Direct Oral Anticoagulants

From Pharmacology to Clinical Practice

Riccardo Proietti
Ahmed AlTurki
Nicola Ferri
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T. Jared Bunch
Editors

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The Coagulative Cascade

1

Marina Camera

Introduction

The blood coagulation cascade is an integral part of hemostasis, a biological process evolved as important defense mechanism to prevent bleeding from a damaged vessel and to restore vascular integrity (Davidson et al. 2003). Within the hemostatic process two distinct phases are recognized, primary and secondary hemostasis, where different key players and mechanisms are taking part. Despite this division, the interplay between these processes is very tight.

Primary hemostasis is initiated by accumulation and activation of platelets at the site of vascular injury. During secondary hemostasis, activation of coagulation reinforces the platelet plug through deposition of an insoluble fibrin network generated by thrombin activity on fibrinogen molecules (Smith et al. 2015).

Under normal conditions, anticoagulant mechanisms ensure careful control of coagulation and they prevail over the procoagulant forces. Aberrant activation of coagulation can, however, lead to the formation of intravascular clots that underpin pathological thrombotic disorders, including myocardial infarction, stroke, and venous thromboembolism (Furie and Furie 2008).

The *restitutio ad integrum* of the damaged vessel is mediated by fibrinolysis, the last phase of hemostasis. During this process, the activation of plasminogen and urokinase leads to accelerated degradation of blood clots, with generation of fibrin degradation products, including D-dimers.

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The Cell-Based Model of Blood Coagulation

The coagulation cascade consists of an ordered sequence of reactions that lead to the careful and balanced generation of thrombin, key effector enzyme, at the level of vascular damage.

Coagulation reactions lead to activation of zymogens (inert precursors of enzymes) to functional enzymes via limited proteolysis. At each stage, a zymogen is converted to an active protease by cleavage of one or more peptide bonds in the precursor molecule. The final active protease generated is thrombin with the role of converting fibrinogen into the fibrin mesh to stabilize the platelet plug. The enzymes generated during this process are catalytically active serine proteases, yet they have low inherent enzymatic activity as isolated proteins. Binding of a typical clotting protease to a specific protein cofactor on a suitable phospholipid membrane surface markedly potentiates the protease's activity, often by as much as five order of magnitude or more (Bom and Bertina 1990). On this regard, phosphatidylserine (PS) exposure on the membrane of activated platelets is a key event in the control of blood coagulation (Lentz 2003).

In mammalian blood coagulation, five zymogens (factor VII [FVII]; factor IX [FIX]; factor X [FX]; protein C [PC], and prothrombin [PT]) act with five cofactors (tissue factor [TF]; factor V [FV]; factor VIII [FVIII]; thrombomodulin and protein S) to control the generation of fibrin. The protein cofactors of the blood coagulation cascade also generally circulate in the plasma as inert procofactors that must be converted into active cofactors via limited proteolysis. When zymogens and procofactors are converted to the active form, an "a" is appended to the Roman numerals (i.e., FVII → FVIIa).

According to the most recent theory, in a cell-based model, blood coagulation is initiated by the binding of FVII to membrane-associated TF (also called tissue thromboplastin or FIII or CD142; Fig. 1.1) leading to activation of FVIIa (Kirchhofer and Nemerson 1996). A fraction of FVII (~1%) circulates in blood as active enzyme. Free FVIIa is a very weak enzyme, but the TF:FVIIa complex is an extremely potent activator of coagulation. TF binds both FVII and FVIIa.

TF has several characteristics that make it unique among the coagulation proteins (Morrissey 2001). First, TF is the only coagulation factor that is not synthesized by the liver and released into circulation as a mechanism to avoid unintended activation of coagulation. Second, membrane anchoring is essential for full procoagulant activity. Indeed, it is an integral membrane protein constitutively expressed at high levels by fibroblasts of the adventitial layer of the vessel wall, as well as by epithelial cells, and at sites where bleeding could be catastrophic (brain, lungs) (Drake et al. 1989; Fleck et al. 1990). This pattern of TF localization has been described as a hemostatic envelope to stop bleeding at sites of injury. When the vessel wall is damaged, extravascular TF-bearing cells come in contact with blood components and the hemostatic processes take place.

Notably, a discrete amount of TF is also stored in the cytoplasm of a subpopulation of platelets and it can be exposed on the cell membrane upon activation by the common platelet agonists (Camera et al. 2003, 2010; Brambilla et al. 2015). Based

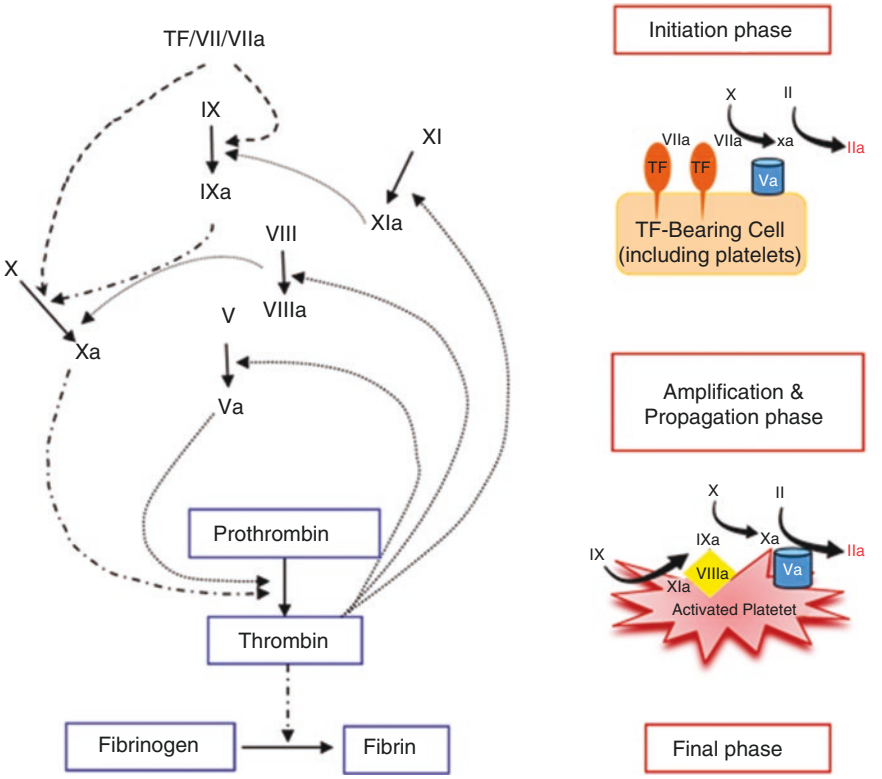

Fig. 1.1 The cell-based model of the blood coagulation cascade

on these findings, the role of platelets in secondary hemostasis has been revised by assigning to these cells the task not only to support the activation of clotting factors, as already known for many years, but also to trigger themselves blood clotting (Camera et al. 2015). Neutrophils and monocytes, along with circulating microvesicles are additional sources of TF, whose importance is increasingly been recognized in a variety of thrombotic disorders (von Bruhl et al. 2012; van Es et al. 2015). Finally, unlike the other cofactors, TF does not require proteolysis for activity.

Once formed, the TF/FVIIa complex then catalyzes the conversion of two downstream substrates via limited proteolysis, FIX to FIXa and of FX to FXa (Figs. 1.1 and 1.2, Extrinsic Xase). Formation of FXa is the key step in the "initiation" stage, formerly known as "extrinsic pathway" or "TF pathway" of the coagulation cascade, because it requires that plasma comes into contact with something "extrinsic" to the blood, i.e., TF, to trigger it. The TF pathway is the mechanism of triggering blood clotting that functions in normal hemostasis, and probably also in many types of thrombosis (Tilley and Mackman 2006).

The initial FXa produced by this mechanism combines with FVa and generates sufficient thrombin to induce local platelet aggregation. The amount of fibrin produced through this pathway is however by far insufficient (only 3–5%) for the

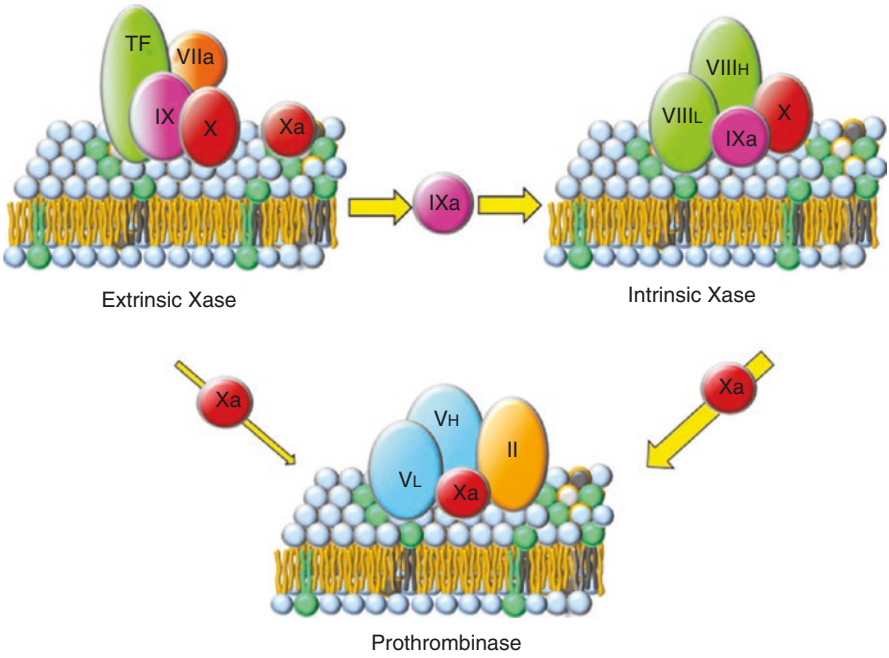

Fig. 1.2 FXa generation through the extrinsic and intrinsic Xase complexes organized on a phosphatidylserine expressing (green phospholipids) plasma membrane. The catalytic efficiency of the intrinsic Xase complex is highlighted by the thicker arrow. FXa assembled into the prothrombinase complex leads to the explosive generation of thrombin during the propagation phase

stabilization of the platelet plug because of rapid FXa-dependent inactivation of TF-FVIIa by the TF pathway inhibitor (TFPI). It is exactly at this point that the formerly known "intrinsic pathway" or "contact pathway" of blood coagulation gives its contribution. Indeed, the trace amounts of thrombin formed in the "initiation" stage of coagulation, although insufficient to initiate significant fibrin polymerization, are able to back-activate FV and FVIII by limited proteolysis, along with the conversion of FXI to FXIa that feeds back to activate FIX.

FVIII and FV are procofactors. FVIII circulates in plasma bound to von Willebrand factor, which serves to stabilize it. FV circulates in plasma, is stored in platelets in a partially activated form, and is released when platelets are activated. Thrombin releases von Willebrand factor from FVIII and activates FV and FVIII to yield FVa and FVIIIa, respectively. Once activated, the cofactors bind to the surface of activated platelets and serve as receptors; FVIIIa serves as the receptor for FIXa, while FVa serves as the receptor for FXa. In addition to binding FIXa and FXa, FVIIIa and FVa bind their substrates, FX and prothrombin (factor II), respectively (Fig. 1.2).

The formation of the intrinsic tenase (FVIIIa-FIXa) and of the prothrombinase (FXa-FVa) complexes (Fig. 1.2) lead to the explosive generation of thrombin during the "propagation" phase through conversion of prothrombin (FII) to thrombin (FIIa)

followed by activation of fibrinogen to fibrin that ultimately leads to generation of a fibrin clot. FXIa, a contact factor protein of the intrinsic pathway, may be required to produce additional FIXa if insufficient quantities are generated by the TF-FVIIa complex, or if fibrinolysis is particularly active. The remaining components of the intrinsic system are important in vitro, but do not appear to have an important hemostatic role. The labile association of fibrin monomers is finally stabilized by the formation of covalent bonds between adjacent fibrin strands, a process catalyzed by the transglutaminase FXIIIa.

Notably, active thrombin also remain bound within the fibrin clot, where it can rapidly cleave additional fibrinogen and reinforce the clot structure if it is mechanically or enzymatically disrupted. Within the hemostatic process thrombin not only exert a procoagulant activity. Indeed, when bound to thrombomodulin expressed on the surface of endothelial cells activates protein C generating an antithrombotic effect. Finally, thrombin not only is the key enzyme in the coagulation process, but it is also a powerful platelet activator through protease-activated receptors.

The Effect of Oral Anticoagulants on the Coagulation Cascade

The direct anticoagulants (DOACs) are orally active small molecule (<500 MW) with high specificity and relatively high affinity for a single coagulation protease. Dabigatran binds at the active site of thrombin and rivaroxaban, apixan and edoxaban bind at the active site of FXa (Fig. 1.3). DOACs are competitive inhibitors, thus each molecule competes with substrate for binding at the active site of its target protease. The fact that DOACs interact with the active site of the target protease means that binding only occurs after the zymogen form of the target protease has been activated by the coagulation reactions.

The primary physiological inhibitors of thrombin, FXa and FIXa are the plasma serine protease inhibitors (SERPINs) antithrombin and α-1-proteinase inhibitor, and the non-SERPIN inhibitor α-2-macroglobulin. FXa within the TF/FVIIa/FXa complex is also inhibited by TFPI. Like the DOACs, SERPINs and α-2-macroglobulin only interact with coagulation factors after they have been activated to functional proteases. However, SERPINs and α-2-macroglobulin inactivate their target proteases by formation of complexes that are essentially irreversible (Huntington et al. 2000; Barrett and Starkey 1973). By contrast, DOACs form reversible complexes with the active site of their target proteases.

Antithrombin and TFPI are large proteins, ≈58 kDa and 34 to 40 kDa, respectively. Thus, antithrombin is sterically hindered from interacting with thrombin that is sequestered within a fibrin clot or bound to a cofactor, such as thrombomodulin. Likewise, FXa on a platelet surface is relatively protected from inhibition by either antithrombin or tissue factor pathway inhibitor. By contrast, DOACs can inhibit coagulation by acting at sites where the natural inhibitors are ineffective. Indeed, due to their small molecular weight (<500 MW) DOACs can inhibit thrombin and FXa at sites on cells surface where they are relatively inaccessible to the plasma protease inhibitors (Haynes et al. 2012). They can also reach their target proteases

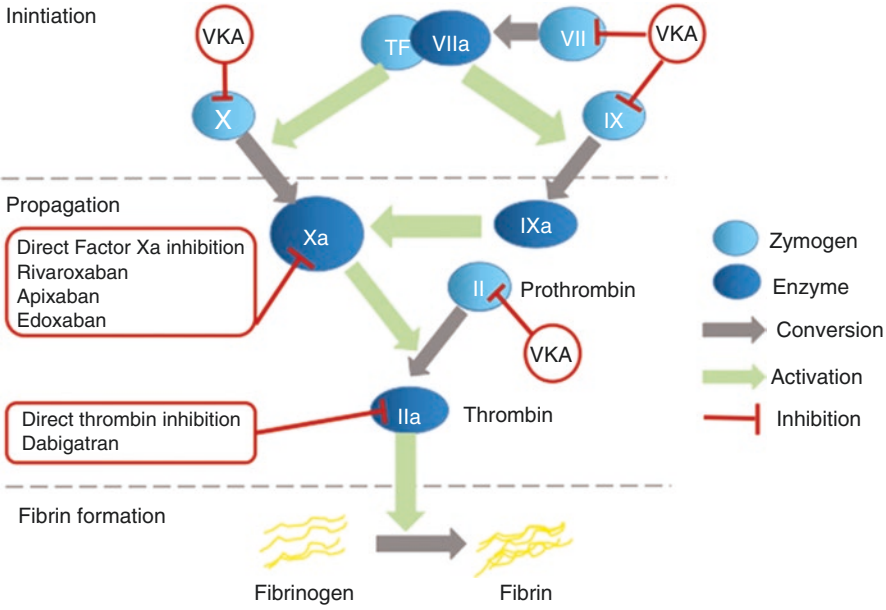

Fig. 1.3 The cell-based model of the blood coagulation cascade and targets of the oral anticoagulant drugs. Targets of direct oral anticoagulant as well as of Vitamin K Antagonists (VKA) are shown

within the structure of a fibrin clot. Since dabigatran not only inhibits the procoagulant effects of thrombin but also inhibits thrombin in complex with thrombomodulin (Kamisato et al. 2016), the reduction in protein C activation could potentially exert an unintended prothrombotic effect.

Vitamin K antagonists (VKAs) interfere with the γ carboxylation of all vitamin K-dependent coagulation factors (FII, VII, IX, and X) as well as of the antithrombotic factors protein C, S, and Z (Jerkeman et al. 2000) (Fig. 1.3). Because multiple factors are affected, the net effect of any given dose of a VKA is difficult to predict. By contrast, the relationship between the plasma levels of a DOAC and the degree of protease inhibition is much more predictable, thus the laboratory monitoring of their anticoagulant activity is not needed.

The vitamin K-dependent post-translational modification of specific glutamic acid residues is critical for the activity of the coagulation factors. Thus, while the proteins are synthesized, their undercarboxylated forms do not have normal activity. VKAs thereby reduce the levels of active proteases that can be produced in response to a procoagulant stimulus rather than inhibiting them after they have been activated. If less FX is available to be activated, then less FXa/FVa complexes will be available to trigger thrombin formation. The reduced levels of prothrombin further slow the rate of thrombin generation. Overall, VKAs predominantly impact the propagation phase of thrombin generation (Dargaud et al. 2013).

On the contrary, dabigatran mostly affects the amplification phase of coagulation, whereas direct FXa inhibitors impact on the initiation and propagation phases (Hoffman and Monroe 2017). Furthermore, the reversible binding of DOACs to their targets enables FXa or thrombin produced as a result of coagulation activation to overcome the effect of the drug, thus supporting hemostasis. This property may contribute to the safety of DOACs including the fact that patients treated with DOACs experience a significantly reduced incidence of intracranial hemorrhage compared to patients treated with VKA (Granger et al. 2011; Hart et al. 2012; Giugliano et al. 2013; Hankey et al. 2014). On this regard, based on the mechanisms described, if a microbleeding occurs in the brain of a patient treated with a DOAC, the large amount of TF present will trigger the coagulation cascade leading to the generation of FXa that, by displacing DOAC, will activate the other coagulation factors leading to fibrin generation. On the contrary, in the case of a patient treated with a VKA, the low concentration of circulating VK-dependent zymogens will not allow the coagulation cascade to be triggered.

Conclusions

The coagulation cascade consists of a cascade of enzyme activation events in which serine proteases activate zymogens and procofactors in the next step of the cascade via limited proteolysis. By taking place on the surface of activated platelets, aim of coagulation is to lead, at the level of vascular damage, to the careful and balanced generation of thrombin, key effector enzyme of the process with the role of converting fibrinogen into the fibrin mesh necessary to stabilize the platelet plug. This process is protective since it evolved as important defense mechanism to prevent bleeding from a damaged vessel. Unfortunately, the blood clotting system can also lead to unwanted blood clots inside blood vessel. This pathologic thrombus formation (thrombosis) is a leading cause of disability and death in the developed world.

DOACs are direct competitive inhibitors of FXa and of thrombin and form reversible complexes with the active site of their target proteases. The small molecular size of DOACs allow them to inhibit FXa and thrombin assembled on the platelet surfaces and within a fibrin clot, sites where the natural inhibitors, such as antithrombin, are ineffective. Unlike VKA, the relationship between the plasma levels of a DOAC and the degree of protease inhibition is much more predictable and therapy laboratory monitoring of their anticoagulant activity is no more needed.

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Clinical Indications for Direct Acting Oral Anticoagulants

2

Ahmed AlTurki and Riccardo Proietti

Introduction

Anticoagulation is an important therapeutic option to prevent and treat thrombus formation in a variety of clinical settings. While there are several options for parenteral therapy, oral therapy was limited to vitamin K antagonists, namely warfarin therapy. However, there are several limitations to warfarin including the need to be within a relatively narrow therapeutic and safety range, which requires frequent monitoring, as well as long onset and offset effects and numerous interactions. Direct oral anticoagulants (DOACs) are anticoagulation pharmacotherapy designed to overcome the limitations of warfarin and are categorized into two main classes based on mechanism of action: oral direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, and betrixaban) and direct thrombin inhibitors (dabigatran). The advantages of DOAC therapy compared with VKAs include the absence of the need for monitoring, more immediate drug onset and offset effects, which has important periprocedural and bleeding management implications as well as less drug interactions. In the past decade since DOACs were approved, there have been a plethora of studies examining the safety and efficacy of DOACs across a variety of clinical settings. In this chapter, clinical scenarios in which DOACs may be used will be examined and the major evidence for and against their use will be reviewed.

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Nonvalvular Atrial Fibrillation

Oral anticoagulation is one of the mainstays of treatment of patients with atrial fibrillation (AF) for the prevention of stroke and systemic embolism. The majority of patients with AF require anticoagulation with the decision to anticoagulate being based on the estimated risk of stroke. This is done via an assessment for clinical risk factors that increase the risk of stroke, namely congestive heart failure, hypertension, age, diabetes mellitus, history of cerebrovascular events, and history of vascular disease with a variety of scores available to estimate the annual risk of stroke and systemic embolism. The presence of at least one risk factor, especially age greater than 65 years, is enough for oral anticoagulation to have a net clinical benefit and warrant use. For many years, the only available option was vitamin K antagonists, namely warfarin. In 2009, the situation was irrevocably altered with the publication of the first landmark trial comparing the DOAC, dabigatran with warfarin in patients with nonvalvular AF. This was followed by three other landmark trials as well as numerous other studies comparing DOAC to warfarin in a variety of clinical setting and patient subgroups with nonvalvular AF.

Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a trial that randomized 18,113 patients (mean age 71 years; males 64%; mean CHADS2 score = 2.1) in a 1:1:1 ratio to receive one of the two fixed doses of dabigatran (110 mg or 150 mg), in a blinded manner, with open-label use of warfarin in patients who had nonvalvular AF and an increased risk for stroke (Connolly et al. 2009). After a median follow-up of 2 years, the annual incidence rate of stroke or systemic embolism was 1.53%, 1.11%, and 1.69% in those receiving dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively. Both doses of dabigatran were noninferior to warfarin ($P < 0.001$) and the 150-mg dose of dabigatran was also superior to warfarin (relative risk [RR] 0.66; 95% confidence interval [CI], 0.53 to 0.82; $P < 0.001$). The annual incidence of hemorrhagic stroke was 0.38% per year in those who received warfarin, compared with 0.12% in the 110 mg dabigatran group (RR 0.31; 95% CI, 0.17 to 0.56; $P < 0.001$) and 0.10% in the 150 mg dabigatran group (RR 0.26; 95% CI, 0.14 to 0.49; $P < 0.001$). The annual incidence of major bleeding was 3.36% in the warfarin group, compared with 2.71% per year in the 110 mg dabigatran group (RR 0.80; 95% CI, 0.69 to 0.93; $P = 0.003$) and 3.11% in the 150 mg dabigatran group (RR 0.93; 95% CI, 0.81 to 1.07; $P = 0.31$). Dyspepsia occurred in 5.8% in the warfarin group compared to 11.8% and 11.3% in the 110-mg and 150-mg dabigatran groups, respectively ($P < 0.001$ for both comparisons). Of note, there was a signal for increased myocardial infarction and gastrointestinal bleeding with dabigatran in the RE-LY trial. However, in a pooled analysis of 24 studies including 588,047 patients, there was no significant association between the use of dabigatran and the higher risk of myocardial infarction (Wei et al. 2018).

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) was a multicenter, randomized trial that enrolled 14,264 patients with nonvalvular AF who were at increased risk for stroke to receive either rivaroxaban or dose-adjusted warfarin (Patel et al. 2011). The annual incidence of

stroke or systemic embolism was 2.1% in the rivaroxaban group and 2.4% in the warfarin group (hazard ratio [HR] 0.88; 95% CI, 0.74 to 1.03; $P < 0.001$ for noninferiority; $P = 0.12$ for superiority) and the annual incidence of major and nonmajor clinically relevant 14.9% in the rivaroxaban group and 14.5% in the warfarin group (HR 1.03; 95% CI, 0.96 to 1.11; $P = 0.44$). Intracranial hemorrhage (0.5% vs. 0.7%, $P = 0.02$) and fatal bleeding (0.2% vs. 0.5%, $P = 0.003$) were significantly reduced in the rivaroxaban group. On the other hand, major bleeding from a gastrointestinal site was more common in the rivaroxaban group (3.2%), as compared with the warfarin group (2.2%, $P < 0.001$).

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, 18,201 patients with AF and at least one additional risk factor for stroke were randomized to receive either apixaban or warfarin (Granger et al. 2011). After a median duration of follow-up of 1.8 years, the annual incidence of stroke or systemic embolism was 1.27% in the apixaban group, compared with 1.60% in the warfarin group (HR, 0.79; 95% CI, 0.66 to 0.95; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). In addition, the incidence of major bleeding was 2.13% in the apixaban group and 3.09% in the warfarin group (HR 0.69; 95% CI, 0.60 to 0.80; $P < 0.001$), and the incidence of all-cause mortality were 3.52% and 3.94%, respectively (HR 0.89; 95% CI, 0.80 to 0.99; $P = 0.047$). Hemorrhagic stroke was also lower with apixaban (0.24%) than warfarin (0.47%) (HR 0.51; 95% CI, 0.35 to 0.75; $P < 0.001$).

In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, 21,105 patients were randomized into one of three groups (warfarin, edoxaban 60 mg, or edoxaban 30 mg) and followed for a median 2.8 years (Giugliano et al. 2013). At completion, the annual incidence of stroke or systemic embolism was 1.50%, 1.18% (HR 0.79; 97.5%CI 0.63 to 0.99; $P < 0.001$ for noninferiority, $P = 0.02$ for superiority), and 1.61% (HR 1.07; 97.5% CI, 0.87 to 1.31; $P = 0.005$ for noninferiority, $P = 0.44$ for superiority) in the warfarin, high-dose edoxaban, and low-dose edoxaban groups respectively. In addition, the annual incidence of hemorrhagic stroke was 0.47%, 0.26% (HR, 0.54; 95% CI, 0.38 to 0.77; $P < 0.001$), and 0.16% (HR 0.33; 95% CI, 0.22 to 0.50; $P < 0.001$) and the annual incidence of major bleeding was in the warfarin, high-dose edoxaban, and low-dose edoxaban groups, respectively. Finally, the annual incidence of intracranial bleeding was 0.85%, 0.39%, and 0.26% warfarin, high-dose edoxaban, and low-dose edoxaban groups, respectively but the annual incidence of major gastrointestinal bleeding was higher with high-dose edoxaban than with warfarin (1.51% vs. 1.23%), with the lowest rate with low-dose edoxaban (0.82%).

In summary, compared to warfarin, DOACs reduce major bleeding including intracranial hemorrhage and are noninferior with regard to prevention of stroke and systemic embolism. Apixaban and the higher dose of dabigatran, 150 mg, were superior to warfarin for the prevention of stroke and systemic embolism (Connolly et al. 2009; Granger et al. 2011). Apixaban was also associated with a reduction in mortality compared to warfarin. Pooled analyses of the four DOAC trials (Fig. 2.1) showed that DOACs reduced stroke or systemic embolism by 19% compared with

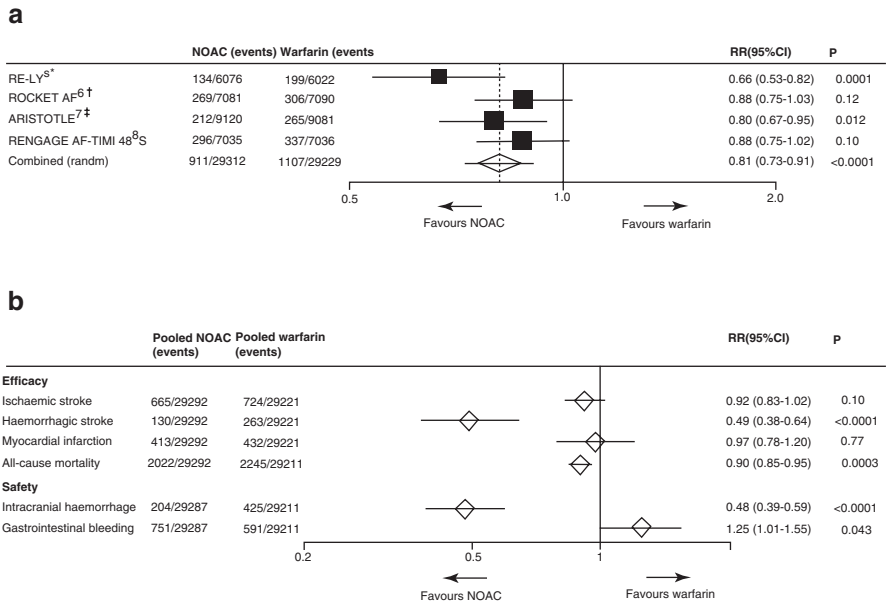

Fig. 2.1 (**a**) Pooled analysis of the landmark clinical trials of atrial fibrillation comparing the incidence of stroke and systemic embolism between those receiving direct oral anticoagulants and those receiving warfarin. (**b**) Combined data from the landmark trials across individual efficacy and safety outcomes in landmark trials of atrial fibrillation that compared direct acting oral anticoagulants and warfarin. (Used with permission from Ruff et al. (2014))

warfarin (RR 0.81, 95% CI 0.73–0.91; $P < 0.0001$), including a reduction in hemorrhagic stroke (RR 0.49, 95% CI 0.38–0.64; $P < 0.0001$) (Ruff et al. 2014). Furthermore, DOACs also reduced all-cause mortality (RR 0.90, 95% CI 0.85–0.95; $P = 0.0003$) and intracranial hemorrhage (RR 0.48, 95% CI 0.39–0.59; $P < 0.0001$), but increased gastrointestinal bleeding (RR 1.25, 95% CI 1.01–1.55; $p = 0.04$). Current guidelines now recommend that DOACs be used in preference to warfarin for the prevention of stroke in patients with nonvalvular AF (January et al. 2019; Andrade et al. 2020).

Subsequent studies have looked at specific clinical situations and patient subgroups providing insight for DOAC use in these patients. Dabigatran was a safe alternative in patients undergoing cardioversion (Nagarakanti et al. 2011). The rates of periprocedural bleeding was similar to warfarin in those undergoing urgent surgery (Healey et al. 2012). Concomitant antiplatelet use was associated with an increased incidence of bleeding without improving efficacy, particularly those receiving the higher dose of 150 mg (Dans et al. 2013). Both dabigatran dosages displayed significantly lower rates of major bleeding in patients with glomerular filtration rate ≥80 mL/min (Hijazi et al. 2014). In a sub-analysis of RE-LY, the presence of mitral regurgitation, aortic regurgitation, aortic stenosis, or tricuspid regurgitation did not affect the efficacy and safety of dabigatran compared to warfarin

(Ezekowitz et al. 2016). In patients undergoing catheter ablation for AF, uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin (Calkins et al. 2017). There have been many questions put forward as to whether DOACs provide adequate coverage in patients with bioprosthetic valves. These concerns were addressed in the Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation (RIVER) trial in which 1005 patients with AF and a mitral bioprosthetic valve were randomized to either rivaroxaban or warfarin (Guimarães et al. 2020). Death from cardiovascular causes or thromboembolic events occurred in 3.4% in the rivaroxaban group and in 5.1% in the warfarin group (HR, 0.65; 95% CI, 0.35 to 1.20). In addition, the incidence of stroke was 0.6% in the rivaroxaban group and 2.4% in the warfarin group (HR, 0.25; 95% CI, 0.07 to 0.88) and major bleeding was observed in 1.4% in the rivaroxaban group and 2.6% in the warfarin group (HR 0.54; 95% CI, 0.21 to 1.35). Therefore, DOACs appear to be noninferior to warfarin in patients with AF and bioprosthetic valves.

