were deposited at CARIM for research only. The other authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Choi SE, Sagris D, Hill A, Lip GYH, Abdul-Rahim AH. 2023. Atrial fibrillation and stroke. *Expert Rev. Cardiovasc. Ther.* 21(1):35–56

2. Ryu R, Tran R. 2022. DOACs in mechanical and bioprosthetic heart valves: a narrative review of emerging data and future directions. *Clin. Appl. Thromb. Hemost.* 28:10760296221103578
3. Knight JS, Branch DW, Ortel TL. 2023. Antiphospholipid syndrome: advances in diagnosis, pathogenesis, and management. *BMJ* 380:e069717
4. Verma R, Latter DA. 2023. Anticoagulation for rheumatic mitral stenosis, INVICTUS in perspective. *Curr. Opin. Cardiol.* 38(2):55–60
5. Werth S, Breslin T, NiAinle F, Beyer-Westendorf J. 2015. Bleeding risk, management and outcome in patients receiving non-VKA oral anticoagulants (NOACs). *Am. J. Cardiovasc. Drugs* 15(4):235–42
6. Beyer-Westendorf J, Forster K, Pannach S, Ebertz F, Gelbricht V, et al. 2014. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood* 124(6):955–62
7. Archontakis-Barakakis P, Li W, Kalaitzoglou D, Tzelves L, Manolopoulos A, et al. 2022. Effectiveness and safety of intracranial events associated with the use of direct oral anticoagulants for atrial fibrillation: a systematic review and meta-analysis of 92 studies. *Br. J. Clin. Pharmacol.* 88(11):4663–75
8. Kosciuszek ND, Kalta D, Singh M, Savinova OV. 2022. Vitamin K antagonists and cardiovascular calcification: a systematic review and meta-analysis. *Front. Cardiovasc. Med.* 9:938567
9. Posma JJ, Grover SP, Hisada Y, Owens AP 3rd, Antoniak S, et al. 2019. Roles of coagulation proteases and PARs (protease-activated receptors) in mouse models of inflammatory diseases. *Arterioscler. Thromb. Vasc. Biol.* 39(1):13–24
10. Dólleman SC, Agten SM, Spronk HMH, Hackeng TM, Bos MHA, et al. 2022. Thrombin in complex with dabigatran can still interact with PAR-1 via exosite-I and instigate loss of vascular integrity. *J. Thromb. Haemost.* 20(4):996–1007
11. ten Cate H, Guzik TJ, Eikelboom J, Spronk HMH. 2021. Pleiotropic actions of factor Xa inhibition in cardiovascular prevention: mechanistic insights and implications for anti-thrombotic treatment. *Cardiovasc. Res.* 117(9):2030–44
12. d'Alessandro E, Becker C, Bergmeier W, Bode C, Bourne JH, et al. 2020. Thrombo-inflammation in cardiovascular disease: an expert consensus document from the Third Maastricht Consensus Conference on Thrombosis. *Thromb. Haemost*. 120(4):538–64
13. Nagy M, van der Meijden PEJ, Glunz J, Schurgers L, Lutgens E, et al. 2022. Integrating mechanisms in thrombotic peripheral arterial disease. *Pharmaceuticals* 15(11):1428
14. Frere C, Farge D, Schrag D, Prata PH, Connors JM. 2022. Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated venous thromboembolism: 2022 updated systematic review and meta-analysis of randomized controlled trials. *J. Hematol. Oncol.* 15(1):69
15. Farge D, Frere C, Connors JM, Khorana AA, Kakkar A, et al. 2022. 2022 International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol.* 23(7):e334–47
16. Falanga A, Ay C, Di Nisio M, Gerotziafas G, Langer F, et al. 2023. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline. *Ann. Oncol.* 34(5):452–67
17. Shevell L, Ochs M, Schaefer J. 2023. Prophylactic anticoagulation in patients with cancer: when and how? *Curr. Oncol. Rep.* 25(3):201–9
18. Spyropoulos AC. 2022. To prophylax or not, and how much and how long? Controversies in VTE prevention for medical inpatients, including COVID-19 inpatients. *Hematol. Am. Soc. Hematol. Educ. Program* 2022(1):506–14
19. Swan D, Thachil J. 2022. Challenges in managing patients on anticoagulation: thrombocytopenia, resumption after bleeding and recurrent thrombosis. *J. R. Coll. Physicians Edinb.* 52(4):341–49