Venous Thromboembolism

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, may result in the debilitating long-term complications of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension. In addition, pulmonary embolism may result in pulmonary hemorrhage and death. Anticoagulation is the mainstay therapy in VTE for prevention of complications and the standard of care has been warfarin with initial bridging with parenteral heparin. The introduction of DOACs into clinical practice provided a possible alternative therapy that would not require parenteral therapy allowing outpatient therapy in stable cases. There are several situations with VTE in which DOACs have been trialed: prophylaxis for VTE; initial therapy for VTE; extended therapy for VTE as well as VTE in patients with active malignancy.

There is a significant risk of VTE in hospitalized patients, with a higher risk in acutely ill patients in intensive care units and surgical patients. The perioperative administration of subcutaneous heparin has been shown to reduce the risk of fatal pulmonary embolism and venous thrombosis in patients undergoing general, orthopedic, and urologic surgery (Collins et al. 1988). In the Acute Medically Ill VTE Prevention with Extended-Duration Betrixaban (APEX) trial, the efficacy, and safety of full-dose (80 mg) and reduced-dose (40 mg) betrixaban were evaluated relative to enoxaparin in 3065 patients (Gibson et al. 2017). The primary efficacy outcome, which consisted of asymptomatic proximal deep vein thrombosis, symptomatic deep vein thrombosis, symptomatic nonfatal pulmonary embolism, or VTE-related mortality, was significantly reduced among subjects treated with 80 mg of extended-duration betrixaban versus enoxaparin (6.27% vs. 8.39%, RRR = 0.26 [0.04–0.42], $P = 0.023$). Major bleeding was similar between the two groups (0.49% with betrixaban versus 0.66% with enoxaparin; $P = 0.51$). The Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing

Rivaroxaban with Enoxaparin (MAGELLAN) was designed to assess the efficacy and safety of rivaroxaban administered for 35 days, as compared with enoxaparin administered for 10 days and followed by placebo (Cohen et al. 2013). The primary efficacy outcomes, a composite of asymptomatic proximal or symptomatic venous thromboembolism up to day 10 (noninferiority test) and up to day 35 (superiority test), occurred in 2.7% receiving rivaroxaban and 2.7% receiving enoxaparin at day 10 (RR = 0.97; 95% CI 0.71 to 1.31; $P = 0.003$ for noninferiority) and in 4.4% who received rivaroxaban and 5.7% who received enoxaparin followed by placebo at day 35 (RR 0.77; 95% CI, 0.62 to 0.96; $P = 0.02$). However, the principal safety outcome, a composite of major or clinically relevant nonmajor bleeding, occurred in 2.8% and 1.2% at day 10 ($P < 0.001$) and 4.1% and 1.7% at day 35 ($P < 0.001$) in the rivaroxaban group and in the enoxaparin group, respectively. Due to the findings of this study, low-molecular-weight heparin remains the standard of care for VTE prophylaxis in the medically ill population. In the Prophylaxis in Nonmajor Orthopedic Surgery (PRONOMOS) trial, the effect of rivaroxaban (10 mg) was compared with that of enoxaparin (40 mg) in the prevention of major VTE in 3604 patients after lower-limb nonmajor orthopedic surgery (Samama et al. 2020). Major VTE occurred in 0.2% in the rivaroxaban group and 1.1% in the enoxaparin group (RR 0.25; 95% CI, 0.09 to 0.75; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). The incidence of bleeding did not differ significantly between the rivaroxaban group and the enoxaparin group. Based on this trial as well as previous studies, DOACs have been increasingly used for VTE prophylaxis in the orthopedic surgery population. In the Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients (AVERT) trial, the efficacy of apixaban thromboprophylaxis in ambulatory patients with active cancer at intermediate-to-high risk for venous thromboembolism, apixaban (2.5 mg twice daily) was compared to placebo in 574 patients. A placebo comparator was used as there is no evidence/recommendations for prevention of VTE in cancer patients (Carrier et al. 2018). Venous thromboembolism occurred in 4.2% in the apixaban group and 10.2% in the placebo group (HR 0.41; 95%CI 0.26 to 0.65; $P < 0.001$). Major bleeding occurred in 3.5% in the apixaban group and in 1.8% in the placebo group (HR 2.00; 95% CI, 1.01 to 3.95; $P = 0.046$).

Numerous trials have demonstrated the efficacy and safety of the DOACs in the treatment of VTE and have led to recommendations that DOACs be used as first-line therapy for the treatment of VTE. Rivaroxaban was tested through the EINSTEIN program with 3 separate trials assessing its efficacy and safety for the treatment of acute pulmonary embolism, acute deep vein thrombosis, and extended therapy. In the first trial, 3449 patients with acute DVT received either rivaroxaban or enoxaparin plus a vitamin K antagonist (EINSTEIN Investigators et al. 2010). The primary efficacy of recurrent venous thromboembolism occurred in 2.1% of the rivaroxaban group versus 3.0% of the enoxaparin-vitamin K antagonist group (HR 0.68, 95%CI 0.44 to 1.04; $P < 0.001$). The principal safety outcome of major bleeding or clinically relevant nonmajor bleeding occurred in 8.1% of the patients in each group. In the second trial, 4832 patients who had acute symptomatic pulmonary embolism received either rivaroxaban (15 mg twice daily for 3 weeks, followed by

20 mg once daily) or standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist (The EINSTEIN–PE Investigators 2012). The primary efficacy of symptomatic recurrent venous thromboembolism was similar in both groups: 2.1% of the rivaroxaban group versus 1.8% of the enoxaparin-vitamin K antagonist group. The principal safety outcome of major bleeding or clinically relevant nonmajor bleeding was also similar in both groups (10.3% and 11.4%, respectively). Importantly, major bleeding was lower in the rivaroxaban group (1.1%) than in the standard-therapy group (2.2%) (hazard ratio, 0.49; 95% CI, 0.31 to 0.79; $P = 0.003$). Another important situation in patients with VTE is extended therapy beyond 6 to 12 months when clinical equipoise exists as to the net clinical benefit of extended therapy. In this scenario, low-dose aspirin had been suggested in clinical guidelines. In the Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN CHOICE) trial, in patients with VTE who had completed 6 to 12 months of anticoagulation therapy and for whom there was equipoise regarding the need for continued anticoagulation, two doses of rivaroxaban were compared to aspirin in 3365 patients (Weitz et al. 2017). The primary efficacy outcome, symptomatic recurrent fatal or nonfatal VTE occurred in 1.5% receiving 20 mg of rivaroxaban, 1.2% receiving 10 mg of rivaroxaban, and 4.4% receiving aspirin (HR for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% CI 0.20 to 0.59; HR for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; $P < 0.001$ for both comparisons). Rates of major bleeding were similar in all three groups: 0.5% (20 mg of rivaroxaban), 0.4% (10 mg of rivaroxaban), and 0.3% (aspirin group). In the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial, patients were assigned to receive either apixaban (10 mg twice daily for the first 7 days, followed by 5 mg twice daily for 6 months) or conventional therapy (enoxaparin at a dose of 1 mg per kilogram of body weight every 12 h for at least 5 days and warfarin for 6 months) (Agnelli et al. 2013). Apixaban was noninferior to conventional therapy with regard to the primary efficacy outcome of recurrent symptomatic VTE or VTE-related mortality (2.3% vs. 2.7%; $P < 0.001$). Major bleeding was lower in the apixaban group (0.6%) than in the conventional therapy (1.8%) (RR 0.31; 95% CI, 0.17 to 0.55; $P < 0.001$ for superiority). In another trial, edoxaban (at a dose of 60 mg once daily, or 30 mg once daily if low renal function or body weight) was compared to warfarin in patients with acute VTE who had received parenteral therapy (The Hokusai-VTE Investigators 2013). Edoxaban was noninferior to warfarin with respect to the primary efficacy outcome of recurrent symptomatic VTE (3.2% vs. 3.5%) but was superior with regard to the primary safety outcome of major bleeding or clinically relevant nonmajor bleeding (8.5% vs. 10.3%; HR 0.81, 95% CI, 0.71 to 0.94; $P = 0.004$ for superiority). Dabigatran was also shown to be noninferior to warfarin in the treatment of acute VTE (Schulman et al. 2009). Given that both groups received parenteral therapy in the dabigatran and edoxaban trials, it is recommended to use parenteral therapy initially before starting dabigatran (The Hokusai-VTE Investigators 2013; Schulman et al. 2009). Pooled analysis showed that DOACs had similar efficacy and safety compared to warfarin for the treatment of VTE (Fig. 2.2) (Kakkos et al. 2014). Given the trend

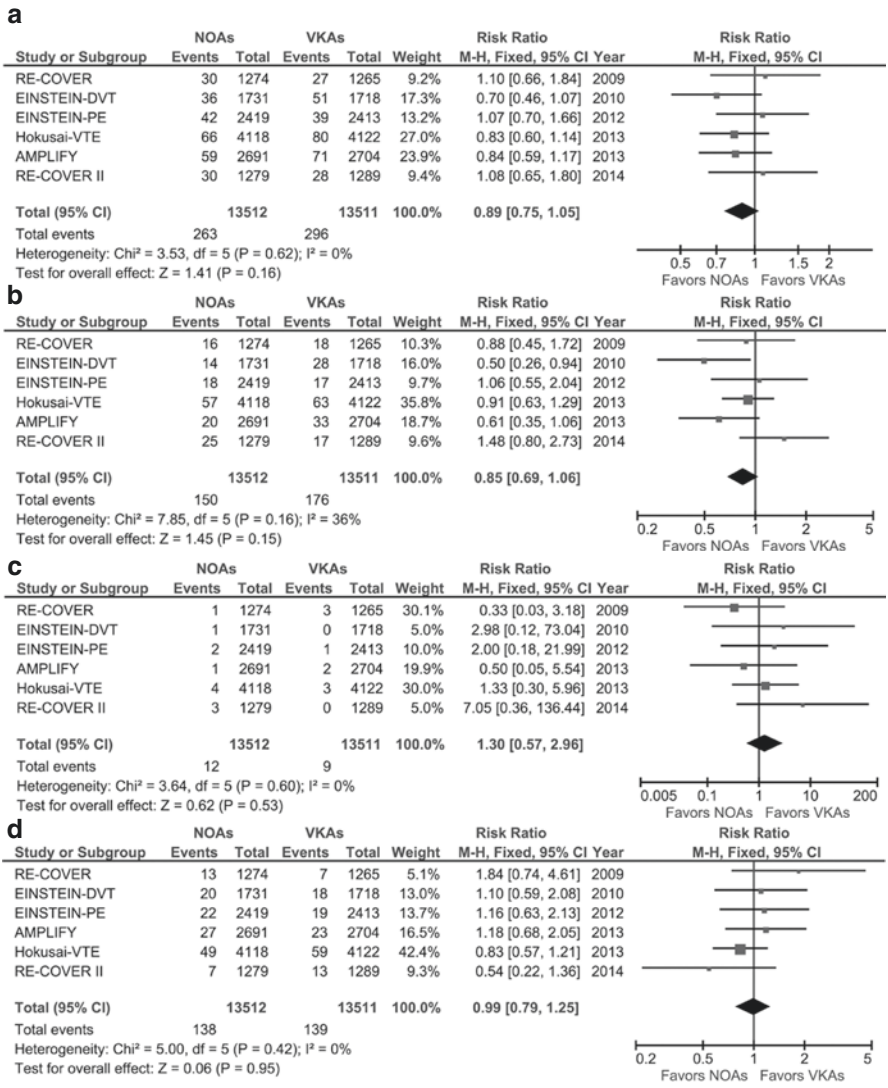

Fig. 2.2 Pooled analysis of the landmark trials comparing direct acting oral anticoagulants and warfarin in patients with venous thromboembolism. (**a**) recurrent venous thromboembolism; (**b**) deep venous thrombosis; (**c**) fatal pulmonary embolism; (**d**) nonfatal pulmonary embolism. (Used with permission from Kakkos et al. (2014))

towards less bleeding with DOACs as well as the ease of administration, DOACs have become first-line therapy for the treatment of VTE.

The treatment of VTE in patients with active malignancy is another important consideration. The CLOT trial had established that the standard of care was treatment with low-molecular-weight heparin given its superiority over warfarin.

Recently, DOACs have been compared to the standard of care to assess for noninferiority; due to the ease of administration, if DOACs were noninferior, they would become the standard of care similar to the treatment of VTE in the general population. In the Hokusai VTE Cancer trial, edoxaban was compared with dalteparin for the treatment of patients with cancer-associated VTE (Raskob et al. 2017). The primary outcome, a composite of recurrent VTE or major bleeding at 12 months, occurred in 12.8% of the edoxaban group and 13.5% of the dalteparin group (HR 0.97; 95%CI, 0.70 to 1.36; $P = 0.006$ for noninferiority; $P = 0.87$ for superiority). Interestingly, there were less recurrent VTE events in the edoxaban group (7.9% vs. 11.3%) but more major bleeding (6.9% vs. 4.0%) compared to dalteparin. In the Caravaggio trial, apixaban was found to be noninferior to dalteparin for the treatment of patients with cancer-associated VTE (Agnelli et al. 2020). Recurrent VTE occurred in 5.6% in the apixaban group and 7.9% in the dalteparin group (HR 0.63; 95% CI 0.37 to 1.07; $P < 0.001$ for noninferiority) and major bleeding occurred in 3.8% in the apixaban group and in 4.0% in the dalteparin group (HR 0.82; 95% CI, 0.40 to 1.69; $P = 0.60$). DOACs are now used as first-line therapy for the treatment of patients with cancer-associated VTE.

Coronary Artery Disease

DOACs have been tested in two settings in patients with coronary artery disease: acute coronary syndrome and secondary prevention in patients at high risk of recurrent major adverse cardiovascular events with stable cardiovascular disease. In the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial, 15,526 patients with a recent acute coronary syndrome receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months (Mega et al. 2011). Rivaroxaban (8.9%) significantly reduced the primary efficacy end point, a composite of death from cardiovascular causes, myocardial infarction, or stroke, compared to placebo (10.7%) (HR 0.84; 95% CI 0.74 to 0.96; $P = 0.008$), with significant improvement using both rivaroxaban doses. However, rivaroxaban increased the rates of major bleeding (2.1% vs. 0.6%, $P < 0.001$) and intracranial hemorrhage (0.6% vs. 0.2%, $P = 0.009$), without a significant increase in fatal bleeding (0.3% vs. 0.2%, $P = 0.66$) compared to placebo. Importantly, rivaroxaban was added to standard of care dual antiplatelet therapy (>92% of patients). Despite the promising efficacy results in this trial, rivaroxaban is not considered a therapeutic option in acute coronary syndrome due to the important limitations observed. The ATLAS ACS 2–TIMI 51 trial suffered from a significant proportion of missing data, in particular the vital status of patients. In addition, the lack of an expected dose response (5-mg dose did not have greater efficacy compared with the 2.5-mg dose of rivaroxaban) was also troubling. Furthermore, there was divergent effects with the two doses on the primary outcome; cardiovascular death, but not myocardial infarction, driving the treatment benefit with 2.5 mg, whereas myocardial infarction, but not cardiovascular death,

driving benefit with the 5-mg dose (Krantz and Kaul 2013). Finally, trials using other DOACs and a meta-analysis of studies failed to show any benefit of adding low-dose DOAC to standard therapy with regard to major adverse cardiovascular events (Oldgren et al. 2011, 2013; Alexander et al. 2011).

The second situation is patients at high risk of recurrent cardiovascular events who have stable disease. These patients are often on aspirin monotherapy though some may be receiving extended dual antiplatelet therapy; despite this therapy, many patients have significant residual risk of cardiovascular events. In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, 27,395 participants with stable atherosclerotic vascular disease were randomized to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily) (Eikelboom et al. 2017). The primary outcome, a composite of cardiovascular death, stroke, or myocardial infarction, was reduced in patients in the rivaroxaban-plus-aspirin group compared to the aspirin-alone group 4.1% vs. 5.4% (HR 0.76; 95% CI 0.66 to 0.86; $P < 0.001$). However, major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (3.1% vs. 1.9%; HR 1.70; 95% CI, 1.40 to 2.05; $P < 0.001$). Interestingly, rivaroxaban alone did not significantly lower the risk of major adverse cardiovascular events compared to aspirin alone, with a significantly higher risk of major bleeding. The finding of this trial has led to recommendations to consider low-dose rivaroxaban in this patient population.

Left Ventricular Thrombus

Another important indication for oral anticoagulation is the development of left ventricular thrombus, which usually occurs after a large anterior myocardial infarction with apical akinesis and may occur in the setting of mid-ventricular hypertrophic cardiomyopathy with apical aneurysm formation, Takotsubo cardiomyopathy, and post ventricular tachycardia ablation. Left ventricular thrombus can have devastating complications by embolizing systemically (Vaitkus and Barnathan 1993). Patients with left ventricular thrombus have been traditionally treated with warfarin therapy though this was based on clinical experience and observational studies (Cregler 1992). Data on DOAC use for left ventricular thrombus is sparse though they are often used off-label by physicians for this indication. A systematic review of case series up to 2018 suggested that DOAC use is a feasible alternative to warfarin (Kajy et al. 2020). In a small randomized trial of 25 patients who received either apixaban or warfarin, after 3 months of treatment, thrombus completely resolved in all patients in the warfarin group and in 92% in the apixaban group (one patient with a very large thrombus had a significant reduction in size) (Alcalai et al. 2020). There were no death, stroke, or systemic embolism in either group. There were two patients with major bleeding in the warfarin group, and one patient discontinued treatment. No major bleeding events or treatment discontinuations were recorded in the apixaban group. However, in a cohort study of 514 patients with

echocardiogram diagnosed left ventricular thrombi, anticoagulation with DOACs was associated with a higher risk of ischemic stroke and systemic emboli than warfarin treatment (Robinson et al. 2020). After a median follow-up of 351 days and on multivariable analysis, anticoagulation with DOAC compared to warfarin (HR, 2.64; 95% CI, 1.28–5.43; $P = 0.01$) was significantly associated with stroke or systemic embolism. While the study has many inherent limitations, it highlights the urgent need for a clinical trial in this area.

Rheumatic Heart Disease

Mitral stenosis due to rheumatic heart disease significantly increases the risk of thromboembolism. Anticoagulation with warfarin has been recommended for patients with mitral stenosis and AF or prior embolism or left atrial thrombus. These patients were generally excluded from DOAC trials assessing the utility of thromboembolic prevention in patients with AF (Biase 2016). Data is limited on the use of DOACs in rheumatic mitral stenosis. The largest experience was published by Kim et al. (2019). There were 2230 patients enrolled from a database in the Republic of Korea, and it included patients who were diagnosed with mitral stenosis and AF and either were prescribed DOACs for off-label use or received conventional treatment with warfarin. Thromboembolic events occurred at a rate of 2.22%/year in the DOAC group, and 4.19%/year in the warfarin group (HR 0.28; 95% CI 0.18 to 0.45). Intracranial hemorrhage occurred in 0.49% of the DOAC group and 0.93% of the warfarin group (HR 0.53; 95% CI 0.22 to 1.26). This result is very promising though only hypothesis generating and clearly a large, randomized trial is needed.

Heparin-Induced Thrombocytopenia

The literature is extremely limited regarding the efficacy and safety of DOACs in heparin-induced thrombocytopenia. In a systematic review, published in 2019, of 104 cases who received DOACs, treatment with DOACs prevented new and recurrent thrombosis in 98% ($n = 102$) of cases, and bleeding complications occurred in 3% ($n = 3$) (Barlow et al. 2019). These results suggest that DOACs may have a role in the treatment of heparin-induced thrombocytopenia. Current hematology guidelines give its use a conditional recommendation (Cuker et al. 2018).

Myocardial Injury After Noncardiac Surgery

Myocardial injury after noncardiac surgery is due to myocardial ischemia which may be either due to supply-demand mismatch or thrombus formation and is associated with an increased risk of mortality and major vascular complications

at 30 days as well as possible up to 2 years after noncardiac surgery (Devereaux and Szczeklik 2020). Diagnostic criteria for myocardial injury after noncardiac surgery are an elevated post-operative troponin measurement judged as resulting from myocardial ischemia, during or within 30 days after noncardiac surgery, and without the presence of symptoms or electrocardiographic findings of ischemia. In the dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE) trial, patients ≥45 years who had undergone noncardiac surgery and were within 35 days of myocardial injury were randomly assigned to receive dabigatran 110 mg orally twice daily or placebo (Devereaux et al. 2018). The primary efficacy outcome, a composite of vascular mortality and nonfatal myocardial infarction, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism, was observed less in patients randomized to dabigatran (11%) than placebo (15%) (HR 0.72, 95% CI 0.55–0.93; $p = 0.0115$). The primary safety outcome, a composite of life-threatening, major, and critical organ bleeding, was similar in both groups (3% vs. 4%). While the authors recommend that dabigatran be used in patients with myocardial injury after noncardiac surgery, there are several limitations to the trial that have tempered this approach including the early termination of the trial, the high proportion of drug discontinuation (46%), and alteration of the primary efficacy end point in the middle of the trial.

Heart Failure in Sinus Rhythm

Although heart failure has been shown to be an important risk factor for stroke, attempts to lower that risk of with anticoagulation in patients without history of AF has not borne fruit. Several smaller trials using warfarin in patients with heart failure and sinus rhythm have not shown any net clinical benefit. This led to the design of the A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER HF) trial. In this trial, 5022 patients who had chronic heart failure, a left ventricular ejection fraction of 40% or less, coronary artery disease, and elevated plasma concentrations of natriuretic peptides and who did not have atrial fibrillation were randomly assigned to receive rivaroxaban at a dose of 2.5 mg twice daily or placebo in addition to standard care after treatment for an episode of worsening heart failure (Zannad et al. 2018). After a median follow-up of 21 months, the primary efficacy outcome, a composite of death from any cause, myocardial infarction, or stroke, occurred in 626 (25.0%) of 2507 patients assigned to rivaroxaban and in 658 (26.2%) of 2515 patients assigned to placebo (hazard ratio, 0.94; 95% confidence interval [CI], 0.84 to 1.05; $P = 0.27$). There were no differences in fatal bleeding or all-cause mortality between the two groups (Zannad et al. 2018). Therefore, DOACs should not be used solely because of heart failure with sinus rhythm.

Embolic Stroke of Undetermined Source

Cryptogenic strokes constitute 20 to 30% of ischemic strokes; the majority of cryptogenic strokes are considered to be embolic of undetermined source. Due to the efficacy of anticoagulants in the prevention of embolic stroke in patients with AF, investigators hypothesized that anticoagulants would be more effective than antiplatelet therapy in preventing recurrent strokes in those with embolic stroke of undetermined source. In the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial, 7213 participants were randomly assigned to receive rivaroxaban or aspirin (Hart et al. 2018). The annualized incidence rate of recurrent ischemic stroke was 4.7% in the rivaroxaban group and 4.7% in the aspirin group. The annualized incidence rate of major bleeding occurred in 1.8% in the rivaroxaban group and 0.7% in the aspirin group (HR 2.72; 95% CI, 1.68 to 4.39; $P < 0.001$). Therefore, rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke and was associated with a higher risk of bleeding in those after an initial embolic stroke of undetermined source. Similarly, in the Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS) trial, 5390 patients were randomly assigned to receive dabigatran or aspirin (Diener et al. 2019). During a median follow-up of 19 months, the annual incidence of recurrent strokes was 4.1% in the dabigatran group and 4.8% in the aspirin group (HR 0.85; 95% CI 0.69 to 1.03; $P = 0.10$). The annual incidence of major bleeding occurred in 1.7% in the dabigatran group and 1.4% in the aspirin group (HR 1.19; 95% CI, 0.85 to 1.66). Therefore, dabigatran was not superior to aspirin with regard to the prevention of recurrent stroke but was not associated with a higher risk of bleeding in those after an initial embolic stroke of undetermined source. On the basis of these trials, DOACs are not indicated for embolic strokes of undetermined source.

Mechanical Valves

Mechanical valves are more durable than bioprosthetic valves and are therefore preferred in younger patients. However, unlike bioprosthetic valves, mechanical valves require lifelong anticoagulation therapy. Warfarin is the standard of care in this population but after the publication of the landmark trials in those with nonvalvular AF, investigators set out to assess the efficacy and safety of DOACs in patients with mechanical valves. The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) sought to shed some light on the feasibility of DOACs (Eikelboom et al. 2013). The trial was terminated early due to an excess of thromboembolic and bleeding events among patients in the dabigatran group: 5% had a stroke event compared to no stroke events in the warfarin group and major bleeding

occurred 4% and 2% in those receiving dabigatran and warfarin, respectively. Due to this trial, DOACs are now contraindicated in patients with mechanical valves. There have been some criticisms of these recommendations given that it is based on one phase 2 trial that was terminated early. Also, the trial was done using dabigatran with the results extrapolated to all other DOACs (Aimo et al. 2018). A small observational study suggested that rivaroxaban may be safe (Durães et al. 2018). However, at this time there are no plans for further trials with DOACs in patients with mechanical heart valves.

Left Ventricular Assist Device

Anticoagulation is mandatory in patients with left ventricular assist devices. The effectiveness and safety of DOACs in patients with left ventricular assist devices has not been adequately investigated. In part, this is due to the results of the RE-ALIGN trial in patients with mechanical valves. In a pilot randomized trial to assess for feasibility in which patients with left ventricular assist devices were randomized to receive either phenprocoumon or dabigatran in addition to aspirin for long-term anticoagulation (Andreas et al. 2017), the trial was stopped early due to an excess in thromboembolic complications in the dabigatran arm (50%). In AF, thrombosis is driven by stasis and endothelial dysfunction in the left atrial appendage and the inhibition of one key factor in the coagulation cascade in these patients is enough to prevent thrombus formation (den Exter et al. 2020). In contrast, in patients with left ventricular assist devices, coagulation is principally triggered by blood contact with the artificial surfaces activating the contact pathway in which vitamin K antagonists are more effective by inhibiting both thrombin and the tissue factor induced pathway (den Exter et al. 2020).

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Pharmacokinetics and Pharmacodynamics of DOAC

3

Nicola Ferri

Introduction

Oral anticoagulants are used for the treatment and prevention of stroke and venous thromboembolism in patients with chronic non-valvular atrial fibrillation (NVAF). Until 2010, vitamin K antagonists, such as warfarin, were the only oral anticoagulants available in the clinic. However, warfarin therapy is associated with numerous limitations: (a) delayed onset of action, (b) restricted therapeutic window, (c) numerous interactions with other drugs or food, (d) variable and unpredictable pharmacological response, (e) influence of the genetic polymorphism of CYP2C9 and VKORC1, (f) requirements of frequent monitoring of the coagulation. These limitations led to the development of new oral anticoagulants (NAO) or the so-called direct oral anticoagulants (DOACs) (Yeh et al. 2015).

Physico-Chemical Properties

The chemical structure of DOACs currently approved internationally is shown in Fig. 3.1. Dabigatran is an aromatic amide obtained by formal condensation of the carboxy group of 2-{[(4-carbamimidoylphenyl) amino] methyl}-1-methyl-1H-benzimidazole 5-carboxylic acid with the secondary amino group of N-pyridin-2-yl-beta-alanine. Dabigatran can be orally administered as the prodrug, dabigatran etexilate which differs from dabigatran by an ethyl group at the carboxylic acid and a hexyloxycarbonyl side chain at the amidine. Dabigatran etexilate is rapidly and completely metabolized, via two intermediates, to dabigatran by carboxyl liver and intestinal esterases and plasma esterases present in the portal blood (Fig. 3.1).

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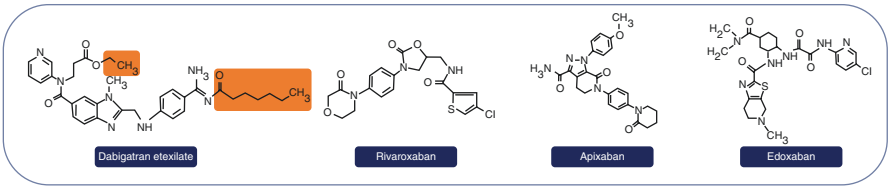

Fig. 3.1 Chemical structures of DOACs. Orange boxes highlight the chemical moieties of prodrug of dabigatran hydrolyzed by esterases

Rivaroxaban (5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl) thiophene-2-carboxamide)) and apixaban (1-(4-Methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide) are both orally administered as active drugs.

Finally, the last DOAC that has been approved for clinical use is edoxaban (N′-(5-chloropyridin-2-yl)-N-[(1S,2R,4S)-4-(dimethylcarbamoyl)-2-[(5-methyl-6,7-dihydro-4H-[1,3]thiazolo[5,4-c] pyridine-2-carbonyl)amino]cyclohexyl] oxamide;4-methyl benzenesulfonic acid). Differently from the other DOACs, edoxaban is the only one that is metabolized to form active molecules with similar potency than parental drug.

Pharmacodymanics of DOACs

Mechanism of Action

Warfarin acts by inhibiting vitamin K epoxide reductase complex 1 (VKORC1), also a polymorphic enzyme, which generates the reduced form of vitamin K that is an essential co-factor for carboxylation of glutamate residues on proteins such as coagulation factors II, VII, IX, and X by gamma glutamyl carboxylase (Ansell et al. 2008). Carboxylation of these proteins is essential for their biological activity. Differently, DOACs directly inhibit biological activity of factor Xa (fXa) or thrombin (factor IIa), key proteases in the coagulation cascade (Fig. 3.2). In particular, apixaban, rivaroxaban, and edoxaban reversibly inhibit fXa while dabigatran is a selective inhibitor of the downstream protease thrombin (Fig. 3.2) (Wang and Bajorek 2014).

Since fXa is the common enzyme of both extrinsic and intrinsic coagulation pathways, rivaroxaban, apixaban, and edoxaban can inhibit the thrombin generation from both ways, leading to a complete and effective anticoagulant action. Differently, dabigatran acts at a downstream step of the coagulation cascade, i.e., by inhibiting thrombin activity with a K_i of 4.5 nM (Stangier et al. 2007, 2008).

FXa has also emerged as a particularly promising target for effective anticoagulation because one molecule of fXa results in the generation of more than 1000

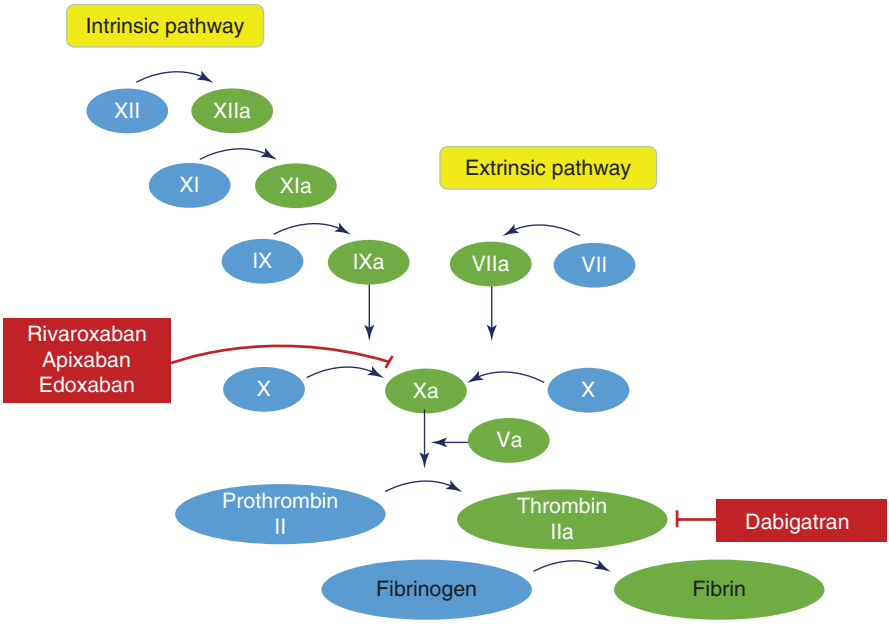

Fig. 3.2 Schematic view of the mechanism of action of DOACs

thrombin molecules (Mann et al. 2003). Thus, inhibiting fXa may block this burst of thrombin generation, thereby diminishing thrombin-mediated activation of coagulation and platelets (Gerotziafas et al. 2007).

Apixaban is the most potent fXa inhibitor with a binding affinity (K_i) of 0.08 nM (Stangier et al. 2007, 2008). The selectivity of action of apixaban is demonstrated by the fact that the inhibitory potencies against thrombin, plasma kallikrein, and chymotrypsin are around 10,000 times higher (K_i ~ 3 μM) (Pinto et al. 2007). Rivaroxaban inhibits fXa in a concentrated manner (K_i ~ 0.4 nM) (Perzborn et al. 2005). Similarly, to rivaroxaban and apixaban, edoxaban binds the catalytic site of the fXa with a K_i of 0.56 nM (Furugohri et al. 2008). Apixaban, rivaroxaban, and edoxaban seem to inhibit also fXa present in the clot.

The antithrombotic effect of DOACs is primarily attributed to the inhibition of fXa without any significant in vitro effect on platelet aggregation. However, these drugs may decrease platelet activation in vivo indirectly via inhibition of thrombin generation and may thereby affect thrombin-induced aggregation.

From a pharmacodynamic point of view, DOACs have a direct effect which is maximal after 2–3 h from their administration in accordance with the time to peak concentration (T_{max}) (Table 3.1) and with the direct correlation between plasma concentrations and anticoagulant effect. These characteristics distinguish these drugs from warfarin, which through the inhibition of the activation of several clotting factors, it takes 3–5 days to manifest its anticoagulant action (Desai et al. 2013).

Table 3.1 Pharmacokinetic and pharmacodynamic characteristics of DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	fXa	fXa	fXa
K_i (nmol/L)	4.5	0.4	0.08	0.56
Bioavailability	6.5% (absolute)	80%	50% (absolute)	60% (absolute)
Effect of food	Delayed and not reduced absorption	Increased absorption (20 mg)	None	None
Administered with food	No	Yes[a]	No	No
V_d	60–70 L	50 L	21 L	>300 L
Protein bound	35%	>90%	87%	40–59%
Prodrug	Yes	No	No	No
T_{max} (h)	1–3	2–4	3–4	2
Half lifetime (*h*)	12–17	5–9 (healthy)	8–15	8–11
Metabolism (CYP)	Conjugation	3A4, 2J2, and CYP independent	3A4	3A4
P-gp substrate	Yes (only prodrug)	Yes	Yes	Yes
Substrate of other transporters	Not known	BCRP/ABCG2	BCRP/ ABCG2	Not known
Renal elimination	80%	35%	27%	50%
Hemodialysis elimination	60–70%	Unlikely	Unlikely	Possible
Administration frequency	Double daily dose	Double daily dose	Double daily dose	Double daily dose

V_d volume of distribution, T_{max} time to reach the maximal plasma concentration, *CYP450* Cytochrome P 450, *P-gp* P-glycoprotein

[a]The drug at 15 and 20 mg must be administered with food

Similar situation is observed for the reversibility of the pharmacological effect, which is much faster for DOACs, both for short half-life and for the reversibility of their mechanism of action, compared to warfarin.

From all these considerations, it is evident that DOACs have intrinsic characteristics which are deeply distinct, not only from the classic vitamin K inhibitors, but also between them. So, in order to better use these new pharmacological agents, it is important to know and understand their pharmacological properties.

Pharmacokinetics of DOACs

Absorption

The pharmacokinetics parameters of DOACs are summarized in Table 3.1. Dabigatran differs from the other DOACs due to its low bioavailability (6.5%) which entails an important variability in the absorbed portion (Stangier et al. 2008). As previously descried, in order to achieve oral absorption, dabigatran is administered as a prodrug (dabigatran etexilate), which once it reaches the systemic circle,

it is hydrolyzed by liver and serum esterases that produce the active form of the drug. Its absorption increases in an acid environment and, for this reason, the drug is formulated in the presence of tartaric acid. Phase I studies with increasing doses of dabigatran show that low oral bioavailability is not caused by a saturable first-pass process, considering that plasma concentrations increase linearly and dose-dependently following a first order kinetic (Stangier et al. 2007; Gong and Kim 2013).

The capsules containing dabigatran etexilate are designed to release the drug into the stomach allowing the absorption in the duodenum. Indeed, dabigatran is thought to be absorbed in the lower stomach and duodenum because of the rapid time to peak levels. The identification of the site of dabigatran absorption is also supported by a case report showing reduced absorption in short bowel syndrome contributing to insufficient anticoagulation and drug levels below published values of therapeutic doses of dabigatran. The drug not absorbed will remain in the gastrointestinal tract where could undergo to enzymatic activation dabigatran and eliminated in the feces.

Considering the pH-dependent solubility of the drug, co-administration with H2 antagonists and proton-pump inhibitors, which causes an increase in intestinal pH, limits dabigatran bioavailability reducing its exposure by respectively 12% and 30% (Heidbuchel et al. 2013). However, this interaction is thought not to be clinically meaningful (Steffel et al. 2018). On the contrary, the pharmacokinetics of rivaroxaban, apixaban, and edoxaban are not altered by drugs that increase gastric pH.

Co-administration of food resulted in a delay in absorption of dabigatran etexilate, with the median T_{max} increasing from 2 to 4 h. However, bioavailability (AUC and C_{max}) was essentially unchanged in the fasted state compared with fed conditions (Fig. 3.3). Thus, dabigatran can be administered either in the presence or absence of food.

Rivaroxaban appears to be absorbed primarily in the stomach, as there is reduced absorption (29% decrease in AUC and 56% decrease in C_{max}) when the drug is released into the proximal small intestine, with further reduction as the drug is released more distally into the small intestine and colon (Mani et al. 2013; Douros et al. 2014). More importantly, the bioavailability of rivaroxaban is not linear with the administered dose. At the dose of 10 mg, the bioavailability is estimated to be 80–100%, compared to 66% at the dose of 20 mg (Stampfuss et al. 2013). The presence of food significantly increases the bioavailability of rivaroxaban (20 mg, Fig. 3.3), and reduces the interindividual variability of its plasma concentrations (Stampfuss et al. 2013). This effect is probably due to a positive effect of food on the solubilization and dissolution of the drug. It is important to highlight that food intake is meant a meal of at least 1300 Cal with a 30–40% fat content. For this reason, it is fundamental to take rivaroxaban after meals (Fig. 3.3).

Apixaban is absorbed primarily in the proximal small intestine, with some gastric absorption and limited colonic absorption and reaches the maximum concentration (C_{max}) after 2–3 h from the oral administration (Frost et al. 2013a, b). Its bioavailability is approximately 50% and approximately 35% of the unabsorbed portion is eliminated with feces (Table 3.1). Unlike rivaroxaban, intestinal

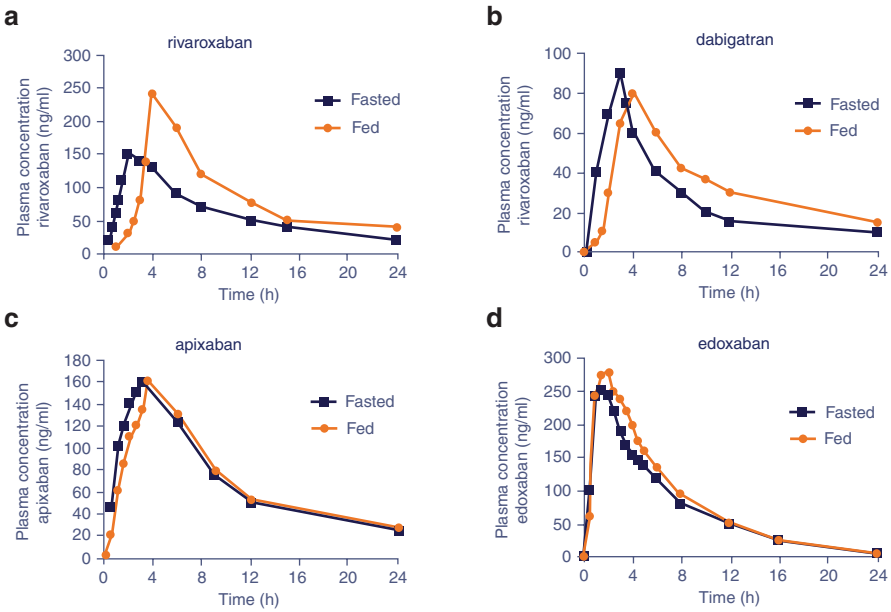

Fig. 3.3 Effect of food on the pharmacokinetic of DOACs. (**a**) Rivaroxaban; (**b**) Dabigatran; (**c**) Apixaban; (**d**) Edoxaban. Food determines a significant increase of rivaroxaban exposure (C_{max} and AUC) and a delay of dabigatran absorption (T_{max})

absorption of apixaban is not affected by food (Fig. 3.3) (Frost et al. 2013a, b). Similar considerations can be made for edoxaban, which reaches its C_{max} after 2 h from the oral administration and its pharmacokinetic profile which is not affected by the food (Fig. 3.3) (Mendell et al. 2012).

Edoxaban is rapidly absorbed after oral administration with a time to peak plasma concentration of 1–2 h, and a bioavailability of 62% (Table 3.1). Its absorption, which is not related to solubility, occurs predominantly in the proximal small intestine and it is limited in the colon (13%) (Parasrampuria et al. 2015). Edoxaban has a low intrasubject variability and dose linearity suggesting a predictable and consistent pharmacokinetic profile.

Terminally ill patients with dysphagia may result in reduced patient adherence to medications. Therefore, solid oral formulations crushed and mixed into food or provided as a water suspension via a nasogastric tube are often utilized as alternative methods of drug administration. However, these manipulations may alter the bioavailability of a drug. Within this clinical setting, a phase I, open-label, randomized trial was conducted to assess the pharmacokinetic, safety, and tolerability profiles of the edoxaban 60-mg tablet in healthy adults when crushed and administered either via a nasogastric tube or mixed with apple puree and ingested (Duchin et al. 2018). The results demonstrated that edoxaban tablet crushed and administered either via a nasogastric tube or with apple puree displays similar total exposure, although time to maximum plasma concentration was significantly shorter for the nasogastric tube

suspension and apple puree vs. the whole tablet (Duchin et al. 2018). Thus, edoxaban can be considered a valid option for patients who are unable to swallow solid oral dose formulations. In contrast, when rivaroxaban is administered using a nasogastric tube followed by a liquid meal, a significant 18% reduction in C_{max} was observed, although the AUC values were similar (Mueck et al. 2014).

Dabigatran, due to the low bioavailability, and rivaroxaban, due to the once-daily posology, are expected to have a higher variability of peak and trough concentrations and may undergo more easily to clinically relevant drug–drug interaction.

In consideration of the mechanism of drug absorption in the gastrointestinal track, it is relevant to know that all DOACs are substrate of the P-glycoprotein (P-gp) and potentially other drug transporters (Gong and Kim 2013). The P-gp partially limits the disposition of the drugs by reducing their intestinal absorption and facilitating their elimination by the kidney and the liver (Wolking et al. 2015). For this reason, all DOACs are expected to have important pharmacological interactions with potent P-gp inhibitors, such as antifungals, macrolides, antiretroviral protease inhibitors, which significantly increase DOACs absorption and thus the anticoaugulant effect.

Among the cardiovascular drugs, diltiazem, amiodarone, dronedarone, quinidine, and verapamil are considered the most potent P-gp inhibitors and potentially increasing the exposure of all DOACs (Steffel et al. 2018). Considering the inducers of P-gp, rifampin, most antiepileptic drugs and St. John's wort, should not be administered in combination with DOACs (Chap. 4) (Steffel et al. 2018).

Distribution

As shown in Table 3.1, DOACs are characterized by different volumes of distribution (V_d) and plasma protein binding (Table 3.1). Dabigatran is highly hydrophilic with poor plasma protein binding and prevalent renal clearance, characteristics that make this drug the only DOAC that can be hemodialyzed (Khadzhynov et al. 2013). However, the dialysis is effective only if performed after the first hours from the last administration, otherwise the volume of distribution of the drug (60 L), after distribution is complete, prevents dialysis removal.

The plasma protein binding for rivaroxaban is high (approximately 92–95% in vitro) and reversible. Serum albumin is the main plasma binding component. Owing to its high plasma protein binding, rivaroxaban is not expected to be dialyzable. V_d at steady state is approximately 50 L, indicating its low-to-moderate affinity to peripheral tissues (Dias et al. 2016).

Apixaban is characterized by a reduced apparent volume of distribution (21 L), suggesting a distribution mainly in the systemic circulation, with a limited extravascular localization (Mavrakanas et al. 2017). The binding to plasma proteins is 87%, therefore not particularly high, excluding possible interactions with drugs that can displace the binding (Table 3.1).

The mean apparent V_d of edoxaban is approximately 300 L and 100 L after oral and intravenous administration, respectively (Ogata et al. 2010; Parasrampuria and

Truitt 2016). This difference indicates biliary excretion of edoxaban and a possible enterohepatic circulation through glucuronidation processes. The relatively high V_d of edoxaban in comparison to other DOACs is not predicted to have any clinically relevant implication on the safety or efficacy of the drug according to the large experience in the phase III trials, including patients with frailty, obesity, older age, and mild to moderate chronic kidney disease (CKD). Edoxaban shows a relatively low total plasma protein binding (≈55%), whereas the human-unique metabolite M-4 is approximately 80% bound to plasma proteins over a concentration range of 0.2–2 μg/mL (Parasrampuria and Truitt 2016).

Metabolism

In general, all DOACs do not undergo to an extensive phase I and phase II metabolism. As an ester prodrug, dabigatran etexilate undergoes two sequential activation steps to form its pharmacologically active metabolite dabigatran. Following oral administration, dabigatran etexilate is first metabolized to its intermediate metabolite dabigatran ethyl ester (M2) by carboxylesterase 2 (CES2) in the intestine, and M2 is further converted to the final active metabolite DAB by carboxylesterase 1 (CES1) in the liver (Blech et al. 2008). Once activated, dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate (Stangier et al. 2007). The cumulative urinary excretion of dabigatran accounted for less than 5% of the dose (Stangier et al. 2007).

Dabigatran, being a polar drug, exhibits only a little oxidative metabolism. Instead, the acylglucuronide of the carboxylate functional group is formed, and this is the major metabolite in humans (Ebner et al. 2010). After oral administration, approximately 20% of dabigatran is conjugated by glucuronosyltransferases to the pharmacologically active glucuronide conjugates. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each account for less than 10% of total dabigatran in plasma (Ebner et al. 2010). Conjugates of dabigatran in urine represented 0.4% of the dabigatran dose. Thus, CYP3A4 is not involved in the metabolism of dabigatran, excluding possible drug–drug interactions with inhibitors or inducers of cytochromes (Heidbuchel et al. 2013).

Conversely, approximately 2/3 of a rivaroxaban dose undergo metabolic transformation. Rivaroxaban is metabolized by CYP3A4/5 by about 18%, while CYP2J2 ensures metabolization of approximately 14% (Mueck et al. 2014). CYP-independent amide bonds hydrolysis contributes other 14%. About 36% of the drug is eliminated unchanged with urine: 30% through active renal secretion, 6% via glomerular filtration. Thus, CYP3A4-dependent elimination is relevantly involved in the hepatic clearance of rivaroxaban and strong CYP3A4 inhibition or induction may affect plasma concentrations and should be evaluated in context.

Most of the hepatic clearance of apixaban is as unchanged molecule, with only a minority being metabolized (in part via CYP3A4), which makes CYP3A4 interactions of low importance for this drug (Wang et al. 2010). In addition, non-metabolic clearance of apixaban is diverse (including excretion of the unchanged drug by

>50%), which reduces the potential for drug–drug interaction (Wang et al. 2010). Nevertheless, apixaban should be used with caution if co-administered with strong inducers of both CYP3A4 and P-gp and is contraindicated in combination with strong inhibitors of both CYP3A4 and P-gp (Steffel et al. 2018).

In healthy human subjects, six phase 1 metabolites (M-1, M-2, M-4, M-5, M-6, and M-8) and a glucuronide (M-3) metabolites of edoxaban have been detected in plasma (Parasrampuria and Truitt 2016). M-4 is the major metabolite and it is produced from the CES1. CYP3A4 mediates the formation of M-5, while a minor metabolite M-8 derives spontaneously (non-enzymatically) from an intermediary, hydroxymethyl edoxaban, formed via CYP3A4/5 (Parasrampuria and Truitt 2016).

Three of the metabolites (M-4, M-6, and M-8) have anticoagulant activity, with IC_{50} values for anti-FXa of 1.8 nM (M-4), 6.9 nM (M-6), and 2.7 nM (M-8), thus similar to the parental drug (0.56 nM) (Parasrampuria and Truitt 2016). However, due to the low plasma concentration and high protein binding, the most abundant metabolite, M-4, is not expected to contribute significantly to the overall pharmacological activity of edoxaban. Importantly, the relative increase in edoxaban and M4 systemic exposure is identical, and the AUC ratio (M4 over edoxaban) is constant over varying kidney function, body weight, and doses; however, a significant increase of M4/edoxaban ratio is predictable in the presence of drugs that induce edoxaban metabolism (see Chap. 4). Thus, unlike rivaroxaban, CYP3A4-dependent elimination is marginally involved in the hepatic clearance of edoxaban (Parasrampuria and Truitt 2016).

Excretion

The relative contribution of renal drug excretion varies considerably among DOACs. Most of a dabigatran dose is excreted by the kidneys unchanged (80%) or in the form of active glucuronides (4%). Edoxaban, rivaroxaban, and apixaban are excreted unchanged by 50%, 33%, and 27% of the bioavailable dose, respectively (Heidbuchel et al. 2013; Ferri and Corsini 2015). Renal clearance of dabigatran amounted to 50–100 mL/min.

The contribution of glomerular filtration, active secretion, and tubular reabsorption differs among DOACs. In particular, renal clearance of dabigatran is slightly lower than the glomerular filtration at any level of renal impairment, indicating that tubular reabsorption does occur to some extent (Padrini 2019). Indeed, dabigatran is the most lipophilic compound of the group (log P = 2.37) and the only one which does not undergo tubular secretion by P-gp. Conversely, the renal clearance of rivaroxaban and edoxaban is four times higher than glomerular filtration rate, most probably due to extensive tubular secretion by P-gp, as shown by the increase in the AUCs of rivaroxaban and edoxaban by P-gp inhibitors (Padrini 2019). Lastly, apixaban is characterized by nearly coinciding values of renal clearance and glomerular filtration rate, indicating lack of drug secretion and reabsorption or, rather, a null sum of the two processes. The latter hypothesis seems more plausible, since apixaban is also a substrate of P-gp but, having lipophilicity similar to that of dabigatran (log P = 2.23), may also be reabsorbed (Padrini 2019).

The limited involvement of renal excretion for the apixaban elimination pathway, and a very diversified hepatic clearance, including metabolism, biliary secretion, and direct elimination in the intestine, confers to this drug a greater margin of safety in patients with partial kidney and hepatic impairment.

The renal clearance of apixaban is also lower than for all DOACs and in particular with edoxaban (15 mL/min vs. 183 mL/min) (Table 3.1). In fact, the calculation of the clearance involves the involvement of both the V_d value and the half-life time. With the same half-life time between edoxaban and apixaban, the much higher V_d of the former inevitably determines a much higher clearance value. This difference is caused by the fact that apixaban is eliminated from the kidney exclusively by glomerular filtration, or alternatively the active tubular secretion processes are equivalent to those of tubular reabsorption. On the contrary, the renal elimination of edoxaban involves active tubular secretion processes. These differences are clinically relevant in "so-called hyperfiltration" patients in whom edoxaban loses efficacy precisely because of its excessive renal elimination (Bohula et al. 2016).

The different renal clearance may determine variations of dosage and choice of DOAC based on the pathophysiological characteristics of the patient. According to European guidelines (Steffel et al. 2018), dabigatran is contraindicated in patients with a creatinine clearance <30 mL/min, while rivaroxaban and edoxaban can be used with caution at lowered dose with a clearance between 15 and 29 mL/min and with a close monitoring of patient's kidney function. In patients with moderate renal insufficiency (creatinine clearance between 30 and 50 mL/min), dabigatran, rivaroxaban, and edoxaban can be used at lowered dose (Table 3.2). The choice of the

Table 3.2 Comparison between FDA, EMA, and HC guidelines on dose adjustment recommendations in patients with atrial fibrillation and various degrees of renal impairment

Drug	CLcr (mL/min)	Recommendations
Dabigatran	<15	Not recommended by FDA
	<30	Contraindicated by EMA and HC
	15–30	Dose reduction (75 mg bid) by FDA
Rivaroxaban	<15	Not recommended by FDA and contraindicated by EMA
	<30	Not recommended by HC
	15–50	Dose reduction (15 mg qd) by FDA and EMA
	30–49	Dose reduction (15 mg qd) by HC
Apixaban	Hemodialysis	No dose reduction (5 mg bid) by FDA
	<15	Contraindicated by EMA and HC
	15–29	Dose reduction (2.5 mg bid) by EMA
	Crs ≥ 1.5 mg/dL and age ≥ 80 or body weight ≤ 60 kg	Dose reduction (2.5 mg bid) by FDA, EMA and HC if two of the parameters are present
Edoxaban	<15	Contraindicated by FDA, EMA, and HC
	<30	Contraindicated by HC
	15–50	Dose reduction (30 mg qd) by FDA
	>95	Not recommended by FDA (reduced efficacy)

CLcr creatinine clearance, *Crs* serum creatinine, *qd* once daily, *bid* twice daily, *FDA* Food and Drug Administration, *EMA* European Medicines Agency, *HC* Health Canada

posology for apixaban is based on the presence of at least two of the following parameters: serum creatinine ≥1.5 mg/dL, age ≥ 80, or body weight ≤ 60 kg. In the presence of this condition, apixaban should be used at lower dose with a clearance ≥30 mL/min. With a clearance between 15 and 29 mL/min, the recommended dose of apixaban is 2.5 mg bid. The elimination characteristics of apixaban entail the possibility of using the drug at full dose (5 mg bid) even in hemodialysis patients, as suggested by the FDA guidelines (Table 3.2) (Heidenreich et al. 2016).

Due to the relevant renal clearance, in a pharmacokinetic study of patients with NVAF, the edoxaban exposure has been shown to be lower in subjects with creatinine clearance above 90 mL/min. Thus, in patients with a CrCl >95 mL/min edoxaban has been shown a lower relative efficacy compared to warfarin. On this basis, the Cardiorenal Division of the US Food and Drug Administration (FDA) recommended that edoxaban should not be used in patients with a CrCl >95 mL/min for stroke prevention in NVAF (US Food and Drug Administration 2015). The position of FDA was not followed by other regulatory agencies both in Europe by the European Medicines Agency (EMA), as well as in Canada (Table 3.2).

All DOACs are, however, contraindicated in patients with severe liver impairment (Child–Pugh C), while rivaroxaban is also contraindicated in case of Child–Pugh B (Steffel et al. 2018). This difference is due to the fact that rivaroxaban is the DOACs with a higher rate of elimination through CYP-mediated metabolism.

Unlike dabigatran, not metabolized by cytochromes, the dose of apixaban, rivaroxaban, and edoxaban must be reduced in case of co-administration with potent CYP3A4 inhibitors.

Among the characteristics of DOACs, the elimination half-life time deserves important considerations. This parameter is approximately equal to 12 h for dabigatran, apixaban, and edoxaban, and significantly lower for rivaroxaban, 5–9 h (Table 3.1). This characteristic suggests a bid administration. The ratio between the maximum and minimum concentration at steady state in once-daily administration is equal to 4.5 for dabigatran (Clemens et al. 2012), 10 for rivaroxaban (Mueck et al. 2014), 10 for apixaban (Frost et al. 2013a) and 10–30 for edoxaban (Ogata et al. 2010). The higher the ratio, the greater is the fluctuation of plasma levels in 24 h. The clinical consequences of these fluctuations can lead to bleeding in the case of the peak or thromboembolic events at minimum concentrations. It is therefore plausible to minimize these variations by opting for the bid administration. However, rivaroxaban and apixaban are administered as once daily, modality that leads to a pharmacokinetic profile with very high peak concentrations compared to dabigatran and apixaban. The high C_{max} peak levels with rivaroxaban, together with a nonlinear kinetic at dosages higher than 10 mg and the influence by food on its gastrointestinal absorption, are associated to a high pharmacokinetic variability. A cross-over study that directly compared rivaroxaban to apixaban, clearly demonstrated a lower variability with a bid administration of apixaban (23% vs. 46% for apixaban and rivaroxaban, respectively) (Frost et al. 2014). This high variability of rivaroxaban could be associated to increased risk of gastrointestinal bleeding observed compared to warfarin in the clinical trial ROCKET AF (Patel et al. 2011).

The variability in the plasma concentration of edoxaban, administrated once daily, is less problematic compared to rivaroxaban since the former is characterized by a linear kinetic profile and a half-life elimination time significantly slower (12 h). Surprisingly, when edoxaban is administered bid, a higher risk of major bleeding was observed compared to qd (Weitz et al. 2010). This apparent discrepant effect can be explained by high V_d that leads to the accumulation of the drug. Indeed, the increased bleeding of edoxaban correlates with high minimum concentrations (C_{min}) that are found with the dosage bid (Weitz et al. 2010).

Conclusions

The DOACs, on the basis of their pharmacological profile and the results of clinical trials conducted by a direct comparison to warfarin, represent an important evolution of the therapeutic armamentarium available for the treatment of patients at risk of thromboembolic complications.

The pharmacokinetics characteristics of DOAC represent an important tool in order to customize the treatment based on the characteristics of patients, and to obtain the best therapeutic efficacy by minimizing adverse effects. Thus, the selection among the four currently available DOACs should be done by considering important pathophysiological parameters, such as kidney function, dyspepsia, the risk of bleeding and ischemic events, as well as other concomitant therapies which could determine clinically relevant drug–drug interactions. Finally, the compliance of bid or single daily administration should also be considered.

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Drug–Drug Interaction with DOACs

4

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Introduction

Four direct oral anticoagulants (DOACs) have been approved for clinical use by many regulatory medicines' agencies around the world. The use of these drugs is increasing in routine practice for the treatment of non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE). AF is the most common sustained arrhythmia in clinical practice, especially in the elderly (Boriani et al. 2006, 2018; Lip et al. 2014) and, even if the arrhythmia is asymptomatic, is associated with adverse outcomes, with a significantly increased risk of stroke, death, and heart failure (Giuseppe et al. 2014). VTE, categorized as deep venous thrombosis (DVT) and pulmonary embolism (PE), is associated with high morbidity and a relevant financial burden on patients and health system. Both acquired and hereditary risks factors contribute to VTE, in particular VTE is a common complication of cancer and its therapy (Perera et al. 2020).

Oral anticoagulant therapy significantly reduces the risk of AF-related thromboembolic events and mortality, and is recommended in every patient at risk, according to guidelines (Steffel et al. 2018a). The class DOACs are nowadays an effective treatment with as safer profile compared to vitamin K antagonist (VKA) and are currently implemented in "real-world" clinical practice, in patients with so-called NVAF and VTE, settings characterized by patients with complex clinical scenarios, in terms of comorbidities and polypharmacy. Comorbidity and polypharmacy are at high prevalence in elderly patients, a population where the estimated prevalence of

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NVAF is particularly high (9%–10% at age over 80 years and lower than 0.1% in patients at age below 55 years) (Go et al. 2001; Lloyd-Jones et al. 2004; Miyasaka et al. 2006). In addition, NVAF is associated with a four- to fivefold increased risk of embolic stroke with an estimated increased stroke risk of 1.45-fold per decade in aging (Go et al. 2014; Coppens et al. 2013). Since VKA warfarin shows many clinical significant interactions with drugs, foods, and herbal medicines (Nutescu et al. 2006; Teklay et al. 2014), resulting in frequent adjustment of its dosage in order to achieve a safe and effective anticoagulant effect, the use of new DOACs may represent a significant clinical advantage.

Thus, in view of the need to prescribe oral anticoagulants to patients with various concurrent diseases and on treatment with various drugs or agents, in the present chapter, the predicted drug–drug interactions (DDIs) of DOACs will be described. Considering that many DDIs are not specifically studied, only theoretical pharmacological considerations can be done of specific anticoagulant in order to predict if an interaction is possible. In view of the increasing number of patients with oncological pathologies who need treatment with anticoagulants, for VTE or NVAF (Perera et al. 2020; Ay et al. 2017), we will include interactions between DOACs and chemotherapies.

General Considerations

As discussed in Chap. 3, all DOACs are substrates for P-gp, therefore strong inhibition of P-gp can increase absorption and exposure of DOACs, thus increasing the bleeding risk. On the other hand, an induction of P-gp can reduce DOACs absorption, therefore reducing their antithrombotic therapeutic effect. Indeed, an important interaction mechanism for all DOACs consists of significant gastrointestinal re-secretion over a P-gp transporter after absorption in the gut and in their renal clearance (Gnoth et al. 2011).

The intensity of the inhibition or induction of P-gp transporters can help to predict the entity of the change in drug exposure (Table 4.1). This approach was adopted by the recently published "The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation" (Steffel et al. 2018a). Thus, strong P-gp inhibitors may increase systemic absorption and decrease elimination of P-gp substrates resulting in increased exposure. On this regard, it is relevant to consider that the extent of the inter-individual variability of a drug plasma concentration may have a significant impact of the interaction with P-gp inhibitors or inducers. For instance, dabigatran and rivaroxaban, which are expected to have a higher variability of peak and trough concentrations, in comparison to edoxaban and apixaban, may undergo more easily to clinical relevant DDI (Gosselin et al. 2018; Testa et al. 2016).

Since edoxaban metabolism, by CES1, CYP3A4 and via glucuronidation, is only marginally involved in its clearance, inhibitors or inducers of these enzymes are unlikely involved in clinically relevant interactions with edoxaban (Parasrampuria

Table 4.1 Inducers and inhibitors of CYP3A and P-gp

	P-gp inhibitor	Non-P-gp inhibitor	P-gp inducer
Strong CYP3A inhibitor	Itraconazole, ketoconazole, clarithromycin, lopinavir, indinavir, ritonavir, telaprevir	Voriconazole	
Moderate CYP3A inhibitor	Erythromycin, verapamil, diltiazem, dronedarone	Not identified	Doxorubicin
Weak CYP3A inhibitor	Lapatinib, quinidine, cyclosporine, felodipine, azithromycin, ranolazine, ticagrelor, chloroquine, hydroxychloroquine	Cimetidine	Vinblastine
CYP3A inducers			Carbamazepine, phenytoin, phenobarbital, rifampin, dexamethasone, tocilizumab, St. John's Wort

Modified from Kubitza et al. (2016)
CYP Cytochrome P450, *P-gp* P-glycoprotein

and Truitt 2016). Indeed, unlike other direct anti-Xa inhibitors such as rivaroxaban and apixaban, edoxaban is minimally involved in hydrolysis, conjugation, and oxidation through CYP3A4 metabolism (< 4%) and theoretically we could expect fewer DDIs with agents that strongly inhibit or induce cytochrome P450 enzymes, in particular the CYP3A4 variant.

In the following paragraphs, we will summarize the clinical evidence of DDI of DOACs with different classes of drugs and also some tools to predict non-studied DDIs. These predictions are based on the pharmacological profile of DOACs and the profile of the specific class of drugs that are being considered. The issue of how to identify and distinguish the clinically relevant DDIs from non-relevant interactions will also be discussed.

DDI with Antiarrhythmic Drugs

Many classes of cardiovascular drugs might interact with DOACs via inhibition of P-gp and/or CYP3A4, thus leading to increase in exposure and possibly bleeding risk. Many cardiovascular drugs are commonly prescribed with DOACs in patients with AF.