20. Tsoukalas N, Brito-Dellan N, Font C, Butler T, Rojas-Hernandez CM, et al. 2022. Complexity and clinical significance of drug-drug interactions (DDIs) in oncology: challenging issues in the care of patients regarding cancer-associated thrombosis (CAT). *Support. Care Cancer* 30(10):8559–73
21. Musgrave KM, Power K, Laffan M, O'Donnell JS, Thachil J, Maraveyas A. 2022. Practical treatment guidance for cancer-associated thrombosis—managing the challenging patient: a consensus statement. *Crit. Rev. Oncol. Hematol.* 171:103599

22. Frere C, Font C, Esposito F, Crichi B, Girard P, Janus N. 2022. Incidence, risk factors, and management of bleeding in patients receiving anticoagulants for the treatment of cancer-associated thrombosis. *Support. Care Cancer* 30(4):2919–31
23. Khorana AA, Mackman N, Falanga A, Pabinger I, Noble S, et al. 2022. Cancer-associated venous thromboembolism. *Nat. Rev. Dis. Primers* 8(1):11
24. Carrier M, Blais N, Crowther M, Kavan P, Le Gal G, et al. 2021. Treatment algorithm in cancer-associated thrombosis: updated Canadian Expert Consensus. *Curr. Oncol.* 28(6):5434–51
25. Moik F, Pabinger I, Ay C. 2020. How I treat cancer-associated thrombosis. *ESMO Open* 5(1):e000610
26. Iyengar V, Patell R, Zwicker J. 2022. Challenges in anticoagulation for patients with brain tumors. *Best Pract. Res. Clin. Haematol.* 35(1):101350
27. Benamouzig R, Guenoun M, Deutsch D, Fauchier L. 2022. Gastrointestinal bleeding risk with direct oral anticoagulants. *Cardiovasc. Drugs Ther.* 36(5):973–89
28. Otten LS, Piet B, van den Heuvel MM, Marzolini C, van Geel R, et al. 2022. Practical recommendations to combine small-molecule inhibitors and direct oral anticoagulants in patients with nonsmall cell lung cancer. *Eur. Respir. Rev.* 31(164):220004
29. Brea EJ, Tiu BC, Connors JM. 2021. A comprehensive review of DOACs for cancer associated VTE prophylaxis or treatment. *Postgrad. Med.* 133(Suppl. 1):71–79
30. Sebuhyan M, Crichi B, Abdallah NA, Bonnet C, Deville L, et al. 2020. Drug-drug interaction (DDI) with direct oral anticoagulant (DOAC) in patients with cancer. *J. Med. Vasc.* 45(6S):6S31–38
31. Bellesoeur A, Thomas-Schoemann A, Allard M, Smadja D, Vidal M, et al. 2018. Pharmacokinetic variability of anticoagulants in patients with cancer-associated thrombosis: clinical consequences. *Crit. Rev. Oncol. Hematol.* 129:102–12
32. Leader A, Hofstetter L, Spectre G. 2021. Challenges and advances in managing thrombocytopenic cancer patients. *J. Clin. Med.* 10(6):1169
33. Falanga A, Leader A, Ambaglio C, Bagoly Z, Castaman G, et al. 2022. EHA guidelines on management of antithrombotic treatments in thrombocytopenic patients with cancer. *Hemasphere* 6(8):e750
34. Lee AYY. 2017. When can we stop anticoagulation in patients with cancer-associated thrombosis? *Blood* 130(23):2484–90
35. Becattini C, Di Nisio M, Franco L, Lee A, Agnelli G, Mandala M. 2021. Treatment of venous thromboembolism in cancer patients: the dark side of the moon. *Cancer Treat. Rev.* 96:102190
36. Weitz JI, Prandoni P, Verhamme P. 2020. Anticoagulation for patients with venous thromboembolism: When is extended treatment required? *TH Open* 4(4):e446–56
37. Sanfilippo KM, Moik F, Candeloro M, Ay C, Di Nisio M, Lee AYY. 2022. Unanswered questions in cancer-associated thrombosis. *Br. J. Haematol.* 198(5):812–25
38. Jimenez-Fonseca P, Gallardo E, Arranz Arija F, Blanco JM, Callejo A, et al. 2022. Consensus on prevention and treatment of cancer-associated thrombosis (CAT) in controversial clinical situations with low levels of evidence. *Eur. J. Intern. Med.* 100:33–45
39. O'Connell C, Escalante CP, Goldhaber SZ, McBane R, Connors JM, Raskob GE. 2021. Treatment of cancer-associated venous thromboembolism with low-molecular-weight heparin or direct oral anticoagulants: patient selection, controversies, and caveats. *Oncologist* 26(1):e8–16
40. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, et al. 2014. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J. Am. Coll. Cardiol.* 63(4):321–28