Therefore, it is relevant to verify the possible pharmacological interaction with drugs for the treatment of concomitant cardiovascular diseases, such as antihypertensives and heart failure drugs (Table 4.2). To this end, Frost and collaborators conducted a pharmacokinetic (PK) study with apixaban in the presence and absence of digoxin and atenolol. Only 16% of digoxin is metabolized, while 50–70% is

Table 4.2 Predicted effects of cardiovascular drugs on DOACs exposure

Concomitant Drug		Effect on DOACs concentration			
Cardiovascular drugs	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Amiodarone	Moderate P-gp competition	+12 to 60%	Minor effect	Modest increase of concentrations	+40% AUC
Digoxin	P-gp competition	No effect	No effect	No effect	No effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect	No effect	Increase in AUC (1.4-fold) and Cmax (1.3-fold)	significant effect on AUC predicted
Dronedarone	P-gp inhibitor and CYP3A4 inhibitor	+70 to 100%	Moderate effect, should be avoided	No data: caution	+85% AUC
Quinidine	P-gp competition	+53%	Extent in increase unknown	No PKs data	+77% AUC
Verapamil	P-gp competition and weak CYP3A4 inhibition	+12 to 180%	No effect	No PK data	+53% AUC
Atenolol	P-gp substrate	No PK data	No PK data	AUC and Cmax unchanged	No PK data

AUC area under the curve, *CYP* Cytochrome P450, *P-gp* = P-glycoprotein. *Yellow*: consider dose adjustment or different DOAC if 2 or more "yellow" factors are present. *Orange*: consider dose adjustment or different DOAC. *Red*: contraindicated/not recommended

eliminated unmodified with urine. Digoxin metabolism is also independent of CYP450 and does not appear to induce expression of these enzymes, while it is a substrate of P-gp. Fifty percent of atenolol is eliminated unmodified through feces, and the second half by kidney. Therefore, atenolol is not metabolized by CYP450 and it is a substrate, as well as apixaban, of P-gp. However, beta-blockers may interact with other drugs by reducing liver flow, although this should not affect the clearance of apixaban, being a low hepatic extraction drug. For these reasons, the interaction between apixaban and digoxin or atenolol is considered marginal. As expected, the results of the PK study confirmed this hypothesis by demonstrating the absence of interaction between apixaban and digoxin or atenolol (Frost et al. 2017).

No significant PK changes of dabigatran are observed with digoxin, a P-gp substrate, which also had a negligible impact on dabigatran blood coagulation time, activated partial thromboplastin time (aPTT), and ecarin clotting times (ECT)

(Stangier et al. 2012). Contrary to P-gp substrates, the PK of dabigatran is significantly influenced by the co-administration with P-gp inhibitors. For this reason, dabigatran etexilate should be administered at least 2 h apart from doses of moderate P-gp inhibitors (Hartter et al. 2013a). For instance, dronedarone increases the systemic exposure of dabigatran by 70–100% and verapamil by 12–180% (if taken simultaneously). In the USA, the association with dabigatran and dronedarone is allowed at the dose of 75 mg bid with values of clearance of creatinine between 30 and 50 ml/min. Caution must be exercised with mild-moderate P-gp inhibitors, including amiodarone, quinidine, and verapamil. In healthy subjects, the co-administration of amiodarone increases dabigatran bioavailability by about 50–60%. Since amiodarone has a long half lifetime, the potential for DDIs may persist for weeks after amiodarone discontinuation. Amiodarone increases dabigatran AUC by 12% in patients with non-valvular AF (Liesenfeld et al. 2011). In a recent cohort study, co-administration of amiodarone with dabigatran caused a more significant increase in adjusted rate for major bleeding than with dabigatran alone (Chang et al. 2017).

Multiple doses of dronedarone increase C_{max} and AUC of dabigatran etexilate 150 mg bid by 1.73-fold and twofold, respectively (Gelosa et al. 2018). A single 400 mg dose of dronedarone doubles dabigatran AUC and C_{max}, making the co-administration contraindicated (Gelosa et al. 2018). An increased dabigatran bioavailability is also observed with the co-administration of quinidine. Similar to amiodarone, quinidine increases dabigatran AUC and C_{max} by more than 50% (Steffel et al. 2018a). The exposure to dabigatran, when co-administered with verapamil, depends on the formulation of verapamil and timing of administration. Indeed, exposure to dabigatran is increased when it is administered within 2 h from verapamil, with the greatest increase observed when a single dose of immediate-release verapamil is given 1 h before dabigatran (AUC and C_{max} increase by 143% and 179%, respectively, compared to dabigatran alone). When dabigatran is given 2 h before a double dose of extended-release verapamil, only a slight increase in dabigatran AUC and C_{max} (<20% increase) is observed. As $t_{1/2}$ is not changed, the interaction is most likely related to the absorption of dabigatran, further supporting the notion that DDIs involving P-gp are limited to the gut. Dabigatran does not significantly alter the PK of verapamil (Hartter et al. 2013a).

Digoxin (P-gp substrate with a narrow therapeutic window) co-administration in healthy controls does not affect rivaroxaban PK and pharmacodynamic (PD) (Kubitza et al. 2012). Rivaroxaban does not modify digoxin profile, suggesting that rivaroxaban can be co-administered with digoxin. Rivaroxaban does not induce or inhibit any major CYP isoforms, including CYP3A4, or P-gp/Bcrp transporters.

Mendell et al. reported results from six studies evaluating the potential PK interactions between edoxaban and cardiovascular drugs such as digoxin, atorvastatin, verapamil, quinidine, amiodarone, and dronedarone (Mendell et al. 2013a). The relevance of the inhibition of P-gp on the final exposure of edoxaban was strikingly

demonstrated by comparing the effect of drugs display differing degrees of P-gp inhibition, with verapamil, quinidine, dronedarone, and amiodarone recognized as strong P-gp inhibitors (US Food and Drug Administration 2018), while digoxin and atorvastatin are recognized P-gp substrates (US Food and Drug Administration 2018; Holtzman et al. 2006). Indeed, verapamil, quinidine, dronedarone, and amiodarone increased the AUC of edoxaban by about 50%, while digoxin or atorvastatin had relatively minor effects on the PK of edoxaban (Mendell et al. 2013a). Interestingly, quinidine increases edoxaban exposure by only 35% after intravenous administration, thus significantly less than after oral administration (+77%) (Mendell et al. 2013a) further assessing the effect of P-gp inhibition at gastrointestinal level on the bioavailability of edoxaban (Matsushima et al. 2013).

The potential clinically relevant effect of drug interaction between edoxaban and amiodarone was also investigated by a subgroup analysis of the ENGAGE AF-TIMI 48 trial (Steffel et al. 2015). Amiodarone was associated with significantly increased trough levels of edoxaban 60 mg (High dose, HD). Specifically, the concentrations were 58.5 ± 53.2 ng/mL with amiodarone vs. 43.2 ± 41.1 ng/mL without amiodarone (Steffel et al. 2015). The SmPC does not require reduction of edoxaban dosage with amiodarone concomitant use.

As for quinidine and verapamil, pharmacological data show a total increase in edoxaban exposure of respectively 77% and 53% (Mendell et al. 2013a), but after analysis of phase III data these interactions alone were not considered clinically relevant so no dose reduction is required in the European SmPC, but caution if other factors that might increase edoxaban exposure are present (Steffel et al. 2018a). No action is then recommended with atorvastatin and digoxin (Steffel et al. 2018a) that did not alter edoxaban exposure.

On this regard, it is important to point out that the characterization of edoxaban population PK and the identification of potential intrinsic and extrinsic factors affecting variability in edoxaban exposure, demonstrated that edoxaban exposure in patients with moderate renal impairment receiving strong P-gp inhibitors could potentially increase the AUC and C_{min} exposure up to ~2.5- and threefold of the expected exposure in patients with normal renal function (Salazar et al. 2012). Thus, in the presence of a moderate renal impairment, quinidine and verapamil may significantly increase edoxaban exposure.

DDI with Antiplatelet and Antithrombotic Drugs

Given the common occurrence of coronary artery disease with NVAF, the possible interactions of DOACs with antiplatelet drugs could be clinically relevant (Table 4.3).

Dual antiplatelet therapy with aspirin and $P2Y_{12}$ antagonist is currently recommended after percutaneous coronary intervention (PCI) with stent placement, and further oral anticoagulation is required for patients with NVAF (Steffel et al. 2018a). Therapy with a DOAC, aspirin, and clopidogrel ($P2Y_{12}$ inhibitor) is considered the standard of care for patients with NVAF following coronary stent placement.

Table 4.3 Predicted effects of antiplatelet and antithrombotic drugs on DOAC exposure

Concomitant Drug		Effect on DOACs concentration			
Antiplatelet drugs	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Clopidogrel	No relevant PK interactions known/assumed	+30-40% AUC and C_{max} of dabigatran	No significant effect on AUC predicted; Increase bleeding time	No significant effect on AUC predicted	No significant effect on AUC predicted; Pharmacodynamically increased bleeding time
Ticagrelor	P-gp inhibitor	+25% (give loading dose 2h after dabigatran)	No data	No data	Predicted increased of AUC; Pharmacodynamically increased bleeding time
Aspirin	No relevant effect known/assumed	Pharmacodynamically increased bleeding time			Increased AUC for high doses of aspirin; Pharmacodynamically increased bleeding time
Prasugrel	P-gp substrate	Predicted Pharmacodynamically increased bleeding time			

*Expert opinion, *AUC* area under the curve, *CYP* Cytochrome P450, *P-gp* P-glycoprotein. *Yellow*: consider dose adjustment or different DOAC if 2 or more "yellow" factors are present

However, this triple therapy is associated with three- to fourfold increased risk of bleeding complications (Perera et al. 2020; Steffel et al. 2018a; Lopes et al. 2019).

In detail, no PK or PD interactions were observed when apixaban was co-administered with high-dose aspirin (325 mg once a day) (Gelosa et al. 2018). Similarly, low dose aspirin (100 mg once a day) for 5 days does not influence the PK of edoxaban (60 mg once a day) administered concomitantly (Gelosa et al. 2018). Low dose aspirin (100 mg) did not alter the edoxaban PK parameter, whereas the combination with aspirin 325 mg increased edoxaban systemic exposure by approximately 30% (AUC) and 34% for C_{max} (Mendell et al. 2013b). The reason for increased exposure with high-dose aspirin is not clear and unknown, but high-dose aspirin did not alter the effect of edoxaban on the coagulation biomarkers and the inhibition of platelet aggregation (arachidonic acid induced) by aspirin was not affected by edoxaban (Mendell et al. 2013b). Nevertheless, the administration of edoxaban with aspirin 100 mg (low dose), or aspirin 325 mg (high dose) resulted in an approximately additive effect of the agents administered alone with a final two-fold increase in bleeding time, thus suggesting a potential PD interaction between the two drugs (Mendell et al. 2013b).

Rivaroxaban does not alter the effect of aspirin on platelet aggregation and aspirin does not alter the effects of rivaroxaban on clotting parameters (inhibition of fXa activity, prolongation of prothrombin time, aPTT, and HepTest) (Kubitza et al. 2006). However, in patients treated with rivaroxaban for acute VTE, the risk of clinically relevant bleeding (such as that requiring medical intervention) is increased in those also taking aspirin, compared with those not taking aspirin (hazard ratio 1.8) (Davidson et al. 2014).

Edoxaban exhibited similar relative efficacy and reduced bleeding compared to warfarin, with or without concomitant use of antiplatelet therapies, including clopidogrel and ticagrelor (Xu et al. 2016). Nevertheless, a potential PD interaction with increasing risk of major bleeding is predictable in patients treated with DOACs under mono or dual antiplatelet therapy. Indeed, some of these drugs are substrates (clopidogrel, enoxaparin), or inhibitors (ticagrelor, naproxen) of P-gp (Wessler et al. 2013; Oh et al. 2014; Marsousi et al. 2016), suggesting a possible PK interaction with DOACs.

Concomitant antiplatelet drugs (aspirin or clopidogrel) appear to increase the risk for major bleeding of dabigatran. This is most likely a PD interaction, indeed the concomitant administration of dabigatran etexilate (150 mg twice daily) and clopidogrel (75 mg once daily) in healthy controls did not influence PK and PD profiles of either agent. However, a single loading dose (300 mg or 600 mg) of clopidogrel administered concomitantly with dabigatran etexilate (150 mg twice daily) increased dabigatran AUC and C_{max} by 30–40% (Hartter et al. 2013b).

The interaction between ticagrelor and dabigatran has been observed showing a significant higher exposure of dabigatran when administered simultaneously to ticagrelor, with an increase of AUC and C_{max} by 48.3% and 62.7%, respectively (Medicines 2015). This interaction was less evident when ticagrelor was administered 2 h after morning dose of dabigatran with an increase of AUC and C_{max} of 28.8% and 24.1%, respectively. From this evidence, SmPC is indicated to follow this staggered intake for starting a loading dose of ticagrelor (Medicines 2015). We could predict a similar behavior also for the other DOACs.

Apixaban co-administered with prasugrel (60 mg followed by 10 mg once daily) does not increase bleeding time or further inhibit platelet aggregation (Steffel et al. 2018a).

DDI with NSAIDs Drugs

Patients with NVAF tend to be elderly and to have other inflammatory disorders, which may require the use of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs increase bleeding risk with DOACs due to a pharmacodynamics interaction and the chronic use is not permitted by the respective SmPCs.

Mendell et al. conducted a PK study to assess the potential PK/PD interactions between edoxaban and the NSAID naproxen (Mendell et al. 2013b). Naproxen undergoes to an extensive metabolism through the CYP1A2 and CYP2C9, therefore, the likelihood of PK interaction with edoxaban is minimal, although, a PD

Table 4.4 Predicted effects of NSAIDs drugs on DOAC exposure

Concomitant Drug		Effect on DOACs concentration			
NSAIDs	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Naproxen	P-gp competition; CYP1A2 and CYP2C9 inhibition	No data	No data	+55%	No effect

AUC area under the curve, *CYP* Cytochrome P450, *P-gp* P-glycoprotein. *Yellow*: consider dose adjustment or different DOAC if 2 or more "yellow" factors are present

interaction is likely. Indeed, no significant effect of naproxen was observed in systemic exposure to edoxaban (AUC and C_{max}), whereas it was shown an additive effect on bleeding time (Table 4.4) (Mendell et al. 2013b). Interestingly, naproxen has shown to increase apixaban exposure by more than 50%, an effect potentially related to the inhibition of the intestinal efflux transporter P-gp (Frost et al. 2014). Naproxen use has not been studied with other DOACs (Steffel et al. 2018a). For the acute concomitant use of naproxen, edoxaban could constitute a reasonable choice for a concomitant anticoagulant.

DDI with Statins and Lipid-Modifying Agents

Considering the high rate of CVD in the elderly, especially CHD in concomitance with NVAF, it is quite common the co-administration of a lipid-modifying agent and DOACs. Several statins interact with P-gp and CYP450 (Gelosa et al. 2018). For example, atorvastatin, lovastatin, and simvastatin inhibit or compete with P-gp mediated drug transport and are metabolized by CYP3A4. These characteristics might lead to an increased absorption of DOACs. Lovastatin is a CYP2C9- and P-gp inhibitor. In a population-based, nested case-control study involving 45,991 Ontario residents who started dabigatran, the use of lovastatin was associated with a higher risk of major hemorrhage. Similar effect can also be predicted for other DOACs.

Simvastatin and lovastatin are associated with a higher risk of major hemorrhage (compared to other statins) in patients with NVAF and receiving dabigatran. Relevantly, the adjusted incidence rate for major bleeding was significantly lower for concurrent use of atorvastatin with dabigatran than dabigatran alone.

Table 4.5 Predicted effects of lipid-lowering drugs on DOAC exposure

Concomitant Drug		Effect on DOACs concentration			
Lipid-lowering drug	Effect on P-gp and CYP	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Atorvastatin	P-gp substrate	No PK interaction	No effect	No data	+1.7% AUC −14.2% C_{max}
Simvastatin lovastatin	P-gp moderate inhibitors; CYP3A4 substrate;	Possible increased exposure	No data	Minor effect on AUC predicted	Minor effect on AUC predicted
Fluvastatin	CYP2C9 substrate	No significant effect on AUC predicted			
Fenofibrate	P-gp inhibitor	Minor effect on AUC predicted			
Gemfibrozil	CYP2C8 inhibitor	No significant effect on AUC predicted			
Ezetimibe	None	No data, no significant effect on AUC predicted			
PCSK9 inhibitors	None	No data, no significant effect on AUC predicted			

AUC area under the curve, *CYP* Cytochrome P450, *P-gp* P-glycoprotein

Co-administration of atorvastatin in healthy controls do not affect rivaroxaban PK and PD and rivaroxaban does not modify atorvastatin profile. Similarly, the PK of edoxaban is not affected by atorvastatin. Indeed, atorvastatin induces a non-significant increase of 1.7% in edoxaban AUC and a decrease by 14.2% in C_{max} (Table 4.5) (Mendell et al. 2013a). Other statins have limited involvement in the CYP3A4 metabolism such as pravastatin and rosuvastatin, while fluvastatin is metabolized by CYP2C9. In this respect pravastatin, fluvastatin, and rosuvastatin seem to be safer alternatives when administered concomitantly with other drugs that are known CYP3A4 or P-gp substrates and/or inhibitors such as DOACs.

Other commonly used lipid-lowering agents that might interact with DOAC metabolism are fibrates. The only fibric acid that showed moderate P-gp inhibition in vitro is fenofibrate (Yamazaki et al. 2005). Thus, the only fibrate that might alter DOACs exposure is fenofibrate, because of the possible inhibition on the P-gp transporter, although this interaction may be not clinically relevant.

Another cholesterol-lowering agent that can be used alone or in combination with statins is ezetimibe. Ezetimibe does not induce or inhibit CYP3A4 or P-gp, interactions with DOACs seem to be improbable.

Finally considering PCSK9 inhibitor evolocumab and alirocumab, no CYP and P-gp involvement is expected as its metabolism and elimination follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids, thus no interactions are predicted with edoxaban or other DOACs.

DDI with Antibiotics and Antifungal Drugs

It is well established that antibiotic and fungostatic medications have strong interference with VKAs, but these drugs may also alter DOACs plasmatic concentrations by interfering with the P-gp pathway and with the CYP3A4 metabolism (Table 4.6).

Given that some antibiotics and antifungal drugs such as erythromycin, clarithromycin, rifampin, ketoconazole, fluconazole, and posaconazole have moderate-to-strong inhibition or induction of this pathways, patients treated with DOACs and certain concomitant antibiotic treatments should require accurate evaluation and an eventual dose adjustment.

Table 4.6 Predicted effects of antibiotics and antifungal drugs on DOACs exposure

Concomitant Drug		**Effect on DOACs concentration**			
Antibiotics	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Erythromycin	P-gp subtrate; CYP3A4 inhibition	+15 to 20% AUC	+34% AUC	+60% AUC +30% C_{max}	+85% AUC
Clarithromycin	P-gp subtrate; CYP3A4 inhibition	+15 to 20% AUC	+54% AUC	+60% AUC +30% C_{max}	Predicted increase of AUC
Rifampin	P-gp/ BCRP and CYP3A4/ CYP2J2 inducers	-66% AUC	-50% AUC	-54% AUC	AUC: -35%, compensatory increase of active metabolites
Metronidazole	CYP3A4 inhibitor	No significant effect on AUC predicted			
Levofloxacin, ciprofloxacin	CYP1A2 inhibitor	No significant effect on AUC predicted			
Antifungal	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Fluconazole	Moderate CYP3A4 inhibition	No data	+42% AUC	No data	No data
Ketoconazole, itraconazole, voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% AUC	Up to 160% AUC	+100% AUC	+87 to 95% AUC

AUC area under the curve, *BCRP* breast cancer resistance protein, *CYP* Cytochrome P450, *P-gp* P-glycoprotein. *Yellow*: consider dose adjustment or different DOAC if 2 or more "yellow" factors are present. *Orange*: consider dose adjustment or different DOAC. *Red*: contraindicated/not recommended. *Blue*: the label for edoxaban mentions that co-administration is possible in these cases, despite a decreased plasma level, which are deemed not clinically relevant. Since not tested prospectively, however, such concomitant use should be used with caution, and avoided when possible

Among the different classes of antibiotics, the macrolides, such as clarithromycin and erythromycin, are the best-known P-gp inhibitors which moderately reduce CYP3A4 activity. Macrolide antibiotics have been associated with increased exposure of DOACs.

A slight increase of dabigatran AUC and C_{max} by about 19% and 15%, respectively, is induced by clarithromycin 500 mg bid (Steffel et al. 2018b). The co-administration of rivaroxaban 10 mg in combination with ketoconazole 200 mg once daily significantly increases rivaroxaban AUC and mean Cmax by 82% and 53%, respectively (Mueck et al. 2013). Rivaroxaban clearance is also significantly reduced by a mean of 45% with the combination. Erythromycin and clarithromycin do not have any significant interactions with rivaroxaban, while clarithromycin has a moderate interaction with rivaroxaban (rivaroxaban AUC and C_{max} increase by 54% and 40%) (Mueck et al. 2013). The addition of rivaroxaban 10 mg to erythromycin (500 mg three times daily given for 4 days) significantly increases rivaroxaban AUC and C_{max} (34% and 38%, respectively) and decreases rivaroxaban CL/F by 25% compared with rivaroxaban alone (Mueck et al. 2013). However, these changes are similar to the inter-individual variability observed in patients treated with rivaroxaban and are not considered to be clinically relevant.

The administration of rivaroxaban 20 mg to fluconazole 400 mg (given for 4 days) significantly increases rivaroxaban AUC and C_{max} by 42% and 28%, respectively (Mueck et al. 2013). Concurrent use of fluconazole with rivaroxaban was associated with increased risk of major bleeding.

Everything considered, the available data suggest that the co-administration of rivaroxaban is acceptable with CYP3A4 and/or P-gp substrates/moderate inhibitors, but not with strong combined CYP3A4, P-gp, and ABCG2 inhibitors (azole-antimycotics, apart from fluconazole), which inhibit different pathways involved in rivaroxaban clearance and elimination. An increase by 60% and 30% of AUC and C_{max} of apixaban, respectively, is induced by co-administration of clarithromycin or erythromycin (Steffel et al. 2018b).

The entity of the DDI between edoxaban and erythromycin has been investigated in a PK study on healthy subjects (Parasrampuria et al. 2016). Erythromycin decreased the total apparent clearance of edoxaban by about 47%, which translated to a significant increase in both peak (+68%) and total exposure (+85%) of edoxaban. Similarly, the peak and total exposure of M4 were approximately 75% and 78% higher, respectively, when administered with erythromycin, with no change in the formation of M4 metabolite (Parasrampuria et al. 2016). Given the decreases in both apparent clearance and volume of distribution, these data suggest that bioavailability increased, owing to inhibition of P-gp in the gut by erythromycin (Parasrampuria et al. 2016). This pharmacological interaction is considered clinically relevant and the EHRA indicated dose adjustment (Steffel et al. 2018a), in line with the SmPC.

Open-label, randomized, two-period, two-treatment crossover study in healthy subjects under co-treatment with ketoconazole and edoxaban has tested a possible interaction between these two drugs (Parasrampuria et al. 2016). As predicted, ketoconazole increased total exposure of edoxaban by approximately 90%. Exposure to

the metabolite M4 was higher when edoxaban was co-administered with ketoconazole, with approximately 46% higher total exposures, potentially due to increased bioavailability without a significant alteration of its formation mediated by carboxylesterase 1 (CES-1). On the contrary, both peak and total exposure to the metabolite M6, derived from the CYP3A4 activity, was decreased by 51% and 43%, respectively (Parasrampuria et al. 2016). The inhibitory effect of ketoconazole on CYP3A4 is also demonstrated by the fact that the metabolite-to-parent drug ratio was decreased from 4.44 to 1.45 (Parasrampuria et al. 2016). From this analysis, it is indicated to reduce the dose of edoxaban by 50% in case of a co-administration with antifungals (itraconazole, ketoconazole, and voriconazole) (Steffel et al. 2018a). Similar indication has been decided for posaconazole, whereas fluconazole is not expected to interact with edoxaban (Steffel et al. 2018a). While other DOACs are contraindicated in this eventuality, edoxaban can be used in concomitance reducing the dosage to 30 mg due to increased exposure (Steffel et al. 2018a; Parasrampuria et al. 2016).

Metronidazole is known for having a major interaction with VKAs and dose reductions are often necessary to maintain INR in range. There are not any direct evidences with DOACs but metronidazole has been reported to increase plasma concentration and toxicities in a number of CYP3A4 substrates (Hashikata et al. 2015). It has been suggested that metronidazole, among other drugs, is a CYP3A4 inhibitor and concomitant administrations of certain CYP3A4 substrates should be avoided. On the contrary, a pharmacokinetics study provides evidence that metronidazole does not act as an inhibitor of P-gp-mediated disposition in humans. Given that probably CYP3A4 may account for the major part of metronidazole interactions, we expect that a major DDI between DOACs and metronidazole is unlikely; nonetheless, caution and a careful monitoring of the patient should be applied in this situation.

Rifampin is one of the most potent inducers of CYP3A4/5 and P-gp. Concomitant use of rifampin may lead to a decrease in edoxaban and DOACs exposure due to induction of P-gp and CYP3A4/CYP2J2. The effect of rifampin on edoxaban exposure has been evaluated in a specific pharmacokinetic study of multiple doses of the antibiotics on a single dose of edoxaban and its active metabolites M4 and M6 (Mendell et al. 2015). Rifampin determined an approximate 34% decrease in total exposure to edoxaban (AUC), when compared with administration of edoxaban alone, and unlike other DOACs, a concomitant compensatory five- and fourfold increase of C_{max} values of metabolites M4 and M6, respectively (Mendell et al. 2015). These results suggest that the effect of rifampin on edoxaban was not only to reduce oral bioavailability and increase excretion through potential induction of P-gp, but also to increase its metabolism to form the metabolite M6 through CYP3A4/5. The increase in M4 is likely due to the inhibitory effect of rifampin on OATP1B1 (Vavricka et al. 2002), which is involved in the transport of the active metabolite, as well as potential induction of CES-1 through upregulation. These results demonstrate a drug interaction of edoxaban and its metabolites with rifampin. However, the compensatory increase of the active metabolite M4 led to the suggestion that the co-administration of the two drugs is possible (LIXIANA 2018). Edoxaban is the only DOAC that can be used with rifampicin. Nevertheless, since

not tested prospectively, the EHRA indicated that this combination should be used with caution, and avoided when possible (Steffel et al. 2018a). Apart from edoxaban, other DOACs are contraindicated with rifampin.

Considering quinolones pharmacokinetics, levofloxacin is a CYP1A2 inhibitor while ciprofloxacin is a strong inhibitor of CYP1A2 (Di Minno et al. 2017). Considering that NOACs are minimally involved in CYP1A2, no relevant interactions are predicted. Carbapenem antibiotics such as meropenem are administered intravenously and are not predicted to have inhibitory or induction activity on intestinal P-gp. In vitro assessments have reported an inhibitory effect on CYP3A4 and CYP2C19 enzymes (Branchetti et al. 2013). On this premise, it can be predicted that edoxaban levels should not be significantly altered by the presence of carbapenem antibiotics.

DDI with Antacid Drugs

The prevalence of gastro-esophageal reflux disease is significant worldwide and evidence indicate, especially in the western countries, an increase in its incidence (El-Serag et al. 2014). This suggests that an increasingly higher portion of the population is using antacid medication.

Theoretically, antacid medications are not devoid of risk of DDI with DOACs. Especially considering gastric acidity might play a role in DOAC absorption. From a pharmacological point of view, a small reduction of dabigatran bioavailability has been observed with concomitant proton-pump inhibitors (PPIs) or H2-blockers, while no effect has been observed with other DOACs (Steffel et al. 2018a). The administration of pantoprazole 40 mg bid decreases by 20–30% and by 45% dabigatran AUC and C_{max}, respectively, suggesting that an elevated gastric pH may influence dabigatran oral absorption. Due to dabigatran flat dose-response curve, this reduction in the dabigatran plasma concentration was not considered clinically relevant (Steffel et al. 2018a). In NVAF patients, PPIs decrease dabigatran AUC by 12.5%. Ranitidine treatment showed no clinically relevant effects on dabigatran absorption.

PPIs can also have an influence on cytochrome P450 metabolism, especially CYP2C19 and some PPIs like omeprazole and pantoprazole can also have an inhibitory influence on P-gp. In a pharmacological study, esomeprazole was shown to have no significant effect on the peak and total exposure of edoxaban during concurrent dosing (Parasrampuria and Truitt 2016). Aluminum-magnesium hydroxide tablets have no influence on P-gp or CYP isoenzymes, but they might alter the absorption of drugs that are concomitantly administered if taken within 1 h.

DDI with Antineoplastic and Immune-Modulating Agents

Cancer patients are at higher risk for thromboembolic events due to the presence of comorbidities, surgical interventions, and chemotherapy. Data on the use of DOACs

in cancer patients is very limited and few clinical information is available when considering the effect that specific antineoplastic drugs might have on DOAC exposure. However, the results of the Hokusai VTE Cancer and Caravaggio trials clearly demonstrated that treatment with edoxaban or apixaban is not inferior to treatment with subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding in patients predominantly with advanced cancer and acute symptomatic or incidental venous thromboembolism (Raskob et al. 2018; Agnelli et al. 2018).

Patients treated with edoxaban and apixaban were exposed to many different classes of anticancer drugs, such as antimetabolites, platinum-based chemotherapy, c, topoisomerase inhibitors, alkylating agents, anthracyclines, vinca alkaloids, kinase inhibitors, and antitumor antibiotics. These agents might have significant influence on CYP3A4 and/or P-gp metabolism, thus altering DOAC exposure.

Although there are no pharmacokinetic and clinical studies assessing the interaction between DOACs and specific anticancer agents, it is possible to predict a critical outcome for those with a well-defined effect on P-gp and CYP3A4 (Table 4.7). In particular, the vinca alkaloid vinblastine, the antitumor antibiotic doxorubicin, and the kinase inhibitors vandetanib and sunitinib are strong inducers of P-gp, and for this reason their combination with edoxaban, as well as all DOACs should be avoided (Steffel et al. 2018a). In addition, the Bruton's tyrosine kinase ibrutinib significantly increases risk of NVAF, with an estimated cumulative incidence of 5.9% at 6 months and increasing to 10.3% by 2 years of treatment. The management of NVAF induced by ibrutinib is complicated by the fact that this drug is also a P-gp inhibitor, thereby increasing exposure to substrates such as DOACs.

Similar situation can be envisioned for other chemotherapeutic drugs inducing NVAF, such as alkylating agents (e.g., cisplatin, melphalan, and cyclophosphamide (CTX)), anthracycline agents (e.g., doxorubicin), and cancer targeted therapies (e.g., sorafenib and sunitinib).

DDI with Antiepileptic Drugs

Seizures are seen in up to 10% patients after stroke and previous stroke and accounts for 30–40% of all cases of epilepsy in the elderly. Most of these patients require long-term antiepileptic drug treatment. Furthermore, the same drugs are also prescribed for neuropathic pain, migraine, headaches, or psychiatric disorders. Thus, it is conceivable to conclude that a considerable number of patients under treatment with DOACs would be on concomitant therapy with antiepileptic drugs (Table 4.8).

Few clinical evidences exist regarding interactions between antiepileptic drugs and DOACs. There are evidences that a number of these drugs induce CYP3A4 and P-gp leading to reduced DOAC exposure.