41. Speed V, Green B, Roberts LN, Woolcombe S, Bartoli-Abdou J, et al. 2020. Fixed dose rivaroxaban can be used in extremes of bodyweight: a population pharmacokinetic analysis. *J. Thromb. Haemost.* 18(9):2296–307
42. Upreti VV, Wang J, Barrett YC, Byon W, Boyd RA, et al. 2013. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. *Br. J. Clin. Pharmacol.* 76(6):908–16
43. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. 2007. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. *J. Clin. Pharmacol.* 47(2):218–26

44. Rocca B, Fox KAA, Ajjan RA, Andreotti F, Baigent C, et al. 2018. Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. *Eur. Heart J.* 39(19):1672–86f
45. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. 2016. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J. Thromb. Haemost.* 14(6):1308–13
46. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, et al. 2021. European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 23(10):1612–76
47. Kido K, Shimizu M, Shiga T, Hashiguchi M. 2020. Network meta-analysis comparing apixaban versus rivaroxaban in morbidly obese patients with atrial fibrillation. *Am. J. Cardiol.* 134:160–61
48. Kok T, de Boer H, Witteman B, Hovens M, van Luin M, Monajemi H. 2022. Anti-Xa levels in morbidly obese patients using apixaban or rivaroxaban, before and after bariatric surgery. *Obes. Surg.* 32(3):607–14
49. Kido K, Lee JC, Hellwig T, Gulseth MP. 2020. Use of direct oral anticoagulants in morbidly obese patients. *Pharmacotherapy* 40(1):72–83
50. Grainger B, Holloway R, Merriman E, Booth M, Royle G, et al. 2020. Evidence of impaired dabigatran absorption following laparoscopic Roux-en-Y gastric bypass surgery: the Auckland regional experience (2011–2018). *Br. J. Haematol.* 191(2):e67–69
51. Li MH, Hu LH, Xiong YR, Yu Y, Zhou W, et al. 2020. Association between body mass index and the risk of bleeding in elderly patients with non-valvular atrial fibrillation taking dabigatran: a cohort study. *J. Geriatr. Cardiol.* 17(4):193–201
52. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. 2009. Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 361(12):1139–51
53. Hohnloser SH, Fudim M, Alexander JH, Wojdyla DM, Ezekowitz JA, et al. 2019. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and extremes in body weight. *Circulation* 139(20):2292–300
54. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, et al. 2011. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* 365(10):883–91
55. Lee SR, Choi EK, Park CS, Han KD, Jung JH, et al. 2019. Direct oral anticoagulants in patients with nonvalvular atrial fibrillation and low body weight. *J. Am. Coll. Cardiol.* 73(8):919–31
56. Andreotti F, Geisler T, Collet JP, Gigante B, Gorog DA, et al. 2023. Acute, periprocedural and longterm antithrombotic therapy in older adults: 2022 update by the ESC Working Group on Thrombosis. *Eur. Heart J.* 44(4):262–79
57. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. 2010. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 137(2):263–72
58. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. 2010. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 138(5):1093–100
59. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, et al. 2016. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur. Heart J.* 37(20):1582–90
60. Costa F, van Klaveren D, James S, Heg D, Raber L, et al. 2017. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 389(10073):1025–34
61. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, et al. 2019. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Circulation* 140:240–61
62. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. 2018. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation* 138(1):37–47
63. Silverio A, Di Maio M, Prota C, De Angelis E, Radano I, et al. 2021. Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients. *Eur. Heart J. Cardiovasc. Pharmacother.* 7(FI1):f20–29