Human, animals, and in vitro evidence have demonstrated that carbamazepine, levetiracetam, phenobarbital, and phenytoin are potent inducers of P-gp, and therefore may lead to reduced DOACs plasma concentrations and clinical efficacy.
According to the EHRA practical guide, the use of carbamazepine, phenobarbital,

Table 4.7 Predicted effects of antineoplastic drugs on DOACs exposure

Concomitant Drug		**Effect on DOACs concentration**			
Antimitotic agents	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competition	No significant effect on AUC predicted			
Vinblastine	Strong P-gp induction; CYP3A4/P-gp competition	Significant decrease in AUC predicted			
Docetaxel, Vncristine	Mild CYP3A4 induction; CYP3A4/P-gp compeitiont	No significant effect on AUC predicted			
Vinorelbine	Mild CYP3A4 induction; CYP3A4/P-gp competition	No significant effect on AUC predicted			
Antimetabolites	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Metotrexate	P-gp compeittion; no relevant interaction anticipated	No significant effect on AUC predicted			
Pemetrexed, Purine analogs, Pyrimidine analogs	No relevant interaction anticipated	No significant effect on AUC predicted			
Topoisomerase inhibitors	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Topotecan	No relevant interaction anticipated	No significant effect on AUC predicted			
Irinotecan	CYP3A4/P-gp competition; no relevant interaction anticipated	No significant effect on AUC predicted			
Etoposide	Mild CYP3A4 induction; CYP3A4/P-gp compeittion	No significant effect on AUC predicted			
Anthracyclines/ Anthraceneidones	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Doxorubicin	Strong P-gp induction; Mild CYP3A4 inhibition; CYP3A4/P-gp compeittion	Significant decrease in AUC predicted			
Idarubicin	Mild CYP3A4 inhibition; P-compeittion	No significant effect on AUC predicted			
Daunorubicin	P-gp compeittion; no relevant interaction anticipated	No significant effect on AUC predicted			
Mitoxantrone	no relevant interaction anticipated	No significant effect on AUC predicted			
Alkylating agents	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**

Table 4.7 (continued)

Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition	No significant effect on AUC predicted			
Ciclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competition	No significant effect on AUC predicted			
Lomustine	Mild CYP3A4 inhibition;	No significant effect on AUC predicted			
Busulfan	CYP3A4 competition; No relevant interactions anticipated	No significant effect on AUC predicted			
Bendamustine	P-gp competition; no relevant interaction anticipated	No significant effect on AUC predicted			
Chlorambucil, Melphalan, Carmustine, Procarbazine, Dacarbazine, Temozolomide	No relevant effect anticipated	No significant effect on AUC predicted			
Platinum-based agents	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Cisplatin, Carboplatin, Oxaliplatin	No relevant effect anticipated	No significant effect on AUC predicted			
Intercalating agents	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Bleomycin, Dactinomycin	No relevant effect anticipated	No significant effect on AUC predicted			
Mitomycin C	No relevant interaction anticipated	No significant effect on AUC predicted			
Tyrosine kinase inhibitors	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Imatinib, Crizotinib	Strong P-gp inhibition; Moderate CYP3A4 inhibition; CYP3A4/P-gp competition	Significant increase in AUC predicted			
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition; mild CYP3A4 inhibition; CYP3A4/P-gp competition	Possible increase in AUC predicted			
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition	No significant effect on AUC predicted			
Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competition	No significant effect on AUC predicted			
Vandetanib, Sunitinib	Strong P-gp inhibitor; CYP3A4 competition	Significant increase in AUC predicted			
Erlotinib, Gefatinib	CYP3A4 competition no relevant interaction anticipated	No significant effect on AUC predicted			

(continued)

Table 4.7 (continued)

Ibrutinib	P-gp inhibitor; CYP3A4 competition	Possible increase in AUC predicted			
Monoclonal antibodies	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Brentuximab	CYP3A4 competition; No relevant interactions anticipated	No significant effect on AUC predicted			
Rituximab, Alemtuzumab, Cetuximab, Trastuzumab, Bevacizumab	No relevanteffect assumed	No significant effect on AUC predicted			
Hormonal agents	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Abiraterone	Moderate CYP3A4 inhibition; Strong P-gp inhibition; CYP3A4/P-gp competition	Significantincrease in AUC predicted			
Enzalutamide	Strong CYP3A4 induction; Strong P-gp inhibition; CYP3A4/P-gp competition	Significant increase in AUC predicted			
Bicalutamide	Moderate CYP3A4 inhibition	No significant effect on AUC predicted			
Tamoxifen	Strong P-gp inhibition; Mild CYP3A4 inhibition CYP3A4 competition	Possible increase in AUC predicted			
Anastrozole	Mild CYP3A4 inhibition	No significant effect on AUC predicted			
Flutamide	CYP3A4 competition No relevant interactions anticipated	No significant effect on AUC predicted			
Letrozole, Fulvestrant	CYP3A4 competition No relevant interactions anticipated	No significant effect on AUC predicted			
Raloxifene, Leuprolide, Mitotane	No relevant interactions anticipated	No significant effect on AUC predicted			
Immune-modulating agents-	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Cyclosporine	Strong to moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	Strong increase of AUC predicted	Possible increasein AUC predicted	Possible increase in AUC predicted	+73% AUC

Table 4.7 (continued)

Dexamethasone	Strong CYP3A4/P-gp induction; CYP3A4/P-gp competition	Significant decrease in AUC predicted
Tacrolimus	Strong to moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	Significant increase in AUC predicted
Prednisone	Moderate CYP3A4 induction; CYP3A4 competition	No significant effect on AUC predicted
Temsirolimus, Sirolimus	mild CYP3A4 inhibition; CYP3A4/P-gp competition	No significant effect on AUC predicted
Everolimus	CYP3A4 competition; No relevant interactions anticipated	No significant effect on AUC predicted

AUC area under the curve, *CYP* Cytochrome P450, *P-gp* P-glycoprotein. *Yellow*: consider dose adjustment or different DOAC if 2 or more "yellow" factors are present. *Orange*: consider dose adjustment or different DOAC. *Red*: contraindicated/not recommended

and phenytoin is only possible with edoxaban and apixaban. In this case, the concomitant use should be made with caution if cannot be avoided, because there still is a decreased absorption that might lead to minor efficacy of these DOACs (Steffel et al. 2018a).

A more stringent indication was deserved for valproic acid and levetiracetam, whose co-administration with DOACs is contraindicated (Steffel et al. 2018a), probably due to their more potent effect on P-gp. However, additional data reported that levetiracetam does not induce P-gp and thus can be utilized with DOACs (Mathy et al. 2019). On the contrary, other antiepileptic drugs, that do not affect P-gp function, such as ethosuximide, gabapentin, lamotrigine, pregabalin, and zonisamide, are not predicted to interact with DOACs (Steffel et al. 2018a). Finally, the use of oxcarbazepine and topiramate is possible without relevant DDIs only with edoxaban and dabigatran due to absence of CYP3A4 metabolism. Unfortunately, the clinical relevance of these drug interactions is largely unknown since mainly data from in vitro and animal studies are available.

Although all DOACs are considered to interact with P-gp inducers (Steffel et al. 2018a), the influence of these drugs on edoxaban can be considered less problematic due to the compensatory increase of the active metabolite M4. In addition, the inter-individual variability of drug plasma concentrations, lower for apixaban and edoxaban and higher for rivaroxaban and dabigatran, is a determining factor for triggering a clinically significant DDIs. Indeed, in the EHRA guidelines, differently from dabigatran and rivaroxaban, the use of carbamazepine, phenobarbital, and phenytoin is not contraindicated with edoxaban and apixaban (Steffel et al. 2018a). It can be hypothesized that antiepileptic drugs that do not have an effect on CYP3A4 and P-gp, such as ethosuximide, gabapentin, lamotrigine, pregabalin, and zonisamide can be used with all DOACs without relevant pharmacological interaction (Mathy et al. 2019).

Table 4.8 Predicted effects of antiepileptic drugs on DOACs exposure

Concomitant Drug		Effect on DOACs concentration			
Antiepileptic drugs	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	Strong reduction of AUC	Strong reduction of AUC	-50% AUC	-35% AUC
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed	No significant effect on AUC predicted			
Gabapentin	No relevant interactions known/assumed	No significant effect on AUC predicted			
Lamotrigine	P-gp competition; No relevant interaction known/assumed	No significant effect on AUC predicted			
Levetiracetam	P-gp induction; P-gp competition	No significant effect on AUC predicted			
Oxcarbazepine	CYP3A4 induction; P-gp competition	No significant effect on AUC predicted			
Phenobarbital	Strong CYP3A4/P-gp induction; P-gp competition	Decrease in AUC	Decrease in AUC	Decrease in AUC	Decrease in AUC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	Decrease in AUC	Decrease in AUC	Decrease in AUC	Decrease in AUC
Pregabalin	No relevant interactions known/assumed	No significant effect on AUC predicted			
Topiramate	CYP3A4 induction; CYP3A4 competition	No significant effect on AUC predicted			

Table 4.8 (continued)

Valproic acid	CYP3A4/P-gp induction	Significant decrease in AUC predicted
Zonisamide	CYP3A4 competition; No relevant interactions known/assumed	No significant effect on AUC predicted

AUC area under the curve, *CYP* Cytochrome P450, *P-gp* P-glycoprotein. *Orange*: use with caution or avoid. *Red*: contraindicated/not recommended

DDIs with Anti-Human Immunodeficiency (HIV) and Anti-Hepatitis C Virus (HCV) Drugs

Several combinations of agents belonging to at least two drug families are recommended for treating HIV. Integrase inhibitors (e.g., dolutegravir or raltegravir) and non-nucleoside analog polymerase inhibitors (e.g., rilpivirine) are currently the preferred third agents used along with a two nucleos(t)ide analog backbone, either abacavir/lamivudine or tenofovir/emtricitabine. The use of HIV protease inhibitors has progressively been deferred, due to increased potential for DDI and metabolic complications. Darunavir boosted with ritonavir or cobicistat is the only protease inhibitor still recommended as first-line HIV therapy. With the exception of tipranavir, all HIV protease inhibitors are inhibitors of CYP3A4, with ritonavir being the most potent and saquinavir is the least. Ritonavir is also a strong P-gp inhibitor interfering with many drugs, and it may be expected to increase edoxaban exposure. Therefore, its co-administration with DOACs is not recommended (Steffel et al. 2018a) (Table 4.9). Similarly, the pharmacoenhancer cobicistat, in addition to be a potent inhibitor of cytochrome CYP3A4, also inhibits P-gp and BCRP transporters, and it is predicted to increase DOACs bioavailability.

Among the HCV protease inhibitor, simeprevir is a substrate and inhibitor of CYP3A4 and P-gp enzymes and through this action may increase the exposure of substrates for P-gp, such as edoxaban (Table 4.10). Paritaprevir is an HCV protease inhibitor that is boosted with ritonavir and thus this combination is predicted to increase the exposure of edoxaban. Grazoprevir is not a P-gp inhibitor based on in vitro data, and thus it is not expected to interact with edoxaban.

Nonstructural protein 5AB (NS5B) polymerase inhibitors, sofosbuvir depicts an excellent pharmacokinetic profile, without significant interactions with other drugs because its metabolism does not involve the CYP450 pathway although it is a P-gp substrate.

Daclatasvir was the first-in-class developed HCV nonstructural protein 5A (NS5A) replication complex inhibitor. Daclatasvir is a substrate for CYP3A4 and P-gp and moderately inhibits P-gp and OATP1B1. Its interaction with DOACs has not been evaluated; however, daclatasvir increases rosuvastatin exposure, thus

Table 4.9 Predicted effects of anti-HIV therapies on DOACs exposure

Concomitant Drug		Effect on DOACs concentration			
Anti-HIV	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
DTG + ABC/TDF + 3TC	No inhibition	No significant effect predicted			
DTG + TDF/TAF + FTC	No inhibition	No significant effect predicted			
RAL + TDF/TAF + FTC	No inhibition	No significant effect predicted			
EVGc + TAF/TDF + FTC	Cobicistat is a potent CYP3A4 and P-gp inhibitor	Possible increased exposure			
DRVc + ABC + 3TC	Cobicistat is a potent CYP3A4 and P-gp inhibitor and d arunavir is a CYP3A4 inhibition	Possible increased exposure			
DRVc + TDF/TAF + FTC	Cobicistat is a potent CYP3A4 and P-gp inhibitor and d arunavir is a CYP3A4 inhibition	Possible increased exposure			
ATVc +TDF/TAF + FTC	Cobicistat is a potent CYP3A4 and P-gp inhibitor	Possible increased exposure			
DRVr + TDF/TAF + FTC	Ritonavir is a potent CYP3A4 and P-gp inhibitor	Possible increased exposure			
DRVr + ABC + 3TC	Ritonavir is a potent CYP3A4 and P-gp inhibitor	Possible increased exposure			
EFV + TDF/TAF + FTC	Inhibition of CYP3A4 and P-gp	Possibleincreased exposure			

Table 4.9 (continued)

RPV + TDF/TAF + FTC	Inhibition of CYP3A4 and P-gp	Possible increased exposure
AZT + 3TC + EFV	Inhibition of CYP3A4 and P-gp	Possible increased exposure
TDF + 3TC/FTC + EFV	Inhibition of CYP3A4 and P-gp	Possible increased exposure
TDF + 3TC/FTC + NVP	Inhibition of CYP3A4 and P-gp	Possible increased exposure

3TC lamivudine, *ABC* abacavir, *ATVc* atazanavir + cobicistat, *CYP* Cytochrome P450, *DRVc* darunavir + cobicistat, *DRVr* darunavir + ritonavir, *DTG* dolutegravir, *EFV* efavirenz, *EVG* elvitegravir, *FTC* emtricitabine, *P-gp* P-glycoprotein, *RAL* raltegravir, *RPV* rilpivirine, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate. *Yellow*: consider dose adjustment or different DOAC if 2 or more "yellow" factors are present. Modified from West et al. (2017)

Table 4.10 Predicted effects of anti-HCV drugs on DOACs exposure

Concomitant Drug		**Effect on DOACs concentration**			
Anti-HCV	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Simeprevir	Substrate and inhibitor of CYP3A4 and P-gp	Possible increase in AUC predicted			
Grazoprevir	No relevant interactions predicted	No significant effect on AUC predicted			
NS5B polymerase inhibitors	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Sofosbuvir	P-gp substrate	No significant effect on AUC predicted			
Ledipasvir	P-gp/BCRP substrate and inhibitor	Possible increase in AUC predicted			
NS5A replication complex inhibitor	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Daclatasvir	CYP3A4 and P-gp substrate, P-gp and OATP1B1 moderate inhibition	Possible increase in AUC predicted			

*Expert opinion, *AUC* area under the curve, *BCRP* breast cancer resistance protein, *CYP* Cytochrome P450, *P-gp* P-glycoprotein. *Yellow*: consider dose adjustment or different DOAC if 2 or more "yellow" factors are present

similar effect with the OATP and/or BCRP substrates are predicted. Similar effect has been observed with ledipasvir, a substrate and inhibitor of P-gp/BCRP.

DDIs with Monoclonal Antibodies and Interleukin 6 (IL6)

The clearance of therapeutic monoclonal antibodies (mAbs) typically does not involve CYP450-mediated metabolism or interaction with P-gp, therefore their pharmacokinetic interactions with small molecule drugs are limited (Ferri et al. 2016). However, mAbs directed against circulating cytokines, such as interleukin (IL)-6, IL-1β, or TNF-α, for the treatment of immunologic disorders like rheumatoid arthritis, celiac disease, and Crohn's disease may have a significant impact on drug metabolism. Specific studies have, indeed, demonstrated that IL-6 reduces the CYP3A4, 2B6, and 2C8 mRNA expression. Even more relevant for DOAC disposition, is the observation that IL-6-treated mice displayed a 70% reduction in protein expression of all P-gp isoforms.

On these bases, it is possible that tocilizumab, a monoclonal antibody anti IL-6, may induce P-gp and reduce DOAC intestinal absorption. A case report of possible DDI between tocilizumab and dabigatran has been described. The authors claim that the co-administration of tocilizumab with dabigatran had induced a progressively decreased anticoagulant effect of dabigatran, favoring mesenteric arterial thrombosis. A possible interaction can also be predicted for the other DOACs.

Similar effect can be hypothesized with the monoclonal antibody dupilumab that inhibits IL-4 and IL-13 signaling. An open-label drug–drug interaction study was performed to assess whether a possible interaction of dupilumab with the pharmacokinetics of drugs metabolized by cytochrome P450 (CYP450) enzymes, including warfarin. The results clearly show no significant DDI of drugs metabolized by CYP3A, CYP2C19, CYP2C9, CYP1A2, and CYP2D6 after IL-4/IL-13 signaling inhibition by dupilumab.

Conclusions

DDIs have received a great deal of recent attention from the regulatory, scientific, and health care communities worldwide. A large number of drugs are introduced every year, and new interactions between medications are increasingly reported. The co-administration of multiple therapies (polypharmacy) in patients with concomitant comorbidities may determine a significant and clinically relevant modification of drug's absorption, distribution, metabolism, and excretion phases.

The different pharmacokinetic properties of each DOACs may significantly influence the potential DDIs, although exists some similitudes. For instance, all DOACs are substrate of the P-gp and their bioavailability may be influenced from the presence of inducers or inhibitors of this drug transporter. For this reason, the inter-individual variability of drug plasma concentrations, lower for apixaban and edoxaban and higher for rivaroxaban and dabigatran, is a determining factor for triggering clinically significant DDIs.

The DDIs of DOACs can also be affected by inducers or inhibitors of CYP3A4. Edoxaban involvement in cytochrome catalyzed elimination is negligible, thus less prone to interaction with inducers or inhibitors of CYP3A4 compared to other anti-Xa inhibitors. Furthermore, edoxaban metabolism produces, through hydrolysis, the active metabolite M4. For this reason, the reduction of edoxaban exposure by strong inducers of drug-metabolizing enzymes, i.e., rifampin, may be partially compensated by the formation of M4, an effect that is not observed with other DOACs.

In response to anticipated DDIs, possible strategies, including dosage reduction or different time of administrations, are recommended. In particular, in order to avoid the DDIs, it is possible to administer DOACs 2 h before the interacting drug or after 6 h the use of P-gp inhibitors. For instance, as per the dabigatran SmPC, it is suggested the administration of the loading dose of ticagrelor 2 h after the DOAC. In addition, the use of an immediate-release preparation of verapamil is predicted to avoid the interaction with DOAC when taken at least 2 h before.

The introduction of DOACs in the clinical practice has certainly facilitated the use of anticoagulant therapies in patients under polypharmacy, with significantly lower incidence of clinically relevant DDIs as compared to warfarin. However, additional studies and/or sub-analysis will be necessary to ascertain the DDIs, which are currently mainly derived from hypothetical conclusions.

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5 Direct Oral Anticoagulant Reversal for Management of Bleeding and Emergent Surgery

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Introduction

During the last decade, direct oral anticoagulants (DOACs, also referred to as new/novel/non-vitamin K oral anticoagulants [NOACs] and target-specific OACs) have become widely used within various clinical contexts for which vitamin K antagonists (VKAs, warfarin) were previously indicated. Dabigatran, apixaban, rivaroxaban, edoxaban, and betrixaban are currently approved for stroke and systemic embolism prevention in non-valvular atrial fibrillation (NVAF), acute venous thromboembolism (VTE) treatment, secondary prevention of VTE, VTE prevention after knee or hip replacement surgery (except edoxaban), and stable coronary disease or peripheral artery disease (rivaroxaban) (SAVAYSA 2020; Sinnaeve et al. 2016; Xarelto 2018; Pradaxa 2018; Anand et al. 2018; Connolly et al. 2009; Eikelboom et al. 2017; Giugliano et al. 2013; Granger et al. 2011; Patel et al. 2011).

DOACs are replacing VKAs in most of the above indications (Connolly et al. 2009; Giugliano et al. 2013; Granger et al. 2011; Patel et al. 2011). The reasons for this global paradigm shift in preference of DOACs include their rapid onset of anticoagulant effect, lack of need for routine anticoagulation monitoring, and low propensity for drug and food interactions. Most importantly, the rates of life-threatening bleeding were decreased compared to usual anticoagulants and for some indications this was accompanied by a mortality benefit. A meta-analysis by Ruff et al. of the four major phase 3, randomized trials for DOACs, reviewing efficacy and safety in 71,683 patients treated for NVAF (42,411 on DOAC; 29,272 on warfarin) showed

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that DOACs compared with warfarin significantly reduced risk of haemorrhagic stroke (RR 0.49, 95% CI 0.38–0.64; $p < 0.0001$), intracranial hemorrhage (0.48, 0.39–0.59; $p < 0.0001$), and all-cause mortality (0.90, 0.86–0.95; $p = 0.0003$) (Ruff et al. 2014). In a meta-analysis of 10 trials enrolling 35,029 patients treated for VTE, Gómez-Outes et al. showed that the rates of major bleedings were reduced compared to conventional therapy (parenteral anticoagulant for ≥5 days followed by VKA for ≥3 months; 1.8% per year vs. 3.1% per year, $p = 0.003$), fatal bleeding (0.1% per year vs. 0.3% per year, $p = 0.02$), and adjusted case fatality rates of major bleeding (6% vs. 10%, $p = 0.18$), respectively (Gómez-Outes et al. 2015). Reduced risk of intracranial (ICH) and extracranial hemorrhages were also noted with DOACs compared to warfarin in this meta-analysis (Gómez-Outes et al. 2015).

Nevertheless, bleeding complications, which can be life-threatening, persist with any anticoagulant including DOACs. In the case of DOACs, crucial consideration needs to be given to optimal dosing or discontinuation in patients with severe renal insufficiency as well as hepatic dysfunction, and concerns have been raised about timely DOAC reversal in the emergent setting (Levi 2016; Bauer 2013).

In the last few years, specific antidotes have been approved for commercial use: idarucizumab (Praxbindc, Boehringer Ingelheim) for the reversal of the direct thrombin inhibitor, dabigatran, and andexanet alfa (Andexxa®, Portola), for the reversal of factor Xa inhibitors, rivaroxaban and apixaban (evaluation pending for edoxaban and betrixaban) (Praxbind 2015; Andexxa 2018). Andexanet alfa is only approved in the USA and Europe at this time. We will address in the following chapter the challenges in management of bleeding associated with DOACs and an overview of assessment strategies, available reversal agents, and future perspectives.

Indications for Reversal

When considering DOAC reversal in a patient with an active or imminent high risk of bleeding, clinicians should undertake a careful risk stratification regarding potential bleeding severity, status of anticoagulation, and its indication. The decision to pursue reversal of DOACs must take into account the thrombotic risk of the underlying condition as well as possible risks associated with the reversal agents (Andexxa 2018; Dentali et al. 2011).

Emergency Surgery and Urgent Procedures

Considering the short half-lives of DOACs, it is usually feasible to coordinate the timing of the required intervention to allow for spontaneous clearance of DOACs in patients with normal renal or hepatic functions (SAVAYSA 2020; Sinnaeve et al. 2016; Xarelto 2018; Pradaxa 2018). However, in cases of major trauma, emergency surgery, and other urgent clinical situations (such as acute ischemic stroke in a patient who qualifies for thrombolysis or thrombectomy), time is limited and active reversal

strategies are required to mitigate bleeding prior to and during the intervention (Connolly et al. 2016, 2019; Pollack et al. 2015, 2017). The bleeding risk and urgency of the intervention must be assessed in a team approach in consultation with the appropriate specialists (neurologist, neurosurgeon, gastroenterologist, surgeon).

Life-Threatening and Uncontrolled Bleeding

To select the optimal strategies for anticoagulation reversal in the case of bleeding, severity must be assessed accounting for site, amount, and rate of blood loss. This entails a clinical evaluation including thorough history, physical examination, serial blood tests, close monitoring, and targeted imaging studies if indicated. Bleedings that may initially appear significant but are generally self-limited (for example, epistaxis or hemorrhoidal bleed) may be managed conservatively, without exposing the patient to potential risks of thrombosis associated with anticoagulation withdrawal and reversal. The opposite can also be true; an occult bleed can mask a potentially life-threatening condition (such as retroperitoneal bleeding). Bleedings requiring more aggressive interventions include bleeding with substantial blood loss or requiring transfusion (fall in hemoglobin of ≥20 g/L or leading to transfusion of ≥2 units of red cells), symptomatic bleeding in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial or intramuscularly with compartment syndrome), and bleeding that is life-threatening (Schulman and Kearon 2005). Bleedings that require therapeutic interventions such as surgery, radiology-guided embolization, or endoscopic therapy may also need reversal agents.

General Approach

Assessment of Anticoagulation Status

Upon initial assessment of a bleeding patient on DOAC, clinicians should determine:

- the anticoagulant the patient is taking,
- the timing of the last dose of DOAC,
- intake of any other medications that increase bleeding such as antiplatelets and nonsteroidal anti-inflammatory drugs, as well as herbal supplements,
- whether an overdose—intentional or unintentional—might be in question,
- the presence of any other comorbidity which may exacerbate bleeding either intrinsically or through decreased anticoagulant clearance, most importantly kidney and liver diseases.

Keeping the pharmacology of DOACs in mind, anticoagulation can be deemed negligible beyond five half-lives after the last administration of DOACs in patients with preserved renal and hepatic functions (see Table 5.1) (Connolly et al. 2009; Giugliano et al. 2013; Granger et al. 2011; Patel et al. 2011). In the context of renal

Table 5.1 Clearance of DOACs (SAVAYSA 2020; Sinnaeve et al. 2016; Xarelto 2018; Pradaxa 2018; Connolly et al. 2009; Giugliano et al. 2013; Granger et al. 2011; Patel et al. 2011; Khadzhynov et al. 2013; Scaglione 2013)

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®, Savaysa®)
Onset	Rapid	Rapid	Rapid	Rapid
T_{max} (*h*)	2	2.5–4	1–3	1–2
Half-life (*h*) Five half-lives	12–17 2.5–3.5 days	5–9; elderly: 11–13 1–2 days	8–15 1.5–3 days	10–14 1.3–2 days
Renal clearance	~80–85% Dialyzable (Khadzhynov et al. 2013)	~36% Non-dialyzable	~25% Non-dialyzable	~50% Non-dialyzable
Hepatic clearance	~15% Safe in moderate hepatic impairment (Child-Pugh B) (Stangier et al. 2008); Contraindicated if ALT/AST >2× ULN (Connolly et al. 2009)	~30% Not recommended in moderate-severe hepatic impairment (Child-Pugh B/C)	~25% Not recommended in severe hepatic impairment (Child-Pugh C)	~4% (remainder biliary/intestinal) Not recommended in moderate-severe hepatic impairment (Child-Pugh B/C)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ULN* upper limit of normal, T_{max} time taken to reach the maximum concentration

impairment, offset of anticoagulation is delayed, particularly for dabigatran, which can potentially be dialyzed as hemodialysis removes ~57% over 4 h (Khadzhynov et al. 2013; Getta et al. 2015). Hepatic impairment affects offset of anticoagulation, particularly for apixaban, edoxaban, and rivaroxaban. Severe hepatic dysfunction may result in accumulation of these drugs. Drug interactions should also be carefully reviewed, chiefly those undergoing P-glycoprotein and cytochrome P450 34A (CYP34A) metabolism, such as chemotherapeutic agents, antiviral, anti-seizure medications, anti-rejection therapies, and azole antifungals (SAVAYSA 2020; Sinnaeve et al. 2016; Xarelto 2018; Pradaxa 2018; Scaglione 2013). Dabigatran and edoxaban have interactions with strong P-glycoprotein inhibitors and inducers, while rivaroxaban and apixaban may have interactions with both P-glycoprotein and CYP34A inhibitors and inducers (SAVAYSA 2020; Xarelto 2018; Pradaxa 2018; Eliquis 2018).

Laboratory assessment of the anticoagulant activity of DOACs is challenging. Standard anticoagulation testing with prothrombin time/international normalized ratio (*PT/INR*); activated partial thromboplastin (*aPTT*) can be helpful, especially normalization of aPTT for dabigatran. However, caution is required since they are not sufficiently accurate to provide a reliable evaluation of the anticoagulant status for guidance of reversal.

Dilute thrombin time (TT) assays and ecarin clotting time (ECT) are linearly correlated with the concentration of dabigatran (r^2 = 0.67–0.99) (van Ryn et al. 2010). Anti-Xa assays are also correlated across a wide range of drug concentrations of rivaroxaban, apixaban, and edoxaban (r^2 = 0.78–1.00) (Samuelson et al. 2017). If these tests are not available, TT or aPTT is recommended over PT/INR for assessment of dabigatran, and PT/INR is recommended over aPTT for detection of factor Xa inhibitors (see Table 5.2). As stated above, a clinical estimation of the residual anticoagulation effect considering time since last administration, renal and hepatic function and drug interactions, may be of use when an accurate and precise test for DOACs effect is unavailable. A normal standard coagulation profile does not exclude therapeutic anticoagulant effect for which an intervention may be indicated (Samuelson et al. 2017). It is also important to keep in mind the differential diagnosis of abnormal coagulation tests in a bleeding patient, which should include disseminated intravascular coagulation (DIC) (due to trauma or sepsis). The possibility of DIC should require additional testing with fibrinogen and D-dimer levels.

Table 5.2 Results of Standard Coagulation Assays for DOACs (van Ryn et al. 2010; Samuelson et al. 2017; Cuker et al. 2014)

Coagulation essay/ clinically relevant drug levels (no/yes)[a]	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®, Savaysa®)
PT/INR				
No *Yes*	N N or ↑	N N or ↑	N N (rarely ↑)	N N or ↑
aPTT				
No *Yes*	N or ↑ ↑	N N or ↑	N N (rarely ↑)	N N or ↑
TT				
No *Yes*	↑ ↑ or out of range	N/A	N/A	N/A
Dilute TT				
No *Yes*	N or ↑ ↑	N/A	N/A	N/A
Anti-Xa				
No *Yes*	N/A	N or ↑ ↑	N or ↑ ↑	N or ↑ ↑

PT/INR prothrombin time/international normalized ratio, *aPTT* activated partial thromboplastin, *TT* thrombin time, *N* normal, *N/A* not applicable (insufficient evidence)

[a]Minimum DOAC level that can contribute to bleeding is poorly defined. The International Society on Thrombosis and Hemostasis recommends considering anticoagulation reversal in serious bleeding with a DOAC level >50 ng/mL, and in invasive procedures with high bleeding risk with a DOAC level >30 ng/mL (Schulman et al. 2010)

Specific and Nonspecific Agents

Once it has been determined that a patient is experiencing a serious or life-threatening bleed requiring reversal of anticoagulation, an arsenal of strategies is available, although randomized trial data to guide their uses remains limited.

General management for patients with serious or life-threatening major bleedings should include admission and monitoring in a critical care setting with adequate hemodynamic support. The cornerstone of management is continuous assessment of bleeding severity and hemodynamics with prompt establishment of large-bore intravenous access, airway protection and transfusions as required, as well optimization of acid-base and electrolyte balance (including calcium in the context of possible massive transfusion protocols). Involvement of appropriate specialists should be timely for consideration of a hemostatic intervention, which may include surgery (general or neurosurgery), interventional radiology, and gastroenterology (for endoscopy).

Management of bleeding on DOAC can be undertaken with hemostatic agents such as prothrombin complex concentrates (PCCs), antifibrinolytic agents, desmopressin (DDAVP) and drug removal via oral activated charcoal for recently ingested anticoagulants (potentially hemodialysis for dabigatran). However, during the recent years, we have seen the development of specific reversal agents which will be reviewed in further detail below: idarucizumab (Praxbind®) for the reversal of dabigatran and andexanet alfa (Andexxa®) for the reversal of factor Xa inhibitors, rivaroxaban and apixaban.

Dabigatran Reversal: Idarucizumab (Praxbind®)

Clinical Pharmacology

Idarucizumab is a humanized monoclonal antibody fragment (Fab) with high affinity for dabigatran (~350 times higher vs. thrombin) as well as its acyl glucuronide metabolites (see Fig. 5.1) (Praxbind 2015). It is therefore able to bind free and thrombin-bound dabigatran, resulting in neutralization of its anticoagulant effect within minutes (van Ryn et al. 2010; Schiele et al. 2013). In a mouse model, despite structural similarities to thrombin in mode of dabigatran binding, idarucizumab did not bind to thrombin substrates and did not alter coagulation and platelet aggregation testing (Schiele et al. 2013). Consequently, it should not have any intrinsic prothrombotic effect.

Idarucizumab was originally tested in healthy volunteer subjects (men aged 18 to 45) where its administration reduced plasma concentrations of unbound dabigatran to below detectable thresholds and returned coagulation parameters (dTT, ECT, aPTT, TT, and ACT) to baseline levels (Glund et al. 2015a, b). This normalization

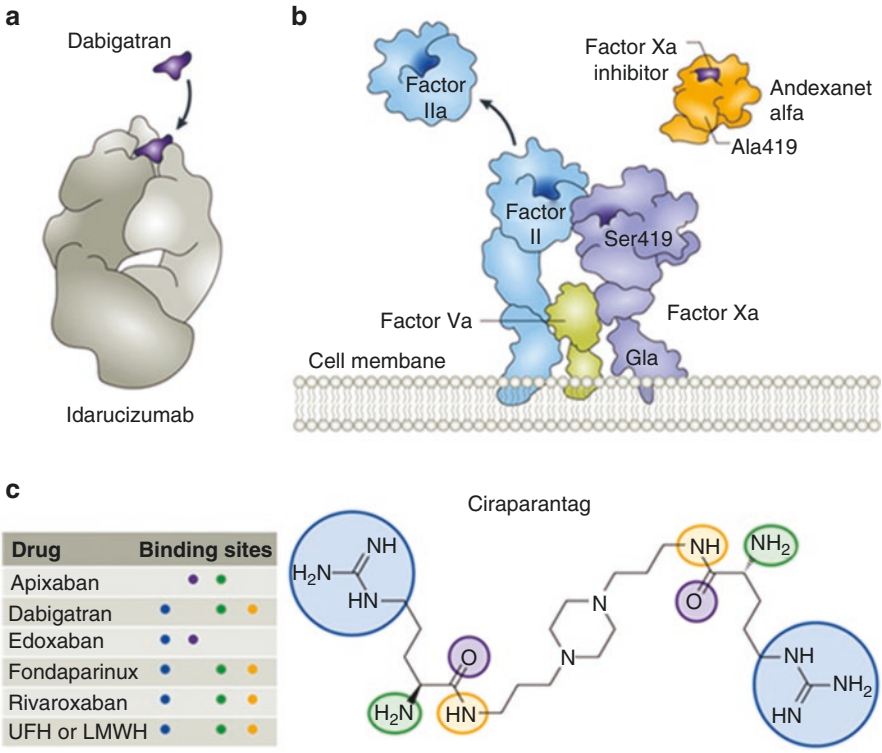

Fig. 5.1 Reversal agents for direct oral anticoagulants. (**a**) Idarucizumab, an antibody antigen-binding fragment (Fab) that binds to dabigatran with an affinity >350 times that of thrombin. (**b**) Andexanet alfa, a modified recombinant coagulation factor Xa that competitively binds factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban). Modified to include amino acid substitutions and deletion of the γ-carboxyglutamic acid (Gla)-rich membrane-binding domain to prevent assembly of factor Xa and factor Va and creation of the prothrombinase complex. (**c**) Ciraparantag, a synthetic inorganic molecule that binds multiple anticoagulation agents through noncovalent hydrogen bonding and charge–charge interactions. *LMWH* low-molecular-weight heparin, *UFH* unfractionated heparin. (Reprinted with permission from Levy et al. Copyright © Springer Nature)

persisted for at least 24 h. Additional investigations in middle-aged and elderly populations (up to 80 years of age), and in volunteers with mild or moderate renal impairment showed similar findings (Glund et al. 2014, 2017). The half-life of idarucizumab approximates 45 min (Glund et al. 2017).

Following an interim report of the RE-VERSE AD study (Reversal Effects of Idarucizumab on Active Dabigatran), this drug was approved by the United States Food and Drug Administration (US FDA) in 2015 (Europe in 2015, Canada in 2016) (Pollack et al. 2015; Food and Drug Administration 2015).

Dosage and Administration

The recommended dose of idarucizumab is 5 g, intravenously, to be administered in two separate vials of 2.5 g (50 mL) each, no more than 15 min apart (Praxbind 2015). They can be given as two consecutive infusions or bolus injections via syringe. This dose reversed the total body load of dabigatran associated with the 99th percentile of the dabigatran levels measured in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (Connolly et al. 2009). Currently, there is limited evidence for administration of additional doses.

Efficacy and Safety

The RE-VERSE AD trial (final report published in 2017) is a phase 3, multicenter, prospective, open-label study ($n = 503$, median age of 78 years) which evaluated the performance of idarucizumab for dabigatran reversal in patients who had uncontrolled bleeding (301 patients with gastrointestinal bleeding, intracranial hemorrhage, and trauma) or who required an urgent intervention (202 patients). The maximum percentage reversal of dabigatran was assessed within 4 h after the administration of idarucizumab (via diluted TT or ECT), and the median was found to be 100%, i.e., complete reversal was achieved within 15 min in most patients. The reversal effect was maintained for 24 h in most patients (Pollack et al. 2017).

Restoration of hemostasis was assessed as a secondary endpoint (Pollack et al. 2017):

- Among patients treated for bleeding, 203 out of 301 patients could be evaluated and the median time to cessation of bleeding was 2.5 h, with 134 patients (68%) achieving documented hemostasis within 24 h.
- In patients undergoing an urgent procedure (median initiation time of 1.6 h), 197 out of 202 patients were evaluated and 184 patients (~93%) had normal periprocedural hemostasis.

The following *safety outcomes* were reported (Pollack et al. 2017):

- Thrombotic events assessed over a period of 90 days: rate of occurrence was 6.3% and 7.4% in patients treated for bleeding and those treated prior to urgent procedures, respectively. Events recorded included pulmonary embolism, deep venous thrombosis, ischemic stroke, and myocardial infarction. Antithrombotic therapy (prophylactic or therapeutic anticoagulation, or antiplatelet) was reintroduced in most patients within ~4–13 days after idarucizumab administration. Considering the half-life of idarucizumab, this delay in reinitiation of therapy for patients having achieved hemostasis may have contributed to thrombotic events. The rates of thrombotic events were comparable to those reported with 4-factor PCCs for VKA reversal in major surgical procedures or uncontrolled bleeding (Sarode et al. 2013; Goldstein et al. 2015).

- Mortality at 30 days approximated 13% in both groups, with an estimated 90-day mortality rate of 19%. This was mainly attributed to the index event severity and underlying comorbidities leading to multiorgan failure.
- Serious adverse events occurred within 5 days in 23% of patients and most events were related to worsening of the index event or the underlying condition. The most frequent events were delirium (2.3%) in patients treated for bleeding, and cardiac arrest (3.5%) and septic shock (3%) in patients treated for urgent procedures. There was no consistent pattern of adverse effect that could be directly linked to idarucizumab. There were no hypersensitivity reactions or immunogenicity which may affect the efficacy of reversal. In healthy volunteers, the most common adverse reactions were headache, constipation, and nausea (all ~5%) (Glund et al. 2014, 2015a, b, 2017).

In summary, idarucizumab can effectively and rapidly reverse the anticoagulant effect of dabigatran in most patients with uncontrolled bleeding or requiring urgent invasive intervention. However, the FDA has included a "black box" warning regarding the risk of venous and arterial thromboembolic events in the package insert (Praxbind 2015). Resumption of anticoagulation is recommended as soon as medically permissible. An important limitation of this landmark trial is the single-arm design (lack of a control group). However, this was justified as there was no established standard of care for reversing dabigatran and giving placebo to patients with uncontrolled bleeding may be deemed unethical.

Use in Clinical Practice

Since idarucizumab's approval, there are some post-marketing "real-life" use. For instance, RE-VECTO was a cross-sectional surveillance program of idarucizumab's use, spanning from August 2016 to June 2018, at 61 institutions and involved 359 patients in North America, Europe, and Asia Pacific (Fanikos et al. 2020). Clinical indications of use and population were largely consistent with data collected from trial settings, with minimal off-label prescribing. Most patients were elderly (75% over 70 years of age). Life-threatening or uncontrolled bleeding was the most common indication for idarucizumab (chiefly gastrointestinal and intracranial), followed by emergency surgery/urgent procedure (majority gastrointestinal/abdominal). The recommended 5 g dosing regimen was correctly used in >98% of dabigatran-treated patients

Kermer et al. (2017) reviewed idarucizumab administration for patients with intracranial hemorrhage or ischemic stroke eligible for fibrinolysis or at 22 German hospitals from January to August 2016 (Kermer et al. 2017). Of the 31 patients who presented with stroke, 19 had ischemic stroke. Following rt-PA, 79% had a positive outcome with a median 5-point improvement in National Institutes of Health Stroke Scale (NIHSS). Out of the 12 patients treated for hemorrhagic stroke, two had increases in the size of the cerebral bleeds, but their overall outcomes were favorable with a median NIHSS improvement of 5.5 points (Kermer et al. 2017). In a

smaller case series where idarucizumab was used for various emergencies including strokes: the three patients who underwent reversal followed by fibrinolysis had partial (NIHSS 3–5 points) to full neurological recovery (Vosko et al. 2017).

Another specific population in which idarucizumab was evaluated was in patients undergoing urgent heart transplantation. A case series of 10 patients at the University Hospitals Leuven showed sustained and complete dabigatran reversal without thrombotic complications and without interference in heparinization required for cardiopulmonary bypass (Van Keer et al. 2019). Therefore, dabigatran may be the anticoagulant of choice for heart failure patients awaiting transplantation (without ventricular assistance device). Further real-world data and post-marketing analysis is needed to better assess the generalizability and effectiveness of idarucizumab use, as well as additional safety outcomes.

Factor Xa Inhibitor (Rivaroxaban and Apixaban) Reversal: Andexanet Alfa (Andexxa®; Ondexxya®)

Clinical Pharmacology

Andexanet alfa (Andexxa®) is a recombinant inactivated modified human coagulation factor Xa. It is devoid of coagulant activity, but able to bind factor Xa inhibitors with high affinity (see Fig. 5.1) (Andexxa 2018). By binding the inhibitors, andexanet alfa restores endogenous factor Xa activity (Lu et al. 2013). Of note, andexanet also reverses indirect factor Xa inhibitor activity by binding to heparins (unfractionated and low-molecular-weight) and to pentasaccharide-activated antithrombin III (ATIII).

Several phase two studies were conducted in healthy volunteers who received factor Xa inhibitors (rivaroxaban, apixaban, edoxaban). Intravenous administration of andexanet reversed anticoagulation effect in a dose-dependent manner, as demonstrated by reduction of anti-Xa activity, unbound factor Xa inhibitor concentration, and recovery of thrombin generation (Crowther et al. 2013, 2014a, b; Mark et al. 2013). In these studies, the pharmacodynamic half-life of andexanet was short and approximated 1 h. Therefore, it was administered as a bolus followed by an infusion (1–2 h), which reliably prolonged its activity for the duration of infusion.

Subsequently, a double-blind, placebo-controlled phase three trial evaluated andexanet in non-bleeding healthy older volunteers (50–75 years of age) receiving apixaban or rivaroxaban (ANNEXA-A, ANNEXA-R; differing andexanet doses based on stoichiometric ratios established in phase two studies) (Siegal et al. 2015). Andexanet was given as a bolus or a bolus followed by a 2-h infusion, with monitoring of mean percent change in anti-Xa activity. In both apixaban- and rivaroxaban-treated participants, anti-Xa activity was reduced within minutes by 92–94% after an andexanet bolus (vs. 18–21%, $p < 0.001$ in the placebo groups) and thrombin generation was fully restored in 96–100% of participants (vs. 7–11%, $p < 0.001$ in the placebo groups), with sustained effect when an infusion of andexanet followed. A subgroup of patients showed transient increases in D-dimer and prothrombin

fragment 1 and 2 levels, resolving within 24–72 h. Although this raised a theoretical concern of prothrombotic effect, there were no serious adverse events reported over a follow-up period of 6 weeks.

Finally, a preliminary report of the pivotal trial ANNEXA-4 (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors) indicated a positive outcome for reversal of factor Xa inhibitors (mostly rivaroxaban and apixaban) in patients presenting with acute major bleeding (Connolly et al. 2016). In 2018, andexanet received approval by the FDA for the reversal of rivaroxaban and apixaban in patients with uncontrolled or life-threatening bleeding (Andexxa 2018).

Dosage and Administration

The recommended dosing regimens for andexanet alfa include low and high dose regimens, each with a bolus followed by a 2-h continuous infusion to achieve ongoing sequestration of factor Xa inhibitors (Andexxa 2018):

- *Low dose*: 400 mg IV bolus at a target rate of 30 mg/min, followed by a continuous infusion of 4 mg/min for up to 120 min.
- *High dose*: 800 mg IV bolus at a target rate of 30 mg/min, followed by a continuous infusion of 8 mg/min for up to 120 min.

The appropriate regimen is determined by differing stoichiometric ratios required for binding of specific factor Xa inhibitors, their doses, and the time since their last administration. It is summarized below in Table 5.3. Andexanet is commercially available in 100 mg and 200 mg vials.

Efficacy and Safety

The ANNEXA-4 trial was a multicenter, prospective, open-label, single-arm study evaluating andexanet in 352 patients (a mean age of 77 years) receiving a factor Xa inhibitor for NVAF (80% of the cohort) or VTE with acute major bleeding and last dose of DOAC taken within 18 h (Connolly et al. 2019). The co-primary outcomes were the percent of change in anti-Xa activity and the proportion of patients

Table 5.3 Andexanet alfa dosing according to DOAC regimen (Andexxa 2018)

Factor Xa Inhibitor *Dosage*	<8 h or unknown time since last dose	>8 h since last dose (<18 h)
Rivaroxaban		
≤ 10 mg *>10 mg or unknown*	Low dose High dose	Low dose
Apixaban		
≤ 5 mg *>5 mg or unknown*	Low dose High dose	Low dose

achieving good or excellent hemostasis at 12 h. The efficacy of andexanet was evaluated in a subgroup of patients with confirmed major bleeding and pre-hoc defined threshold of anti-Xa activity considered to represent higher bleeding risk (at least 75 ng/mL; or ≥0.25 IU/mL for patients on enoxaparin). Most patients were taking rivaroxaban and apixaban, and bleeding was predominantly intracranial (64%) or gastrointestinal (26%).

The following *results* were observed (Connolly et al. 2019):

- Median anti-Xa activity was reduced by 92% for rivaroxaban (95% confidence intervals (CI): 88–94) and apixaban (95% CI: 91–93), and by 75% (95% CI: 66–79) for enoxaparin. A very small number of patients received edoxaban (3%, $n = 10$ patients). Extension of the study is underway in Japan and is expected to yield additional data regarding edoxaban's reversal.
- Excellent hemostasis was achieved in 171 of 249 evaluated patients (69%), and good in 33 of 249 patients (13%): total of 82% of patients (204 of 249). Subgroup analysis showed good to excellent hemostasis for 85% of patients with gastrointestinal bleeding and 80% of intracranial bleeding. The majority of patients could resume anticoagulation after resolution of bleeding.
- Anti-Xa activity was increased at 4 and 8 h after administration of andexanet, albeit it remained relatively low (~60–70% reduced). Reduction of anti-Xa activity was not found to be predictive of hemostasis overall, except for a possible correlation in patients with intracranial hemorrhage whereby the hematoma's size and volumes were tracked serially. Consequently, the clinical response to andexanet cannot be reliably predicted with anti-Xa measurement.

The *safety outcomes* studied (Connolly et al. 2019) were:

- Thrombotic events occurred in 10% of 353 patients ($n = 34$) within 30 days of follow-up. Three percent of the thromboses occurred within 5 days of andexanet. It is unclear whether these events are related to the underlying thrombotic risk of the patients or whether there is a contribution from sustained effects of andexanet alfa. The thromboses included pulmonary embolism, deep venous thrombosis, ischemic stroke, and myocardial infarction.
- Thirty-day mortality was 14%, which is similar to the all-cause mortality rates reported in other studies of major anticoagulant-associated bleeding.
- Most common adverse reactions (≥5%) included urinary tract infections and pneumonia without biological plausibility, as well as infusion-related reactions (≥3%) in healthy volunteers (Andexxa 2018; Siegal et al. 2015). There were no major hypersensitivity reactions or neutralizing antibody development reported in ANNEXA-4.

ANNEXA-4 showed that andexanet reduced anti-Xa activity level as well as provided good or excellent hemostasis in 82% of patients with factor Xa inhibitor-associated acute major bleeding. Further studies are needed to determine if there is a reduction in mortality compared to the reported rates in

anticoagulation-associated bleeding without reversal. Similar to the RE-VERSE AD, the main limitation of ANNEXA-4 was the single-arm design with the lack of a control group. The lack of control group was deemed ethically acceptable, in the setting of bleeding patients and the lack of approved effective reversal strategies for DOACs. In summary, andexanet is a safe and effective option for patients with uncontrolled or life-threatening bleeding associated with rivaroxaban and apixaban. Use of andexanet for edoxaban- or betrixaban-associated bleeding is currently off-label (Cuker et al. 2019). It is also not approved in the case of emergency surgeries and invasive procedures as use in that population was not studied in ANNEXA-4. As for idarucizumab, the FDA has issued a black box warning regarding the risk of venous and arterial thromboembolic events (Andexxa 2018).

Use in Clinical Practice

Since its approval in 2018, there has been limited published data about andexanet in real-life setting. Generalizability of andexanet's safety and efficacy remains to be established outside clinical trial settings. For instance, the ANNEXA-4 investigators included only patients with a Glasgow coma scale >7 and an estimated hematoma volume <60 mL of intracranial hemorrhage (Connolly et al. 2019). Andexanet's effectiveness is particularly relevant for anti-Xa-associated intracranial hemorrhage which is associated with high mortality and morbidity (Purrucker et al. 2016). Additionally, the ANNEXA-4 investigators also excluded patients who required an invasive intervention within 12 h (Connolly et al. 2019). There is an ongoing randomized, controlled clinical trial evaluating the efficacy and safety of andexanet versus usual standard of care in patients with intracranial hemorrhage and receiving a factor Xa inhibitor (NCT03661528) (Karam et al. 2013).

The Mayo Clinic published their experience with andexanet use from July 2018 to April 2019 (Brown et al. 2019). Of 25 patients evaluated, 13 received andexanet for intracranial hemorrhage. Eleven patients had follow-up cerebral imaging showing stability in ~91% of these patients. Additionally, three patients had effective hemostasis, and nine patients received therapy for other major bleeding (four gastrointestinal). No thrombotic events were recorded, and 30-day mortality was 24%. Most treated patients in this series would have been excluded from the ANNEXA-4 trial. Larger post-marketing studies are needed to clarify the optimal use of andexanet alfa in clinical practice.

Other Pro-Hemostatic Therapies

Prior to the approval of idarucizumab and andexanet alfa, off-label use of nonspecific pro-hemostatic products for the management of bleeding in patients on DOAC therapy was endorsed on the basis of studies of animals, healthy volunteers, and expert consensus as detailed below.

Clotting Factor Products

Available products with inactivated or activated coagulation factors include prothrombin complex concentrate (PCC; 3-factor, 4-factor inactivated [Kcentra®/Beriplex®/Octaplex®], 4-factor activated [FEIBA®]), recombinant activated factor VII (rFVIIa) and plasma products (such as fresh frozen plasma, FFP). Data regarding their efficacy in patients with DOAC-associated bleeding is sparse (Ageno et al. 2012; Arellano-Rodrigo et al. 2015; Cheung et al. 2015; Dibu et al. 2016; Eerenberg et al. 2011; Honickel et al. 2016; Lambourne et al. 2012; Marlu et al. 2012; Perzborn et al. 2013; Piran et al. 2019; Pragst et al. 2012; Schulman et al. 2018).

In the case of warfarin, clotting factor products restore hemostasis with a sustainable effect when vitamin K is given. As they inhibit exogenous clotting factors, DOACs are unlikely to have their effect reliably countered by FFP. Indeed, FFP use is not recommended in this context as their risks may outweigh the potential benefits. Nevertheless, FFP may be appropriate for dilutional coagulopathy associated with massive transfusion (Ageno et al. 2012).

Recombinant activated factor VII has been recommended for patients presenting with bleeding associated with dabigatran and apixaban according to the FDA (Sinnaeve et al. 2016; Pradaxa 2018). Evidence for the efficacy of recombinant activated factor VII in reversal of the above DOACs is lacking, aside from in vitro measurement of coagulation (Lambourne et al. 2012) and an inconclusive ex vivo study in healthy volunteers (Arellano-Rodrigo et al. 2015).

PCCs contain high levels of factors II, IV, and X (plus VII, protein C and S in 4-factor PCC), i.e., vitamin K-dependent coagulation factors. PCCs were developed and primarily studied for reversal of warfarin anticoagulation. There were some observational studies of inactivated PCCs for DOAC-associated bleeding (animal models and healthy volunteers) (Cheung et al. 2015; Eerenberg et al. 2011; Lambourne et al. 2012; Marlu et al. 2012; Perzborn et al. 2013; Pragst et al. 2012). In a systemic review, Piran et al. reviewed the use of inactivated PCC for factor Xa inhibitor-associated major bleeding (primarily rivaroxaban and apixaban) in ten studies enrolling 340 patients (Piran et al. 2019). The reported proportion of patients with successful bleeding management varied from 69% (95% CI: 61%–76%) to 77% (95% CI: 63%–92%), depending on the criteria used to define hemostasis. The mortality rate was 16% (95% CI: 7%–26%) and the rate of thrombotic events was 4% (95% CI: 1%–8%). Essentially, it was uncertain whether PCC administration was more effective than conservative measures alone in DOAC-related major bleeding. Use in ICH had been less well studied, but more recently, a multicenter, retrospective, observational cohort study by Panos et al. reviewed patients with apixaban- or rivaroxaban-related ICH who received PCCs from January 2015 to March 2019 (Panos et al. 2020). Of 663 patients included, 433 were evaluated for hemostatic efficacy, of which 354 patients (81.8%, 95% CI: 77.9–85.2) had excellent or good hemostasis (using modified Sarode criteria). In addition, 25 (3.8%) patients had 26 thrombotic events, most of which occurred in the first 14 days after PCC administration. The overall in-hospital mortality of the cohort was 19%. Therefore, in the context of life-threatening or uncontrolled bleeding, unavailability

of specific reversal agents, or cost effectiveness concerns, it may be reasonable to administer inactivated PCC as a one-time dose of 50 U/kg IV or 2000 units (more evidence for four-factor formulation) (Schulman et al. 2018). Similar to idarucizumab and andexanet alfa, PCC has a theoretical and poorly quantified prothrombotic risk. Hence, it must be used with caution in carefully selected patients.

There is limited evidence of the potential benefit of activated PCC (aPCC, FEIBA®) in DOAC-associated bleeding. A prospective study including six patients with DOAC-associated intracranial hemorrhage who underwent reversal with aPCC showed no intracranial hemorrhage expansion or any thrombotic complications (Dibu et al. 2016). In a pig polytrauma model with dabigatran administration, aPCC prevented fatal bleeding compared to placebo (Honickel et al. 2016). In rats and primates treated with rivaroxaban, aPCC corrected the bleeding time (Perzborn et al. 2013). A study in ten non-bleeding volunteers also showed that aPCC restored thrombin generation impaired by rivaroxaban (Marlu et al. 2012).

Other

Additional pro-hemostatic therapies available for use include antifibrinolytic agents, such as tranexamic acid, and desmopressin (DDAVP), which may correct impaired platelet function in uremic patients or with antiplatelets therapy. Again, there is sparsity of data concerning these agents in DOAC-associated bleeding. Nonetheless, considering their low risk of thrombosis and widespread availability, these agents may be appropriate for life-threatening bleeding.

To summarize all available therapeutic options for reversal of DOAC's effects, we described a potential management approach to the reversal of DOACs in Fig. 5.2. These recommendations are in line with the recently published expert consensus decision pathway on management of bleeding in patients on oral anticoagulants by the American College of Cardiology (Tomaselli et al. 2020).

The Search of a Universal Antidote

In addition to the development of class and drug-specific reversal agents, the recent years have seen efforts to find antidotes which can reverse the effects of multiple anticoagulants. The idea of a so-called "universal" antidote is appealing for its practicality and wider clinical applicability.

Ciraparantag

Ciraparantag (previously called PER977, Amag Pharmaceuticals) was synthetically developed to bind to unfractionated heparin, low-molecular-weight heparin, fondaparinux, and DOACs including dabigatran, rivaroxaban, apixaban, and edoxaban (see Fig. 5.1) (Laulicht et al. 2013; Sullivan Jr et al. 2015; Ansell et al. 2014,

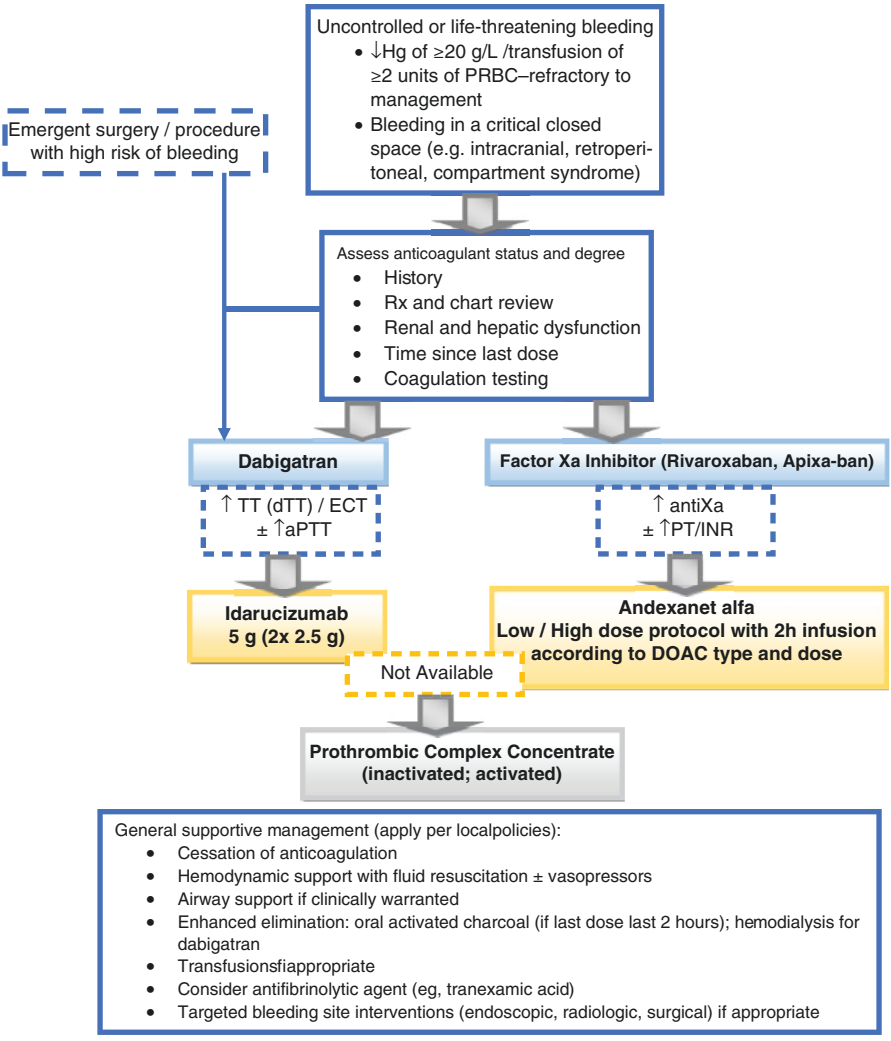

Fig. 5.2 Approach to direct oral anticoagulant reversal *PRBC* packed red blood cells, *TT* thrombin time (dTT diluted thrombin time), *ECT* ecarin clotting time, *PT/INR* prothrombin time/international normalized ratio, *aPTT* activated partial thromboplastin

2017). With noncovalent hydrogen binding of these anticoagulants, ciraparantag prevents their attachment to factor IIa and Xa target sites. There was no demonstrable prothrombotic effect and cross-reactivity of this molecule with other coagulation factors (Sullivan Jr et al. 2015).

In healthy volunteers, ciraparantag reduced safely and effectively whole blood clotting time after exposure to enoxaparin (Costin et al. 2015) and edoxaban (Schulman et al. 2018; Panos et al. 2020). There was no subsequent prothrombotic effect, and no major safety concerns have emerged, except for mild

infusion reactions. In light of the above findings, ciraparantag has been granted fast track designation by the FDA to facilitate its development (Wong 2013). There are currently two phase 2 trials in the recruitment phase, for reversal of rivaroxaban and apixaban by ciraparantag (NCT03172910 and NCT03288454, respectively).

FXa^{I16L}

FXa^{I16L} was developed as a mutant form of factor Xa with introduction of an amino acid substitution and is being studied as a "universal" bypass agent for several anticoagulants (Thalji et al. 2016). It works by circulating in an inactive state and exhibits resistance to active site inhibitors. Upon encounter with factor Va on damaged cellular surfaces, FXa^{I16L} activated and restore hemostasis at the bleeding site. It successfully restored hemostasis in mouses exposed to rivaroxaban. FXa^{I16L} also reversed rivaroxaban- or dabigatran-mediated anticoagulant effect in humans.

Conclusions

During the last decade, DOACs have replaced VKAs for most indications. Although DOACs are associated with less bleeding and in particular less intracranial hemorrhage, uncontrolled or life-threatening bleeding still can occur with DOACs. Patients anticoagulated with DOAC can also develop acute conditions or endure trauma that call for emergent surgery.

Supportive management can be offered in the form of transfusions as appropriate, maintenance of fluid balance, interruption of anticoagulation and nonspecific pro-hemostatic therapies that have limited evidence. In cases of life-threatening bleeding in closed critical organs (e.g., intracranial), refractory hemorrhage on standard therapies, and emergency interventions in patients at high bleeding risk, specific reversal agents should be the treatment of choice when available.

Idarucizumab can provide rapid and sustained reversal of dabigatran for bleeding patients and those undergoing surgery. Andexanet alfa is a factor Xa inhibitor approved for reversal of rivaroxaban and apixaban-associated hemorrhage. Ciraparantag is being studied as a "universal" antidote. It has promising preclinical data and may be effective for counteracting anticoagulant effect of unfractionated heparin, low-molecular-weight heparin, fondaparinux, and DOACs including dabigatran, rivaroxaban, apixaban, and edoxaban.

The landscape of anticoagulation has changed drastically in the last few years, and one of the main concerns from clinicians and patients has been the sparsity of therapeutic options for treatment of DOAC-associated bleeding. This is changing as well, and future research should yield more information about clinical applicability, for instance in patients with ischemic stroke for thrombolysis or thrombectomy candidacy, presurgical patients, and moderate bleedings failing usual supportive therapies.

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Risk Stratification For and Use of DOAC Therapies for Stroke Prevention in Patient with Atrial Fibrillation

6

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia, with an incidence ranging from 0.1% in patients <55 years to >9% in octogenarian patients (Caturano et al. 2019). The most important AF complication is represented by a fivefold increased risk of ischemic stroke, due to a high prevalence of left atrial thrombosis (Fadhlullah et al. 2016; Bertaglia et al. 2017; AlTurki et al. 2019), hence the major role of anticoagulation is in thromboembolism prevention.