64. Shen NN, Wu Y, Wang N, Kong LC, Zhang C, et al. 2020. Direct oral anticoagulants versus vitamin-K antagonists in the elderly with atrial fibrillation: a systematic review comparing benefits and harms between observational studies and randomized controlled trials. *Front. Cardiovasc Med.* 7:132
65. Nixon AC, Bampouras TM, Pendleton N, Woywodt A, Mitra S, Dhaygude A. 2018. Frailty and chronic kidney disease: current evidence and continuing uncertainties. *Clin. Kidney J.* 11(2):236–45
66. Park SH. 2018. Tools for assessing fall risk in the elderly: a systematic review and meta-analysis. *Aging Clin. Exp. Res.* 30(1):1–16
67. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. 1999. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch. Intern. Med.* 159(7):677–85
68. Mahmoodi BK, Gansevoort RT, Naess IA, Lutsey PL, Braekkan SK, et al. 2012. Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. *Circulation* 126(16):1964–71
69. Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, et al. 2010. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am. Heart J.* 159(6):1102–7
70. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, et al. 2011. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Circ. Arrhythm. Electrophysiol.* 4(1):26–32
71. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, et al. 2012. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N. Engl. J. Med.* 367(7):625–35
72. Carrero JJ, Evans M, Szummer K, Spaak J, Lindhagen L, et al. 2014. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. *JAMA* 311(9):919–28
73. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. 2016. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. *Chest* 149(4):951–59
74. Quinn LM, Richardson R, Cameron KJ, Battistella M. 2015. Evaluating time in therapeutic range for hemodialysis patients taking warfarin. *Clin. Nephrol.* 83(2):80–85
75. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, et al. 2011. Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 365(11):981–92
76. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, et al. 2013. Edoxaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 369(22):2093–104
77. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, et al. 2014. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 129(9):961–70
78. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, et al. 2012. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur. Heart J.* 33(22):2821–30
79. Bohula EA, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, et al. 2016. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation* 134(1):24–36
80. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, et al. 2011. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur. Heart J.* 32(19):2387–94
81. Harel Z, Sholzberg M, Shah PS, Pavenski K, Harel S, et al. 2014. Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. *J. Am. Soc. Nephrol.* 25(3):431–42
82. Parker K, Hartemink J, Saha A, Mitra R, Lewis P, et al. 2022. A systematic review of the efficacy and safety of anticoagulants in advanced chronic kidney disease. *J. Nephrol.* 35(8):2015–33
83. Rhee TM, Lee SR, Choi EK, Oh S, Lip GYH. 2022. Efficacy and safety of oral anticoagulants for atrial fibrillation patients with chronic kidney disease: a systematic review and meta-analysis. *Front. Cardiovasc. Med.* 9:885548
84. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, et al. 2018. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation* 138(15):1519–29

85. Reinecke H, Engelbertz C, Bauersachs R, Breithardt G, Echterhoff HH, et al. 2023. A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 study. *Circulation* 147(4):296–309
86. Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, et al. 2022. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. *Circulation* 146(23):1735–45
87. Galli M, Barbui T. 2003. Antiphospholipid antibodies and thrombosis: strength of association. *Hematol. J.* 4(3):180–86
88. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, et al. 2020. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur. Heart J.* 41(4):543–603
89. Pengo V, Hoxha A, Andreoli L, Tincani A, Silvestri E, et al. 2021. Trial of Rivaroxaban in AntiPhospholipid Syndrome (TRAPS): two-year outcomes after the study closure. *J. Thromb. Haemost.* 19(2):531–35
90. Zuily S, Cohen H, Isenberg D, Woller SC, Crowther M, et al. 2020. Use of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome: guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. *J. Thromb. Haemost.* 18(9):2126–37
91. Angiolillo DJ, Bhatt DL, Cannon CP, Eikelboom JW, Gibson CM, et al. 2021. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. *Circulation* 143(6):583–96
92. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, et al. 2013. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 381(9872):1107–15
93. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, et al. 2016. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N. Engl. J. Med.* 375(25):2423–34
94. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, et al. 2017. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N. Engl. J. Med.* 377(16):1513–24
95. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, et al. 2019. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N. Engl. J. Med.* 380(16):1509–24
96. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, et al. 2019. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, Phase 3b trial. *Lancet* 394(10206):1335–43
97. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, et al. 2019. Safety and efficacy outcomes of double versus triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur. Heart J.* 40(46):3757–67
98. Potpara TS, Mujovic N, Proietti M, Dagres N, Hindricks G, et al. 2020. Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of pooled data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials. *Europace* 22(1):33–46
99. Galli M, Andreotti F, Porto I, Crea F. 2020. Intracranial haemorrhages versus stent thromboses with direct oral anticoagulant plus single antiplatelet agent or triple antithrombotic therapy: a meta-analysis of randomized trials in atrial fibrillation and percutaneous coronary intervention/acute coronary syndrome patients. *Europace* 22(4):538–46
100. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, et al. 2019. AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation* 140(2):e125–51
101. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, et al. 2021. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association

for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur. Heart J.* 42(5):373–498
102. Olie RH, van der Meijden PEJ, ten Cate H. 2018. The coagulation system in atherothrombosis: implications for new therapeutic strategies. *Res. Pract. Thromb. Haemost.* 2(2):188–98
103. Plank F, Beyer C, Friedrich G, Stuhlinger M, Hintringer F, et al. 2018. Influence of vitamin K antagonists and direct oral anticoagulation on coronary artery disease: a CTA analysis. *Int. J. Cardiol.* 260:11–15
104. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, et al. 2017. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N. Engl. J. Med.* 377(14):1319–30
105. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, et al. 2012. Rivaroxaban in patients with a recent acute coronary syndrome. *N. Engl. J. Med.* 366(1):9–19
106. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, et al. 2021. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart J.* 42(14):1289–367
107. Varghese D, Ishida C, Haseer Koya H. 2022. *Polypharmacy*. Treasure Island, FL: StatPearls
108. Jaspers Focks J, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, et al. 2016. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *BMJ* 353:i2868