Vitamin K antagonists (VKAs) have been widely used for decades. However, currently, with the marketing of direct oral anticoagulants (DOACs), the therapeutic scenario has changed. The four available DOAC molecules (dabigatran, apixaban, rivaroxaban, and edoxaban) have shown a comparable efficacy, with a lower risk of intracerebral bleeding as compared to well-managed VKAs, as well as an improved expectancy and quality of life (Caturano et al. 2019; Russo et al. 2020a). These findings were further confirmed by real-world data, also including AF patients with clinical characteristics excluded from RCTs (Russo et al. 2016, 2018a, 2019a, b, 2020b; Rago et al. 2019a, b; Stabile et al. 2015; Melillo et al. 2020).

The risk of stroke, though common in the AF setting, is extremely variable. Indeed, diverse risk factors can contribute in different ways to its occurrence. Thus, a risk stratification algorithm would be mandatory to aid therapeutic decision-making for thromboprophylaxis.

Framingham score was among the first point-based algorithms, a weighted score was assigned to each detected risk factor: age (0–10), female sex (6), systolic hypertension (0–4), diabetes mellitus (5), and prior stroke or transient ischemic attack

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(TIA) (6) (Schnabel et al. 2009). A total score ≥8 was suggestive of introducing oral anticoagulant therapy (OAC) (Fang et al. 2008).

Over time, we have witnessed both a refinement and improvement of risk stratification. In 1994, a pooled analysis of five randomized controlled trials by the Atrial Fibrillation Investigators (AFI) has attempted to detect patients' features prognostic of either a high or low risk of stroke (Risk Factors for Stroke and Efficacy 1994). It emerged that AF patients ≤65 years without a history of hypertension, previous stroke/transient ischemic attack, or diabetes were at very low risk of stroke, even in the case thromboembolic prophylaxis was not performed. In 1995, the Stroke Prevention in Atrial Fibrillation (SPAF) also underlined the role of recent onset congestive heart failure (CHF), history of hypertension (systolic blood pressure >160 mmHg), and previous arterial thromboembolism as independent risk factors (Stroke Prevention in Atrial Fibrillation Investigators 1995; The Atrial Fibrillation Investigators 1997).

Over the years, new scores have been developed to stratify both embolic and bleeding risk in AF patients, which are currently used in the clinical practice.

Risk Stratification: An Overview

The most common risk stratification system is represented by the $CHA2DS_2VASc$ score, introduced by the Guidelines of the European Society of Cardiology (ESC) in 2010 (Camm et al. 2012). $CHA2DS_2VASc$ allows to classify each patient according to a definite risk scale: (1) mild risk (if $CHA2DS_2VASc = 0$), (2) moderate risk (if $CHA2DS_2VASc = 1–2$ in women and $= 1$ in men), (3) high risk (if $CHA2DS_2VASc \geq 3$ in women and ≥ 2 in men). Usually anticoagulant therapy, recommended in high risk patients, over the years, has been proven to remarkably reduce the risk of events of about two-thirds. Different is the scenario in the case of mild/moderate stroke risk, for which the anticoagulant treatment should be carefully assessed balancing embolic and bleeding risk factors (Kirchhof et al. 2016a). In fact, in some cases, patients could be predisposed to a higher bleeding risk, which can be in turn estimated by diverse scores, among which the most used is the HAS-BLED.

Embolic Risk Stratification

$CHADS_2$

In 2001, Gage et al. merged AFI and SPAF scoring system to establish the new $CHADS_2$ score, which includes the following risk factors for stroke: cardiac failure, hypertension, age, diabetes, stroke. The relative impact of each risk factor on the incidence of stroke has been assigned a specific score, as follows: 2 points to a previous stroke/TIA event, while all other variables received 1 point.

$CHADS_2$ predictive value, i.e., its validation as risk stratification system, has been assessed in about 1700 patients, aged 65 to 95, with non-valve atrial

fibrillation (NVAF), assisted by Medicare, to whom warfarin was not prescribed at discharge. Few patients collected the lowest (0) and highest (5–6) score values. A score of 0 was associated with a stroke rate per year of 1.9%, while if equal to 6, the stroke rate arose till the 12.5–18.2% (Gage et al. 2001).

According to the $CHADS_2$ score, patients can be classified in three categories of risk: (a) low, if the score is equal to 0, (b) intermediate or intermediate/high, if the score was equal to 1–2, and (c) high to all those with a score ≥3 (Fuster et al. 2011). Hence, a past history of a previous stroke would have assigned the patient to a moderate risk category, even though it is considered the major risk factor for recurrence. In 2010, ESC Guidelines modified this classification scale, assigning a moderate risk with a $CHADS_2$ equal to 1 and high risk with $CHADS_2$ ≥2 in men (Camm et al. 2012).

The discovery of other risk factors not previously validated and the reduced reliability of the algorithm in low risk patients, with a stroke year incidence of 3.2%, have stressed the need for further and better risk stratification algorithms (Cove et al. 2014).

CHA_2DS_2VASc

$CHADS_2$ bias was overcome by the spread of another risk stratification system: CHA_2DS_2VASc (Lip et al. 2010), which has been firstly included in 2010 ESC Guidelines (Camm et al. 2012) and later confirmed by current ESC guidelines as the preferred risk stratification algorithm (Kirchhof et al. 2016a). This novel algorithm, unlike $CHADS_2$, covers additional risk factors (female gender, age 65–74 years, and vascular disease) and enhances the importance of the major ones. CHA_2DS_2VASc ranges from 0 to 9, assigned as follows: 2 points for previous stroke and age ≥75 years, 1 point to vascular disease (myocardial infarction, aortic plaque, and peripheral vascular disease), systolic heart failure, hypertension, diabetes and age 65–74 years.

CHA_2DS_2VASc score was validated in the Euro Heart Survey for AF, a real-world study conducted on a cohort of over 1000 patients (Lip et al. 2010). Benefits from using the new algorithm were remarkable especially in those referred to low risk group (CHA_2DS_2VASc score equal to 0 in males and 1 in females), with an annual stroke incidence <1%, later confirmed also by other studies in larger cohorts of patients (Olesen and Torp-Pedersen 2015; Aspberg et al. 2016; Van Staa et al. 2011; Zhu et al. 2015a). Anticoagulation should be started with a CHA_2DS_2VASc score ≥1 for men and ≥2 for women (Kirchhof et al. 2016a).

Role of female sex either alone or associated to another risk factor did not consistently increase stroke risk. Thus, recently, the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, to avoid different gender thresholds for anticoagulation, have proposed a revision of CHA_2DS_2Vasc score excluding sex (NHFA CSANZ Atrial Fibrillation Guideline Working Group et al. 2018). Currently, complete CHA_2DS_2VASc represents the most common risk stratification scheme.

R_2CHADS_2 Score

Kidney impairment plays a major role in the prognosis of stroke. In fact, subjects with an acute stroke and reduced estimated glomerular filtration rate (eGFR) have a higher mortality both in the short-term follow-up and over a 2 years period (Mostofsky et al. 2009; Guo et al. 2013; Fu et al. 2017). A sub-analysis of the ROCKET-AF trial, in a highly selected population of over 14,000 individuals with eGFR>30 mL/min, disclosed impaired renal function as a potent predictor of both stroke and systemic embolism. Hence, kidney impairment was further added to $CHADS_2$ classification, assigning a score of 2, thus introducing the R_2CHADS_2. Conversely, several studies have shown no added value from renal impairment inclusion either to $CHADS_2$ or CHA_2DS_2VASc (Abumuaileq et al. 2015; Roldan et al. 2013; Friberg et al. 2015).

Atria Stroke Score

In 2013, a derivation from the "AnTicoagulation and Risk factors In AF" (ATRIA) cohort, counting about 11,000 non-valvular AF patients, validated the ATRIA risk score with an improvement of severe events detection (Singer et al. 2013). The novelty of this risk stratification system is the distinction according to patients in primary or secondary stroke prevention, assigning a score between 0 and 12 in primary prevention and between 7 and 15 in secondary. Moreover, many other risk factors were added to the old ones (gender, history of congestive heart failure, hypertension, diabetes, and stroke). Age classes, presence of proteinuria and eGFR<45 mL/min or end-stage renal disease (ESRD) were furtherly included. In primary prevention, patients are considered at low risk if the score is ≤5, thus receiving no anticoagulation. In contrast, all patients in secondary prevention are considered at high risk and anticoagulated.

All these features render the ATRIA score system not of immediate use in clinical practice. In addition, several studies have proven a higher efficacy of CHA_2DS_2VASc than ATRIA in stroke risk prediction (Macle et al. 2015; Hippisley-Cox et al. 2013; Chao et al. 2015; Lip et al. 2014). In a cohort of over 150,000 Swedish AF patients naïve to anticoagulation also during follow-up, $CHADS_2$, CHA_2DS_2VASC, and ATRIA scores were compared to each other. At first, ATRIA seemed to perform better; however, when categorical scores were optimized for local population incidence of stroke, no longer advantage emerged (Aspberg et al. 2016).

QStroke Score

In the view of a more tailored risk stratification of stroke in the general population without history of previous TIA/stroke, a new algorithm was proposed, the QSTROKE (Hippisley-Cox et al. 2013). Considered risk factors were: age, ethnicity, gender, smoking habit, diagnosis of diabetes and type, AF, treated hypertension, kidney disease, rheumatoid arthritis, angina, coronary heart disease, congestive cardiac failure, valvular heart disease, total serum cholesterol to high density lipoprotein cholesterol ratio, body mass index, as well as family history of coronary heart disease in first-degree relatives <60 years. This score was validated in a cohort of

approximately 1.9 million individuals from England and Wales, aged between 25 and 84 years and without a positive anamnesis either for TIA or stroke. The stroke event occurred in about 38,000 cases throughout the follow-up period. Among AF patients QSTROKE performed better than both $CHADS_2$ and CHA_2DS_2VASc score, though not easy in clinical practice.

Garfield AF

The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD AF study) proposed a web-based tool aimed to better stratify lower risk classes (Fox et al. 2017). This model successfully managed to predict all-cause mortality, stroke/systemic embolism and major bleeding, including hemorrhagic stroke, with a higher accuracy than both CHA_2DS_2VASc for stroke and HAS-BLED for bleeding, in the general population, as well as in low stroke risk patients (Fox et al. 2017; Dalgaard et al. 2019).

Factors included in this algorithm are: age, diastolic blood pressure, history of bleeding, kidney disease, smoking habit, carotid occlusive disease, weight, ethnicity, history of heart failure or left ventricular heart failure (ejection fraction, EF <40%), history of coronary artery disease or peripheral vascular disease, dementia, pulse rate, gender, history of stroke, diabetes, current use of antiplatelet drugs. As mentioned for QSTROKE, either in this case its complexity may represent a limit for its application in the clinical practice.

ABC Stroke Risk Score

The ABC stroke score (age, biomarkers, and clinical history) is a simple risk stratification system in AF patients. ABC score was validated in a large cohort of almost 15,000 AF patients with a median follow-up of 1.9 years (Hijazi et al. 2016a), and includes: age, troponin and NT-proBNP, history of TIA/stroke. The ABC stroke score showed a higher accuracy than CHA_2DS_2VASc in predicting stroke risk. This finding was further confirmed by another recent study on about 8700 AF patients (Berg et al. 2019).

Conclusions Though both GARFIELD AF and ABC stroke scores are promising, their knowledge on the long term is still poor; thus further studies are needed.

In addition, note that the role of anticoagulant agents is not risk-free, though also burdened by bleeding risk. Therefore, only an optimal risk-to-benefit ratio between hemorrhagic and stroke risk would represent the key-point to guide us in a better clinical decision-making.

Bleeding Risk Assessment

In patients with a moderate embolic risk (i.e., $CHA_2DS_2VASc = 1$ for men, and $= 2$ for women), some authors reported a potential risk reduction from the use of OACs (Steffel et al. 2018; Kirchhof et al. 2016b). Beyond the assessments of embolic risk, European guidelines also include bleeding risk evaluation (Steffel et al. 2018).

Hence, careful attention must be focused on the risk-to-benefit ratio of anticoagulants due to the adverse effects related to major and minor bleeding (Ding et al. 2020).

Hereinafter we will consider the most important scores for hemorrhagic risk stratification.

In clinical practice, diverse stratification models are available for hemorrhagic risk assessment. Considered parameters are: advanced age, previous major bleeding events, previous stroke, recent myocardial infarction, creatinine >1.5 mg/dL, hematocrit <30%, and diabetes. It appears evident that several of the aforementioned risk factors are common to those for stroke, hence the proposal of the term "shared risk factors" to underline this aspect.

Over the years, various models have been proposed for bleeding risk stratification in patients taking OACs, although few have been validated in AF and many are not easily applicable, as they either require complex mathematical formulas or include parameters not measurable in routine clinical practice (Lip et al. 2011a, 2012). For example, the HEMOR2RHAGES-14 score (liver/kidney disease, abuse of ethanol, neoplasms, old age [>75 years], recurrence of bleeding, thrombocytopenia, uncontrolled hypertension, anemia, genetic factors, risk of falls, and stroke) is characterized by an overlap between bleeding and stroke risk factors, hence creating burdens in the decision on most appropriate antithrombotic therapy (Gage et al. 2006). A further bleeding risk stratification model, validated with a good predictive effectiveness, is represented by the ATRIA score (Anticoagulation and Risk Factors in Atrial Fibrillation), which allows to classify patients into high, medium, and low risk (Fang et al. 2011). The ORBIT score was instead derived from a cohort of almost 7500 patients on warfarin therapy, in which a bleeding incidence of 4% patient-years was reported. In this cohort, age >75 years, a history of anemia or previous bleeding, renal failure or use of ASA were predictive with a *c*-score of 0.67 (O'Brien et al. 2015). A recently introduced score is the ABC-bleeding (or "Age, Biomarkers, Clinical history"), which was developed within the ARISTOTLE study and validated in the same ARISTOTLE (approximately 14,500 patients) and in the RE-LY study (approximately 8500 patients). The ABC score is interesting because it also associates with bio-humoral parameters (GDF-15, troponin T, and hemoglobin) and it is calculated using continuous quantitative data rather than dichotomizing them into qualitative variables. This score reaches a predictive validity of 0.68, higher both than the ORBIT (0.65) (Hijazi et al. 2016b), and the most used HAS-BLED score (*c*-score = 0.59) (Lip et al. 2018).

As the latest ESC guidelines recommend using HAS-BLED for risk stratification of AF patients (Kirchhof et al. 2016b; Pisters et al. 2010), we will further focus in depth on this score.

The HAS-BLED Score

HAS-BLED takes the name from the considered parameters: H "hypertension" (systolic blood pressure >160 mmHg), A "abnormal liver/renal function," S "stroke," B "bleeding history/predisposition," L "labile international normalized ratio (INR)," E "elderly" (i.e., age >65 years) and D "concomitant drugs/alcohol." The HAS-BLED score allows to classify patients into low-to-moderate risk (if the score is

0–2) and high risk (with a score ≥3). Pisters et al. validated in 2010 this practical and easy to use score, which is able to estimate the risk of major bleeding at 1 year, in a real-life cohort of AF patients: the EuroHeart Survey population (Pisters et al. 2010). Of note, the HAS-BLED score has also been validated among non-AF subjects, which renders it applicable at all stages of the patient management pathway (Kooiman et al. 2015; Omran et al. 2012; Smith et al. 2012).

Validation was based on the predictive ability of the score, measured by *c-statistic* of 0.72, higher in the case of concomitant antiplatelet therapy (*c-stat* = 0.91), and was later performed also on warfarin-naïve patients, on subjects under non-warfarin anticoagulants and in those receiving both warfarin and aspirin (Lip et al. 2011b).

HAS-BLED score has proven to be better than the HEMOR2RHAGES and with a good predictive accuracy. Furthermore, unlike some risk factors within the HEMOR2RHAGES, all HAS-BLED risk factors are easily recoverable either from the patient's medical history or from the routine tests (Pisters et al. 2010; Lip et al. 2011b). Of note, HAS-BLED includes the assessment of anticoagulation quality control by considering as a criterion the "labile INR," relevant most of all for VKAs users (Proietti et al. 2016). The superiority of HAS-BLED against both HEMORR2HAGES and ATRIA in bleeding risk prediction was furtherly confirmed by two systematic reviews and meta-analyses by Zhu et al. (2015b) and Caldeira et al. (2014a).

Thus, the usefulness of such a simple and effective bleeding risk stratification model appears evident, especially in view of the recent introduction of new DOACs. As an example, patients considered at a higher bleeding risk according to the HAS-BLED score, could benefit from the lower dose (110 mg × 2) of the direct oral thrombin inhibitor, dabigatran, while to subjects at lower bleeding risk may be administered the higher dose (150 mg × 2) of the drug, which offers a higher efficacy, though a bleeding risk similar to that of warfarin (Steffel et al. 2018).

However, the presence of factors associated with both an increased risk of embolic and hemorrhagic thrombus suggests taking individual decisions based on the net clinical benefit of the patients (Steffel et al. 2018; Kirchhof et al. 2016b).

Direct Oral Anticoagulants in AF: General Outline

Current International guidelines suggest administering DOACs as an alternative to warfarin, in non-valvular AF (NVAF). In fact, DOACs demonstrated an efficacy equal to Vitamin K Antagonists (VKAs) in the prevention of both stroke and major embolic events, net of a lower bleeding risk. Moreover, patients taking DOACs do not need a continuous INR monitoring to control the dosage (Russo et al. 2017a; Proietti et al. 2015).

Up to date, marketed DOACs are four: Dabigatran, a thrombin direct inhibitor and three Xa factor inhibitors (rivaroxaban, apixaban, and edoxaban). All most important registration trials have compared both efficacy and safety of each single drug with those of warfarin, except for apixaban, for which also a comparative trial with aspirin has been led.

DOACs and Risk Stratification

According to the most recent guidelines, risk stratification does not change, still referring to the $CHA2DS_2VASc$ Score. From the sub-analyses of both main clinical trials and post-marketing phase IV studies, further evidence has been provided as regards both efficacy and safety of DOACs in definite subpopulations.

DOACs Efficacy and Safety in Patients with AF and Diabetes

Diabetes and AF are strongly related. Diabetic patients, as compared to healthy subjects, present almost a double risk of experiencing AF. In addition, diverse studies have shown that in these subjects with hypertension, age >65 years, and AF the risk of stroke is double (Ding et al. 2020). As compared with warfarin, all DOACs have shown an equal efficacy in terms of relative risk reduction for stroke (Hijazi et al. 2016a; Zachary and Richter 2018; Prídavková et al. 2019; Brambatti et al. 2015; Ezekowitz et al. 2015). Currently, in the absence of long-term studies on DOACs in the diabetic population, no evidence has affirmed the superiority of one over the others. Their use must also be accompanied by a careful monitoring of the renal function to avoid an over-dosage (Cosentino et al. 2020), as the altered kinetics due to diabetic kidney disease seems the only interaction observed with DOACs (Hernandez et al. 2019; Russo et al. 2020c).

DOACs and Heart Failure

Heart Failure (HF) represents a further indication to the use of anticoagulant therapy in AF patients. The therapeutic approach with DOACs in this specific subpopulation does not differ from that in the general population treated with warfarin. Moreover, no interaction has been found between drugs and HF degree. A recent observational retrospective study of 2019, on about 60,000 patients with both AF and HF, assessed safety and efficacy of DOACs as compared to warfarin. Consistently with the main trials (ARISTOTLE, ROCKET-AF, and RE-LY) and with previous meta-analyses, an equal efficacy of DOACs was observed (Amin et al. 2019; Savarese et al. 2016; Xiong et al. 2015).

DOACs and Age ≥75

A recent meta-analysis on approximately 430,000 subjects aged ≥75 years has shown a similar efficacy of DOACs as compared to warfarin and a lower risk of intracranial hemorrhage, while the risk of gastrointestinal bleeding was higher (Russo et al. 2019c, d, 2020d; Mitchell et al. 2019). Hence, dosage modifications are performed according to each individual's age (Russo et al. 2020e). In particular, for dabigatran a reduction should be assessed on a case by case evaluation for patients aged ≥75 years, while it is always recommended if age >80 years, as well as for apixaban. Conversely, for rivaroxaban and edoxaban no dose adjustments are needed. These changes are due to the presence of an altered metabolism in this specific subpopulation, which could trigger an increased coagulating effect.

DOACs and Hypertension

As known, hypertension represents both a stroke and bleeding risk factor when using anticoagulants. Due to this reason, an appropriate blood pressure monitoring is mandatory to minimize the risk of bleeding (Kirchhof et al. 2016a). DOACs are recommended in hypertensive patients and have no particular metabolic interaction with this status, hence dose adjustments are not scheduled (Zachary and Richter 2018). However, even in this case, kidney function should be periodically monitored.

DOACs and Previous Stroke/TIA

Evidence of the use of DOACs in patients with a previous stroke/TIA is poor, mostly due to the small sample size of the various studies in the literature. Nevertheless, evidence from previous epidemiological studies reports that these subjects have a high risk of experiencing a new event, although under anticoagulant treatment. Findings from the diverse registration trials and meta-analyses, even in this subpopulation, did not show any difference in terms of both efficacy and safety as compared to warfarin (Coleman et al. 2017; Larsen et al. 2014).

DOAC Efficacy and Safety in Female Patients with AF

To date, there is no established sex-related difference in terms of both efficacy and safety between DOACs and warfarin. In addition, no metabolic interaction with the female gender has been observed (Zachary and Richter 2018; Fang et al. 2005; Poli et al. 2009).

DOACs and Kidney Disease

Kidney disease represents a risk factor for both bleeding and embolic events. In patients with chronic kidney disease (CKD) and AF, even with a $CHA2DS_2VASc$ of 0, the stroke risk is fivefold higher than in the general population, while if $CHA2DS_2VASc \geq 2$, it can exceed 7 per 100 person-years. Consistently with these data, some meta-analyses have proven eGFR as an independent risk factor for stroke and systemic embolism. The reasons for this state of hypercoagulability in CKD have been not established yet. Stasis of the left atrium, impaired endothelial function, and increased platelet activity might explain this correlation (Zachary and Richter 2018).

In addition, in the general population, CKD may increase AF risk through several mechanisms (Alonso et al. 2011). Renal and pulmonary diseases were among the factors more significantly associated with all-cause mortality. Patients with stage 3 CKD have been shown a 25% increase in the risk of death associated with a 10-mL/min decrease in creatinine clearance (van Zyl et al. 2020). Considering this evidence, some authors suggest using anticoagulant therapy in ESRD patients and hope eGFR would become part of the embolic risk stratification scales.

As reported in the most recent guidelines and preclinical phase trials, use in severe renal impairment is not recommended for apixaban and rivaroxaban if eGFR <15 mL/min, while for dabigatran already if eGFR <30 mL/min. In fact, the reduced excretory and metabolic capacity can increase the concentration of the drug, thus enhancing its anticoagulant effect and bleeding risk.

However, all main comparative registration trials (ARISTOTLE, RE-LY, ROCKET) demonstrate a higher efficacy of DOACs in preventing the risk of stroke, as compared to warfarin, even in the case of renal failure and either mild or moderate eGFR reduction. As well, also safety has been demonstrated as non-inferior to that of warfarin. Edoxaban administration is recommended only for eGFR values not exceeding 95 mL/min. In addition, usually in dialysis DOACs are not recommended, though a single study has demonstrated both a good tolerance and safety of rivaroxaban, apixaban and edoxaban in this sub-setting (Zachary and Richter 2018). However, further studies would be worthy to modify DOACs contraindications in both dialysis and ESRD patients.

DOACs and Cirrhosis

Only few papers have compared both efficacy and safety of DOACs with heparin and warfarin in subjects with liver cirrhosis. These patients are usually considered not eligible due to the potential drug related liver damage and enhanced anticoagulant effect. However, more in depth, while rivaroxaban is contraindicated in the case of CHILD B and C, CHILD PUGH B subjects do not disclose any alteration due to the exposure to either apixaban or dabigatran. This might suggest their possible use also in this sub-setting (Pokorney et al. 2016; Sakuma et al. 2019).

Although the small sample size, DOACs-treated populations have shown an equal efficacy for stroke with an either lower or equal incidence of bleeding events as compared to warfarin and heparin. Some authors confirmed DOACs efficacy, though disclosing a higher rate of bleeding events, primarily gastrointestinal. Thus, they suggest caution and an endoscopic exam of the gastric and esophagus tract before undertaking DOACs therapy (Cosentino et al. 2020; Coleman et al. 2017; Ruff et al. 2014; Lip et al. 2016; Jacobs et al. 2016).

As most of cirrhotic patients enrolled generally have either a CHILD PUGH A or B (Elhosseiny et al. 2019; Intagliata et al. 2016; Hum et al. 2017; Caldeira et al. 2014b), it would be useful to acquire new data to prove both efficacy and safety of DOACs in this sub-setting, especially for what concerns CHILD PUGH C stage cirrhosis.

A brief mention deserves NAFLD and NASH patients. In such conditions, DOACs have shown an efficacy at least comparable to that of warfarin and a higher safety. Hence, they represent a good therapeutic option for the treatment of both AF and VTE in patients with liver disease. In addition, up to date, management of bleeding complications in these patients can benefit from specific antidotes currently available for all DOACs (Ballestri et al. 2020).

Anticoagulant Selection

DOACs Registration Trials

The introduction of DOACs in clinical practice has opened new scenarios both in the prevention and treatment of thromboembolism (Wigle et al. 2019; López-López et al. 2017). Overall, DOACs disclose a more favorable risk-to-benefit ratio than that of vitamin K antagonists (VKAs) therapy (Czuprynska et al. 2017; Raschi et al.

2016; Almutairi et al. 2017). However, the balance between thrombotic and hemorrhagic risk still remains a fragile clinical junction in the choice of the best oral anticoagulant (OAC) therapy. Evidence about both efficacy and safety of new DOACs thus represents a crucial element.

DOACs share common characteristics. They are all direct inhibitors of factors involved in the common path of coagulation, they have a relatively short half-life (8–15 h) and a rapid absorption (1.5–4 h).

Primary efficacy objective of all registration trials was the prevalence of stroke, either ischemic or hemorrhagic, plus systemic embolism; while the primary safety outcome was instead the prevalence of both major and non-major, but clinically relevant bleeding events (Schulman et al. 2005). Hemorrhagic strokes were included in both the primary outcome and among the adverse safety events. Outcomes were assessed after a median follow-up time of 2 years. As first, non-inferiority was assessed and, subsequently, the potential superiority.

The first DOAC introduced in the marketing was dabigatran. The RE-LY ("Randomized Evaluation of Long-term anticoagulation theraphY") study is a prospective, randomized, "open-label" phase III study, part of the "RE-VOLUTION" clinical study program aimed at evaluating efficacy and safety of dabigatran compared to standard therapy (warfarin) in the prevention of ischemic and hemorrhagic stroke in AF patients (Connolly et al. 2009).

In this open-label study, 18,113 patients were enrolled, divided into two treatment arms based on the dosage of the drug, respectively 110 mg × 2 ($n = 6.015$) and 150 mg × 2 ($n = 6.076$) and a control arm of patients taking warfarin ($n = 6.022$) at the dose necessary to keep INR between 2 and 3. The study population had a mean age of 71 years, for the 60% males. All patients had NVAF and at least one of the following risk factors: history of stroke/TIA, either EF <40% or clinical signs of heart failure in NYHA class II, III, or IV in the last 6 months prior to enrollment, age >75 years (between 65 and 75 years in the presence of T2DM, hypertension, or coronary artery disease). In other words, all enrolled subjects had a $CHADS_2VASC$ score ≥1. Of note, about the 40% was also under aspirin therapy and only the 50% was naïve for warfarin. The RE-LY study proved non-inferiority of dabigatran at a dosage of 110 mg bid with respect to warfarin in the reduction of stroke and systemic embolisms, expressed by a Relative Risk (RR) of 0.91 (95% CI 0.74–1.11). Conversely, no advantages over warfarin emerged for secondary efficacy outcomes: stroke, cardiovascular (CV) mortality, and all-cause death. Indeed, at the higher dosage, even superiority of dabigatran as compared to warfarin was demonstrated (RR 0.66; 95% CI 0.53–0.82), a lower rate of both stroke and CV deaths, while myocardial infarctions (MI) were more frequent. As regards adverse events, prevalence of minor bleeding was significantly lower, while no difference emerged for major bleeding events. Finally, gastrointestinal bleeding was more frequent as compared to warfarin. In 2014, mortality outcomes were furtherly reassessed, though not substantially modifying the previous findings (Connolly et al. 2014).

The ROCKET-AF study ("Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation") focused on the assessment of rivaroxaban for the

prevention of ischemic strokes in AF patients (Patel et al. 2011). ROCKET-AF is a double-blind study on about 14,000 patients comparing rivaroxaban at the dosage of 20 mg/day (dropped to 15 mg/die in the case of glomerular filtrate (GFR) between 30 and 9 mL/min) with a control arm taking warfarin at the dose necessary to maintain INR between 2 and 3. Unlike the RE-LY study, enrolled patients had to present a $CHADS_2VASC \geq 2$ (i.e., a NVAF associated with previous stroke/TIA/systemic embolism or at least 2 of the following risk factors: heart failure/EF <30%, hypertension, age >75 years, T2DM). A severe kidney failure and high bleeding risk were instead considered exclusion criteria.

The study revealed non-inferiority of rivaroxaban 20 mg as compared to warfarin for the primary efficacy outcome, with a HR of 0.79 (95% CI 0.66–0.96), though not reaching the superiority. Non-inferiority was also proven for the secondary outcome of all-cause death. Similar findings also emerged in assessment of the primary safety outcome (frequency of clinically relevant major and minor bleedings) (HR 1.03; 95% CI 0.96–1.11).

A similar study design was applied in the assessment of apixaban. The ARISTOTLE study ("Apixaban for Reduction in Stroke and Other ThromboembolIc Events in atrial fibrillation") is a prospective double-blind randomized clinical trial led on about 18,000 patients. Apixaban at the oral dose of 5 mg bid (dropped at 2.5 mg bid in patients aged >80 years, with a body weight <60 kg and creatinine >1.5 mg/dL) was compared with warfarin (with a dosage appropriate to the INR target value between 2 and 3) in AF patients with at least one other additional risk factor for stroke or systemic embolism (Granger et al. 2011). Enrollment criteria were instead similar to RE-LY, hence a $CHADS_2VASc \geq 1$. Patients with mechanical valve prostheses, severe renal failure and under double antiplatelet therapy were instead excluded. Remarkably, as compared to other molecules, apixaban proved superior to warfarin in reducing the risk of stroke and systemic embolism (HR 0.79; 95% CI 0.66–0.95), as well as all-cause mortality in the study population. Further, the analysis of safety outcome revealed a significant reduction also for what concerned major bleedings.

Likewise, the ENGAGE AF-TIMI 48 study (Effective aNticoaGulation with factor XA next GEneration in Atrial Fibrillation) is a double-blind randomized clinical trial on 21,105 patients, aimed at comparing edoxaban either at the dosage of 60 mg/day ($n = 7.035$) or 30 mg/day ($n = 7.034$) with warfarin at the dosage needed to keep INR between 2 and 3 ($n = 7.036$) (Giugliano et al. 2013). Of note, edoxaban dosages were halved in the case of eGFR between 30 and 49 mL/min, body weight <60 kg or concomitant use of verapamil. In addition, similarly to the ROCKET-AF study, enrolled patients had to have a $CHADS_2VASc \geq 2$. The ENGAGE-AF TIMI 48 proved non-inferiority of edoxaban as compared to warfarin in reducing the risk of stroke at both dosages, while superiority was not demonstrated for the primary outcome. Edoxaban revealed instead superior to warfarin for what concerns safety, i.e., in reducing major bleeding events, while the annual incidence of gastrointestinal hemorrhages was significantly lower than warfarin only at the dosage of 30 mg/day. Later, in a pre-specified analysis of the ENGAGE AF-TIMI 48 study, the clinical

outcome was compared by stratifying patients into 3 groups based on age (<65, 65–74, and ≥75 years). The older group included almost 8500 patients (mainly females, with a lower body weight and reduced GFR, hence requiring lower dosage of edoxaban). No significant differences against warfarin emerged in terms of efficacy and safety, despite the frequently reduced dosage, while major bleeding was significantly lower (HR 0.83, 95% CI 0.70–0.99). This pre-specified analysis once again confirms the close relationship between age and both thromboembolic and hemorrhagic risk in AF patients, even after adjustment for any confounding factors (Kato et al. 2016; O'Donoghue et al. 2015).