109. Piccini JP, Hellkamp AS, Washam JB, Becker RC, Breithardt G, et al. 2016. Polypharmacy and the efficacy and safety of rivaroxaban versus warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation. *Circulation* 133(4):352–60
110. Hodin S, Basset T, Jacqueroux E, Delezay O, Clotagatide A, et al. 2018. In vitro comparison of the role of P-glycoprotein and breast cancer resistance protein on direct oral anticoagulants disposition. *Eur. J. Drug Metab. Pharmacokinet.* 43(2):183–91
111. Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KLR, et al. 2010. Membrane transporters in drug development. *Nat. Rev. Drug Discov.* 9(3):215–36
112. Jungbauer L, Dobias C, Stollberger C, Weidinger F. 2010. The frequency of prescription of P-glycoprotein-affecting drugs in atrial fibrillation. *J. Thromb. Haemost.* 8(9):2069–70
113. Grymonprez M, Vanspranghe K, Capiau A, Boussery K, Steurbaut S, Lahousse L. 2022. Impact of P-glycoprotein and/or CYP3A4-interacting drugs on effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a meta-analysis. *Br. J. Clin. Pharmacol.* 88(7):3039–51
114. Gronich N, Stein N, Muszkat M. 2021. Association between use of pharmacokinetic-interacting drugs and effectiveness and safety of direct acting oral anticoagulants: nested case-control study. *Clin. Pharmacol. Ther.* 110(6):1526–36
115. Hill K, Sucha E, Rhodes E, Carrier M, Garg AX, et al. 2020. Risk of hospitalization with hemorrhage among older adults taking clarithromycin versus azithromycin and direct oral anticoagulants. *JAMA Intern. Med.* 180(8):1052–60
116. Terrier J, Gaspar F, Guidi M, Fontana P, Daali Y, et al. 2022. Population pharmacokinetic models for direct oral anticoagulants: a systematic review and clinical appraisal using exposure simulation. *Clin. Pharmacol. Ther.* 112(2):353–63
117. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, et al. 2013. Dabigatran versus warfarin in patients with mechanical heart valves. *N. Engl. J. Med.* 369(13):1206–14
118. Jawitz OK, Wang TY, Lopes RD, Chavez A, Boyer B, et al. 2020. Rationale and design of PROACT Xa: a randomized, multicenter, open-label, clinical trial to evaluate the efficacy and safety of apixaban versus warfarin in patients with a mechanical On-X aortic heart valve. *Am. Heart J.* 227:91–99
119. Neale T. 2022. Another DOAC fails in the setting of mechanical heart valves. *tctMD*, Sept. 28. **https://www.tctmd.com/news/another-doac-fails-setting-mechanical-heart-valves**
120. Fanaroff AC, Vora AN, Lopes RD. 2022. Non-vitamin K antagonist oral anticoagulants in patients with valvular heart disease. *Eur. Heart J. Suppl.* 24(Suppl. A):A19–31
121. ten Berg J, Rocca B, Angiolillo DJ, Hayashida K. 2022. The search for optimal antithrombotic therapy in transcatheter aortic valve implantation: facts and uncertainties. *Eur. Heart J.* 43(44):4616–34

122. Yin OQP, Antman EM, Braunwald E, Mercuri MF, Miller R, et al. 2018. Linking endogenous factor Xa activity, a biologically relevant pharmacodynamic marker, to edoxaban plasma concentrations and clinical outcomes in the ENGAGE AF-TIMI 48 trial. *Circulation* 138(18):1963–73
123. Akbulut AC, Arisz R, Baaten C, Baildildinova G, Barakzie A, et al. 2023. Blood coagulation and beyond: position paper from the Fourth Maastricht Consensus Conference on Thrombosis. *Thromb. Haemost.* 123(8):808–39
124. Schmohl M, Glund S, Harada A, Imazu S, De Smet M, et al. 2017. Idarucizumab does not have procoagulant effects: assessment of thrombosis biomarkers in healthy volunteers. *Thromb. Haemost.* 117(2):269–76
125. Pollack CV Jr., Reilly PA, Weitz JI. 2017. Dabigatran reversal with idarucizumab. *N. Engl. J. Med.* 377(17):1691–92
126. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, et al. 2013. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat. Med.* 19(4):446–51
127. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, et al. 2019. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N. Engl. J. Med.* 380(14):1326–35
128. Milling TJ Jr., Middeldorp S, Xu L, Koch B, Demchuk A, et al. 2023. Final study report of andexanet alfa for major bleeding with factor Xa inhibitors. *Circulation* 147:1026–38
129. Apostel H, Winckers K, Bidar E, Schreiber JU. 2021. Successful antithrombin administration in andexanet alfa-associated heparin resistance. *J. Cardiothorac. Vasc. Anesth.* 35(3):904–7
130. Lu G, Lin JP, Curnutte JT, Conley PB. 2017. Effect of andexanet-TFPI interaction on in vitro thrombin formation and coagulation markers in the TF-pathway. *Blood* 130:629
131. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, et al. 2015. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N. Engl. J. Med.* 373(25):2413–24
132. Costa OS, Connolly SJ, Sharma M, Beyer-Westendorf J, Christoph MJ, et al. 2022. Andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhage: a propensity score-overlap weighted analysis. *Crit. Care* 26(1):180
133. Cohen AT, Lewis M, Connor A, Connolly SJ, Yue P, et al. 2022. Thirty-day mortality with andexanet alfa compared with prothrombin complex concentrate therapy for life-threatening direct oral anticoagulant-related bleeding. *J. Am. Coll. Emerg. Physicians Open* 3(2):e12655
134. Leentjens J, Middeldorp S, Jung C. 2022. A short review of ciraparantag in perspective of the currently available anticoagulant reversal agents. *Drug Discov. Today* 27(10):103332
135. Sharman Moser S, Chodick G, Ni YG, Chalothorn D, Wang MD, et al. 2022. The association between factor XI deficiency and the risk of bleeding, cardiovascular, and venous thromboembolic events. *Thromb. Haemost.* 122(5):808–17
136. Maas C, Renne T. 2018. Coagulation factor XII in thrombosis and inflammation. *Blood* 131(17):1903–9
137. Hsu C, Hutt E, Bloomfield DM, Gailani D, Weitz JI. 2021. Factor XI inhibition to uncouple thrombosis from hemostasis: JACC review topic of the week. *J. Am. Coll. Cardiol.* 78(6):625–31
138. Fredenburgh JC, Weitz JI. 2021. New anticoagulants: moving beyond the direct oral anticoagulants. *J. Thromb. Haemost.* 19(1):20–29
139. Gigante B, ten Cate H. 2023. Factor XI inhibitors in patients with cardiovascular disease and a high risk of bleeding: a cautionary tale. *Nat. Rev. Cardiol.* 20:511–12
140. Buller HR, Bethune C, Bhanot S, Gailani D, Monia BP, et al. 2015. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N. Engl. J. Med.* 372(3):232–40
141. Nopp S, Kraemmer D, Ay C. 2022. Factor XI inhibitors for prevention and treatment of venous thromboembolism: a review on the rationale and update on current evidence. *Front. Cardiovasc. Med.* 9:903029
142. Rao SV, Kirsch B, Bhatt DL, Budaj A, Coppolecchia R, et al. 2022. A multicenter, Phase 2, randomized, placebo-controlled, double-blind, parallel-group, dose-finding trial of the oral factor XIa inhibitor asundexian to prevent adverse cardiovascular outcomes after acute myocardial infarction. *Circulation* 146(16):1196–206
143. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, et al. 2022. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *Lancet* 399(10333):1383–90

144. Shoamanesh A, Mundl H, Smith EE, Masjuan J, Milanov I, et al. 2022. Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke (PACIFIC-Stroke): an international, randomised, double-blind, placebo-controlled, Phase 2b trial. *Lancet* 400(10357):997–1007
145. Gibson C, Windecker S. 2022. *Hot line session 5*. Congr. Sess., Eur. Soc. Cardiol. Congress 2022, Aug. 28. **https://esc365.escardio.org/Session/37024**
146. Nagy M, ten Cate H. 2022. What to expect from drug targeting factor XI? *Cardiovasc. Res.* 118(10):e72–74
147. Cao Y, Wang Y, Zhou Z, Pan C, Jiang L, et al. 2022. Liver-heart cross-talk mediated by coagulation factor XI protects against heart failure. *Science* 377(6613):1399–406