Apixaban is the only DOAC proven as superior over warfarin in terms of both efficacy and safety for a single dosage, demonstrating a decrease of major bleeding from 3% (warfarin) to 2% patients/year, as well as a reduction in all-cause mortality. In addition, apixaban is the only drug, at full dose, not significantly affecting the rate of major gastrointestinal bleeding. ARISTOTLE efficacy and safety outcomes are generalizable to all $CHADS_2VASC$ and HAS-BLED categories. Furthermore, the reduction of the dosage for apixaban is indicated in a small minority of patients (Pelliccia et al. 2016).

Over recent years, efforts have been made to find which DOAC had the most favorable risk-to-benefit profile according to the recommendations for which they were registered. Due to the lack of comparative studies between the different DOACs, but only vs. warfarin, diverse meta-analyses and systematic reviews attempted to indirectly compare the four DOACs (Ruff et al. 2014; Adam et al. 2012; Dentali et al. 2012).

Real-World Evidence (RWE) studies may provide additional information to that of registration trials and meta-analyses, proposing a picture closer to daily clinical practice (Camm et al. 2018; Garrison et al. 2007; Russo et al. 2015, 2017b, 2018b, 2019e; Verdecchia et al. 2019). Prospective non-interventional studies (Larsen et al. 2013; Maura et al. 2015), such as the XANTUS phase IV study, instead provide highly reliable efficacy and safety information, since they allow to acquire knowledge in real time in different kind of populations. Particularly, the XANTUS study showed that the enrollment of patients with characteristics similar to RE-LY and ARISTOTLE studies was associated with a safety profile of rivaroxaban higher than that observed in the registration study (Camm et al. 2016).

Oral Anticoagulant Selection

Only in few specific conditions warfarin is preferable to DOACs, as follows:

(a) In patients with either mechanical heart valves of any type or with severe mitral stenosis from any cause (January et al. 2019).
(b) In patients with severe end-stage renal disease (ESRD) or in hemodialysis; even though apixaban has also been approved in this condition in the United States (January et al. 2019).

(c) In patients already on warfarin treatment, who are used to INR monitoring, and whose INR is within the therapeutic time range (TTR) for an interval >65% (January et al. 2019; McAlister et al. 2018).
(d) In patients with a scarce adherence in taking the appropriate pharmacological dose of DOAC, thus requiring a closer monitoring of the compliance to the OAC therapy (Garkina et al. 2016).
(e) In subjects taking antiepileptic drugs (particularly phenytoin, carbamazepine, phenobarbital, and valproate) and in patients with human immunodeficiency virus (HIV) infection on antiretroviral therapy based on protease inhibitors (Wigle et al. 2019; Galgani et al. 2018).

A brief consideration deserves patients with COVID-19 receiving antiretroviral therapy in whom, due to their important procoagulant status, anticoagulant strategies alternative to DOACs should be considered, given the diverse pharmacological interactions (Marietta et al. 2020).

Thus, we can conclude that most DOACs represent an advance in the therapeutic safety as compared to warfarin, for the prevention of thromboembolism in AF patients.

OACs unlike VKAs do not exactly exhibit the same indications and availability in all countries. In fact, local factors such as formal committees and costs of therapy may affect their availability (Heidbuchel et al. 2015; Russo et al. 2018c).

Other studies report a more favorable outcome of dabigatran as compared to warfarin in AF ablation (RE-CIRCUIT Trial) (Calkins et al. 2017). As well, over the years, both dabigatran and rivaroxaban have been associated with lower risks of adverse renal outcomes than warfarin in AF patients (Yao et al. 2017). Moreover, for what concerns the elderly AF patients taking OAC therapy, dabigatran has been associated with a lower risk of osteoporotic fracture as compared to warfarin (Lau et al. 2017).

In addition, further data on pharmacologic interactions with DOACs have also been emerging, even though their interpretation must carefully evaluate the trial design, including factors such as the lack of control groups, incomplete laboratory and history data, as well as of data for some drugs (in particular edoxaban) and the variability of DOACs dosage (some doses approved in the United States differ from those in Europe). Hence, prospective RCT focused on DOACs comparison would be worthy to better evaluate the comparative bleeding risk and efficacy (January et al. 2019).

New Scenarios in the Risk Stratification Panorama

Although CHA_2DS_2-VASc is currently the most used score, as well as the most recommended by all international guidelines, several studies have disclosed the presence of other new risk factors, both clinical and laboratory, which could be independently associated with the occurrence of stroke. These might be complementary to the CHA_2DS_2VASc risk scale and increase its discriminatory power.

Besides this, new risk scores have been proposed in the last few years, which could either replace or support $CHA2DS_2VASc$.

New Clinical Risk Factors

BMI

From an analysis of the Japanese registers on about 12,000 NVAF patients assessing the predictive power of the single risk factors for stroke, a statistically significant positive association both with a low body weight (≤50 kg) and low BMI (<18.5 kg/m^2) emerged (HR 1.55; 95% CI: 1.05–2.29; $p = 0.030$). This finding was consistent with two previous studies. However, the same authors observe that, rather than a risk factor, BMI could represent a risk modifier. In fact, the study population also included patients with a BMI <18.5 kg/m^2 not reaching the outcome. Hence, due to the inconsistency with other studies and the small sample size, up to now BMI has been yet considered neither a risk factor nor a modifier. If these findings were confirmed by larger studies, BMI could be included in the most part of risk assessment scales (Yao et al. 2017; Lau et al. 2017; Okumura et al. 2020; Lee et al. 2019; Zhu et al. 2016).

Echocardiography

According to 2016 ESC guidelines for AF, the role of transthoracic echocardiography is currently limited to an assessment of overall cardiac function, hence useful to exclude the presence of thrombi in the atrium in order to practice AF cardioversion and diagnose structural pathologies more likely associated. However, also thanks to the presence of new software and echocardiographic parameters (e.g., strain), some authors suggest that echocardiography might play an important role in identifying new risk factors for stroke in AF. In a recent study, Galderisi and colleagues argued that the function of left atrium assessed by means of strain functionality and its enlargement could represent a stroke risk factor in AF patients (Tufano and Galderisi 2020). Consistent with these findings, another study on about 3000 patients, with a 3-year follow-up, showed that some factors, including the left atrial diameter, were independently associated with either stroke or systemic embolism. Among these, a high Relative Wall Thickness (RWT higher than the median) was significantly associated with stroke/SE. Thus, the authors suggested that RWT could be associated with CHA_2DS_2VASc to improve its discriminatory power (Tezuka et al. 2020). Recently, Olsen et al. in a study led on patients with paroxysmal AF, the SURPRISE echo sub-study, observed that the left atrial reservoir strain was altered in patients suffering from cryptogenic stroke (Olsen et al. 2020)**.**

Despite the evidence, these findings are still divergent and there are still few studies in the literature to establish with a good certainty whether and which of the echocardiographic parameters may be associated with CHA_2DS_2VASc. Therefore, even in the case of echocardiographic parameters, further studies are needed to ascertain their validity as risk factors.

Biomarkers

Several biomarkers have been tested in AF patients to find a correlation between their concentration level and the stroke event. Among them, diverse studies showed an association between high BNP/NT-proBNP levels and an increased risk of thromboembolic events (Tezuka et al. 2020; Hayashi et al. 2018; Roldan et al. 2014). Moreover, the sub-analysis of two of the main registration trials of DOACs (ARISTOTLE and RE-LY) confirmed this finding (Hijazi et al. 2012, 2013). In addition, in a study aimed at evaluating the association of some biomarkers with stroke in AF patients, only high NT-proBNP levels (≥300 pg/mL) have been reported as an independent predictor, indeed positively associated with the incidence of stroke (Shin et al. 2019).

Besides proBNP, T-troponin concentrations have also been assessed as potential biomarkers suggestive of stroke risk. Consistently with RE-LY sub-analyses, another study confirmed this significant association (aHR 2.35; 95% CI: 1.26–4.36; $p = 0.007$) (Vafaie et al. 2019).

Another biomarker proposed as useful to improve the predictive value of CHA_2DS_2VASc is endothelin. In a population of about 200 patients, this emerged as significantly associated with high CHADS2/CHA_2DS_2VASc scores and an increase in the volume of the left atrium (Zheng et al. 2019).

In the most recent years also other biomarkers, such as hemostatic (D-dimer, von Willebrand factor (vWF), soluble E-selectin, and P-selectin) and inflammatory (interleukin-6 (IL-6) and C-reactive protein (CRP)) have been assessed. However, findings were divergent. Moreover, there is still little evidence in favor of their use and sample sizes are too small to include one of these in the current stroke risk scales. Other authors also observe how the concentration of these markers is extremely variable, as well as too high within the same subject to be able to standardize a range usable in risk stratification. Even the laboratory costs of these exams are too high to be subjected to a routine evaluation. These are some of the reasons why, up to now, the use of such biomarkers may only be justified from scientific research purposes, whilst their potential use at a routine clinical level still seems far away.

New Scores

New scores have been proposed, not to replace, though rather to accompany CHA_2DS_2VASc. Among these, the Intermountain Mortality Risk Scores (IMRSs), which is based on a score calculated from both blood count and biochemical parameters. In the past, it has been used to stratify the risk of mortality and cardiovascular pathologies (myocardial infarction, heart failure, coronary artery disease, etc.). A recent study assessed the power of the IMRSs in the stratification of stroke risk in AF patients, both independently of CHA_2DS_2VASc, and complementarily, to increase its discriminating power (*c-statistic*). Individually, the two scores showed a similar predictive power, while overall IMRSs can further differentiate high and low risk patients into the groups identified by the CHA_2DS_2VASc. Thus, such a score

could be useful to identify patients at high risk of stroke among those borderlines at the CHA_2DS_2VASc (Horne et al. 2010; Graves et al. 2018), hence improving and enhancing its performance.

Some authors also observe that a liver dysfunction due to the presence of liver diseases such as HCV related hepatopathy, NAFLD, and cirrhosis is predisposing to the development of various cardiac diseases, including FA. In fact, it seems that an autonomic cardiac dysfunction might be related to the inflammatory status typical of liver disease. Some authors suggest that liver injury indices may be functional for stratifying the risk of both cardiovascular diseases and embolic events. A study on about 3000 AF patients with liver disease has shown that FIB4, a score suggestive of the degree of fibrosis and liver damage, if combined with the CHA_2DS_2VASc, could increase its predictive power for cardiovascular events. As a result, the associated FIB4/CHA_2DS_2VASc improved its c-statistic, bringing it from 0.61 to 0.64 (respectively alone and associated with the FIB4 index) (Saito et al. 2020; Sato et al. 2017; Käräjämäki et al. 2015).

Up to now, the list of risk factors and scores valid for stroke risk stratification cannot be improved. Available evidence is poor, and findings are still divergent. Thus, hopefully, future larger studies will enhance the stratification capacity of the CHA_2DS_2VASc and, perhaps, novel risk factors closely related to the embolic event will be discovered.

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Use of DOAC in Patients with Kidney Disease

7

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Introduction

Atrial fibrillation and chronic kidney disease are on the rise worldwide. Both disorders are strictly related to aging population and may coexist in the same patient. Chronic kidney disease affects 15% of adults, who in turn will suffer from atrial fibrillation in up to 30% of cases depending on the severity of the renal impairment (Tonelli et al. 2012; Wizemann et al. 2012). The factors predisposing to atrial fibrillation in chronic kidney disease patients include hypertension, heart failure, and autonomic imbalance, leading to structural and electrical remodeling of the atria (Kumar et al. 2019).

Moreover, thromboembolic complications typical of atrial fibrillation are amplified in patients with renal dysfunction, who may have a hypercoagulable state due to increased platelet activity, activation of the renin-angiotensin-aldosterone system, altered vessel wall contractility and vascular endothelium changes, resulting in a ≈50% increase of stroke or systemic thromboembolism (Olesen et al. 2012; Providência et al. 2014; Bansal et al. 2013; Proietti et al. 2018).

Oral anticoagulation therapy, nowadays preferably with direct oral anticoagulants (DOACs), represents the cornerstone for stroke thromboprophylaxis in high-risk patients with atrial fibrillation according to CHA2DS2VASc score (Hindricks et al. 2021). The impaired renal function which defines chronic kidney disease directly

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impacts on the anticoagulation regimen, since all four available DOACs are eliminated at least partially by the kidneys. Dabigatran has the highest renal elimination (80%), whereas edoxaban, rivaroxaban, and apixaban have lower values (50%, 35%, and 27%, respectively) (Steffel et al. 2018). Cockcroft–Gault formula is commonly used to calculate, on the basis of serum creatinine levels, the creatinine clearance (CrCl, expressed in mL/min), that is an estimation of the glomerular filtration rate (GFR). Other equations express the GFR in mL/min/1.73 m^2, such as CKD-EPI, which is used to classify the severity of chronic kidney disease (Inker et al. 2014). For the sake of dosing the DOACs on the basis of kidney function (see below), CrCl calculated with Cockcroft–Gault formula should be used as a reference, since it was adopted by all the randomized controlled trials that led to their commercialization (Connolly et al. 2009; Patel et al. 2011; Granger et al. 2011; Giugliano et al. 2013).

A correct prescription is fundamental because adverse events due to supratherapeutic levels include major bleeding such as hemorrhagic stroke. The alterations of hemostatic system in chronic kidney disease include not only the possible aforementioned pro-thrombotic state, but also hemorrhagic diathesis led by platelet dysfunction, compromised platelet aggregation, and intercurrent anemia (Hedges et al. 2007). Regular calculation of CrCl during follow-up is required and European experts recommend monitoring renal function at least yearly, or more often if baseline CrCl is reduced (i.e., <60 mL/min). The proposed formula for calculating the rechecking interval in months of the renal function during DOAC therapy is CrCl/10 (e.g., for CrCl 40 mL/min the rechecking interval is 4 months) (Steffel et al. 2018). Atrial fibrillation favors the progression of chronic kidney disease: in a large study of patients with moderate to severe loss of renal function, incident atrial fibrillation was independently associated with a 67% higher rate of progression to the end-stage phase (Bansal et al. 2013; Winkelmayer 2013). Periodic reassessment of renal function helps to timely identify further CrCl decline, avoiding DOACs accumulation at supratherapeutic plasma levels that may cause major bleedings.

In this chapter, we review the current evidence regarding efficacy and safety profiles of DOACs according to different clinical setting (non-end-stage and end-stage kidney disease). International recommendations (European and American) are presented throughout the text and reassumed in Fig. 7.1.

Non-End-Stage Kidney Disease

In the past decades, warfarin was the preferred anticoagulant used for stroke prevention in patients with atrial fibrillation. The limitations related to warfarin therapy (i.e., slow onset of action, variable pharmacologic effects, several food and drug interactions) were overcome by the advent of DOACs, that in turn demonstrated a similar efficacy and better safety profile. All DOACs show a predictable pharmacokinetic and do not require regular monitoring of the coagulation to optimize their clinical management. Warfarin is metabolized by the liver and so it is routinely used even in patients with end-stage kidney disease. Conversely, DOACs are eliminated by the kidneys to some extent and their use in patients with impaired renal function raises some concerns: the RE-LY, ROCKET AF, and ENGAGE AF-TIMI 48 trials,

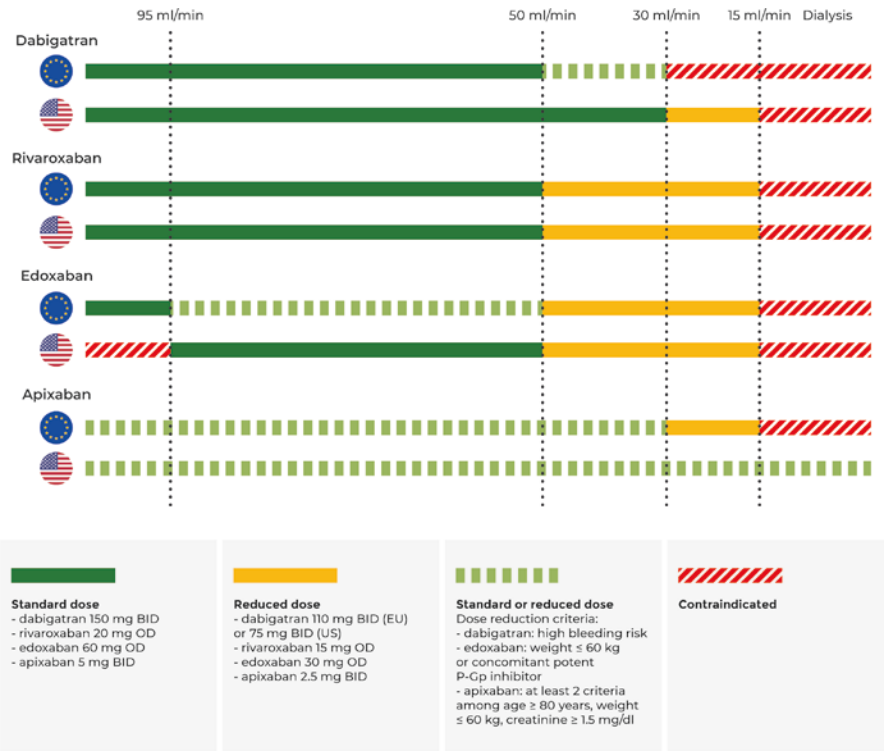

Fig. 7.1 Recommendations for DOACs dosing on the basis of renal function according to European and American guidelines. European and American recommendations are based on the latest 2018 EHRA and 2019 AHA/ACC/HRS documents (Steffel et al. 2018; January et al. 2019). *BID* bis in die, *OD* omne in die, *EU* Europe, *US* United States

that respectively tested efficacy and safety of dabigatran, rivaroxaban, and edoxaban, excluded patients with severe chronic kidney disease (i.e., CrCl <30 mL/min) (Connolly et al. 2009; Patel et al. 2011; Giugliano et al. 2013). The inclusion criteria in the ARISTOTELE trial were slightly less stringent since apixaban has the lowest renal elimination and patients with CrCl >25 mL/min were enrolled (Granger et al. 2011). Numerous post-hoc analysis of these studies investigated whether or not DOACs efficacy and safety were confirmed in patients with mild to moderate chronic kidney disease compared to those with normal renal function.

In the study by Hijazi et al., the efficacy and safety of dabigatran compared to warfarin were analyzed in relation to baseline renal function (Hijazi et al. 2014). After estimating the GFR with CKD-EPI formula instead of Cockcroft–Gault equation used in the trial, he found significant interactions between treatment and renal function: both dabigatran dosages (150 and 110 mg bis in die - BID) displayed lower rates of major bleeding in patients with GFR >80 mL/min, while their efficacy was consistent with the overall trial regardless of renal function (Hijazi et al. 2014). In patients with severe renal dysfunction (GFR 15–29 mL/min),

pharmacological projections suggested a reduced dose of dabigatran 75 mg BID: US Food and Drug Administration allows the administration of such regimen in this case, but dabigatran remain contraindicated in Europe when GFR is <30 mL/min because of safety concerns (Steffel et al. 2018; Lehr et al. 2012; January et al. 2019).

For rivaroxaban, other pharmacokinetics analysis demonstrated that maximal serum concentrations were 25–30% higher in patients with moderate chronic kidney disease (CrCl 30–49 mL/min) (Kubitza et al. 2010). This evidence triggered the reduction of rivaroxaban dosage from 20 mg omne in die (OD) to 15 mg OD in moderate renal insufficiency in the ROCKET AF trial, that involved a sizeable proportion of the study population (one in five study patients) (Patel et al. 2011). The overall study demonstrated a benefit in stroke reduction and systemic embolism comparable to warfarin, with fewer fatal hemorrhages. A post-hoc analysis demonstrated that rivaroxaban 15 mg in moderate renal impairment yielded the same results of the standard 20 mg in preserved kidney function, excluding a heterogeneity in treatment effect across dosing groups (Fox et al. 2011). The administration of rivaroxaban 15 mg OD is permitted both in Europe and in the US even in case of severe renal impairment (GFR 15–29 mL/min), despite this condition represented an exclusion criterion for the trial (Steffel et al. 2018; January et al. 2019).

Another DOAC approved in case of GFR >15 mL/min is edoxaban (Steffel et al. 2018; January et al. 2019). The clearance of edoxaban depends for half percent on renal elimination, and total drug exposure increases by 32 to 72% in patients with mild to severe renal dysfunction (Parasrampuria and Truitt 2016). Therefore, in the ENGAGE AF-TIMI 48 trial the edoxaban dose was reduced from 60 to 30 mg OD in patients with moderate renal insufficiency (CrCl 30–49 mL/min); patients with severe reduction of renal function (CrCl<30 mL/min) were excluded (Giugliano et al. 2013). Other criteria for dose reduction were weight ≤60 kg or administration of a strong P-glycoprotein inhibitor. Compared to warfarin, edoxaban had a comparable efficacy for stroke prevention, carrying a reduced risk for bleeding and cardiovascular death (Giugliano et al. 2013). Bleeding rates were lower at all levels of CrCl, as later assessed by Bohula et al. (2016). A further post-hoc analysis added useful evidence that in patients who developed severe chronic impairment during follow-up (CrCl <30 mL/min) stroke and major bleeding rates were similar between those treated with edoxaban compared to those on warfarin (Chan et al. 2016). On the other hand, edoxaban 60 mg may be less effective for stroke prevention in patients with "supranormal" renal function (CrCl >95 mL/min) and in such cases it is contraindicated in the US, whereas European recommendations indicate a cautionary use (Steffel et al. 2018; Giugliano et al. 2013; January et al. 2019; Bohula et al. 2016).

Apixaban has the minimal renal excretion compared to the other DOACs, only 27% (Steffel et al. 2018). It is commercialized in two dosages, 5 mg or 2.5 mg BID. Criteria for dose reduction include not only creatinine values (≥1.5 mg/dL), but also weight ≤60 kg and age ≥80 years: when at least two out of three criteria are met 2.5 mg BID should be prescribed (Steffel et al. 2018; January et al. 2019). Hohnloser et al. analyzed data of ARISTOTELE trial and found that apixaban compared to warfarin reduced the rate of stroke, death, and major bleeding irrespective

of renal function (Hohnloser et al. 2012). Of note, the patients who benefited the most from reduction of serious bleeding events were those having at least a moderate renal impairment (CrCl <50 mL/min). Corroborative evidence was provided by a recent post-hoc analysis focusing on the enrolled patients with the lowest CrCl (25–30 mL/min): in such patients with severe renal impairment apixaban treatment was associated with a greater reduction in bleedings compared to those having a CrCl >30 mL/min (Stanifer et al. 2020). In severe kidney disease (CrCl 15–30 mL/min), apixaban is approved in the US with the same aforementioned criteria for moderate renal impairment, whether in Europe is permitted at the lowest dosage (2.5 mg BID) irrespective of age and weight (Steffel et al. 2018; January et al. 2019).

End-Stage Kidney Disease

End-stage kidney disease is classified under stage 5 of chronic kidney disease, together with persons with a GFR <15 mL/min/1.73 m^2 (Inker et al. 2014). It is defined as permanent loss of kidney function that invariably leads to death unless dialysis or transplantation is pursued.

Herein are described evidence and current practice regarding oral anticoagulation in these two different clinical scenarios.

Patients on Dialysis

Patients with chronic kidney disease on dialysis have almost a double risk of stroke compared to non-end-stage counterparts (USRDS 2006). In addition, all nephropathic patients show some degree of platelet dysfunction and impaired platelet aggregation, that are even more pronounced in end-stage renal disease; the so-called "uremic platelet dysfunction" further augments the bleeding risk (Seliger et al. 2003; Suzuki et al. 2007).

In this clinical scenario, the side effects of anticoagulation therapy might offset the desired benefit. Available evidence showed that warfarin increased the rate of bleeding events without any impact on stroke prevention or death (Harel et al. 2017). A recent meta-analysis gathered all the literature in the field and confirmed warfarin inefficacy for ischemic stroke prevention among patients on dialysis; hemorrhagic strokes were significantly higher in those receiving treatment, but mortality was comparable between groups (Randhawa et al. 2020). Factors that can explain these observations include the routine administration of heparin during dialysis and the interference of uremic state with the metabolisms of warfarin, making difficult to maintain the international normalized ratio in therapeutic range (Chan et al. 2009; Marinigh et al. 2011; Leblond et al. 2001; Yang et al. 2017). Apart from growing concern in the trade-off between harm and benefit, warfarin seems to accelerate the worsening of renal function either by favoring parenchymal microbleeds or by promoting vascular calcifications (Brodsky et al. 2011; Tantisattamo et al. 2015). All the above-mentioned considerations raised the urgent need for new therapeutic

approaches, looking at DOACs as appealing alternatives to warfarin in this medically complex population.

European recommendations contraindicate the use of all DOACs in patients with CrCl <15 mL/min or on dialysis, whether US Food and Drug Administration allows only apixaban in these cases (Steffel et al. 2018; January et al. 2019). Following this labeling the use of apixaban has grown in American patients with atrial fibrillation on dialysis, accounting for approximately one out of four new anticoagulants prescribed in this population (Siontis et al. 2018). In a recent study, Siontis and colleagues retrospectively compared the rate of stroke/systemic embolism, major bleedings, and death between patients on dialysis treated with apixaban versus warfarin (Siontis et al. 2018). The researchers concluded that both standard and reduced dose of apixaban (5 mg and 2.5 mg BID, respectively) were associated with a lower risk of major bleedings, but only the standard dose significantly reduced thromboembolic events and death compared to warfarin. However, they described also high rates of intracerebral bleedings and drug discontinuations, casting doubts on the real progress in the management of these complex patients.

Despite being contraindicated, Chan et al. found that prescription of dabigatran and rivaroxaban was occurring among patients on dialysis in the US (Chan et al. 2015). The authors reported that either drugs were associated with a higher rate of hospitalization for bleedings and hemorrhagic death, supporting the current labeling of dabigatran and rivaroxaban. More recent evidence showed that a reduced dose of rivaroxaban (10 mg OD) may lower severe bleeding complications compared to warfarin in hemodialysis patients (de Vriese et al. 2020).

New randomized clinical trials are under way and will shed some lights on the outcome of DOACs for stroke prevention in patients with atrial fibrillation on hemodialysis. The RENAL-AF trial (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation trial; ClinicalTrials.gov identifier NCT02942407) was prematurely stopped for failure to enroll a sufficient number of patients (Pokorney 2019). Other ongoing studies are similarly attempting to compare the efficacy and safety of apixaban versus vitamin-K antagonists for stroke prevention in patients with atrial fibrillation and end-stage kidney disease. These studies include the SAFE-HD trial (Strategies for the Management of Atrial Fibrillation in Patients Receiving Hemodialysis; ClinicalTrials.gov identifier NCT03987711) and the AXADIA trial (Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease; ClinicalTrials.gov identifier NCT02933697). The design of the SAFE-HD trial provided for a control arm of patients without anticoagulation, since previous studies pointed out the ineffectiveness and potential harm of oral anticoagulation with warfarin in patients receiving dialysis (Randhawa et al. 2020).

Kidney Transplant Recipients

Atrial fibrillation occurs in over 7% of kidney transplant recipients in the first 3 years after transplantation and is higher in the peri-transplant period (Malyszko

et al. 2018). New onset of atrial fibrillation in kidney transplant recipients confers a worse prognosis and is associated with a reduced graft and patient survival (Malyszko et al. 2018). In high-risk patients according to CHA2DS2VASc score, the start of oral anticoagulation therapy is indicated (Hindricks et al. 2021). Since recent years, vitamin-K antagonists have been the only oral anticoagulant agents available. An analysis performed on a US registry of patients with end-stage kidney disease failed to show a significant reduction of a composite endpoint of mortality and stroke in patients who underwent renal transplant and were treated with warfarin for new onset AF (Lenihan et al. 2015). Accordingly, the authors reported that in the overall population with AF and renal transplant warfarin was underprescribed possibly due to lack of evidence for a clinical benefit and a perceived increased risk of bleeding in hemodialyzed patients (Lenihan et al. 2015).

Direct oral anticoagulants provide a potentially safer option in patients who have had renal transplant. However, they have at least a partial renal excretion and so exposure can increase in patients with chronic kidney disease, including those who received kidney transplant. Ischemia-induced injury to the kidney both during the procurement period and transplant surgery can lead to temporary reduced graft function in the immediate post-transplant period, with delayed or slow graft function that require hemodialysis in 25% of deceased-donor recipient and 3–5% of living donor recipient (Salerno et al. 2017). At the moment, no clinical trial data is available for DOACs use in patients post renal transplant, a population with a unique challenge: maintenance of an effective immunosuppression.

Calcineurin inhibitors, tacrolimus and ciclosporin, are among the most commonly used immunosuppressants; the use of these drugs is not straightforward. Both have a narrow therapeutic index and blood concentrations vary considerably between individuals. A narrow therapeutic index indicates that the blood concentration range between safe and subtherapeutic values is small. In transplant recipients, both supratherapeutic and subtherapeutic drug concentrations can have devastating results. Subtherapeutic levels increase the risk of transplant rejection and supratherapeutic levels (over-immunosuppression) can lead to infection and/or drug-specific side effects (Lenihan et al. 2015). Vanhove et al. assessed the effect of DOACs on the disposition of calcineurin inhibitors in patients underwent renal transplant (Vanhove et al. 2017). The study included 39 kidney recipients (29 on rivaroxaban and 10 on apixaban). The authors reported an increase (<20%) in calcineurin inhibitors through concentration, which was not clinically relevant. A recent statement of European Heart Association on the basis of known pathways of calcineurin inhibitors metabolism, involving CYP3A and efflux pump P-glycoprotein suggests that apixaban may be used in association with tacrolimus and cyclosporin with close monitoring and dose adjustment (Steffel et al. 2018). More recently, a study of drug interaction between apixaban and calcineurin inhibitors has been carried out in a small cohort of healthy volunteers which has shown that the fluctuation of drug levels is within those observed during the development program of the drug (Bashir et al. 2018). Therefore, no dose adjustment of the drug was needed during co-administration of apixaban with calcineurin inhibitors in healthy volunteers (Bashir et al. 2018).

Conclusions

In summary, the use of DOACs in patients with non-end stage kidney disease and atrial fibrillation is effective for ischemic stroke prevention similarly to warfarin, showing an overall better safety profile. European and American recommendations slightly differ with regard to DOACs labeling, particularly in case of severe renal impairment.

The observational data regarding the use of warfarin in atrial fibrillation patients on dialysis warrant caution. Available evidence shows that these patients have no benefit from warfarin treatment in the prevention of ischemic stroke or in the overall mortality. Conversely, they are exposed to a significant higher risk of hemorrhagic stroke. Some retrospective data demonstrated promising results with apixaban, but years will be needed for the conclusion of the ongoing randomized clinical trials. In the meantime, the management of stroke risk among patients with atrial fibrillation on dialysis will remain challenging. Patients who underwent kidney transplant may benefit as well from the use of DOACs but possible interactions with lifesaving immunosuppressants raise some concerns.

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Anticoagulation in Elderly Patients with Atrial Fibrillation Authors

8

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, and age is one of the strongest predictors for ischemic stroke in AF (Krishnamurthi et al. 2013; Go et al. 2001; Lin et al. 1996; Miyasaka et al. 2006; AlTurki et al. 2019). Elderly patients are at higher risk of both ischemic and bleeding events compared to younger patients, and age is an overlapping factor in both the CHA2DS2-VASc score for stroke (Lip et al. 2010) and the HASBLED score for bleeding risk assessment (Pisters et al. 2010). Over the age of 80 years, the annual risk of stroke increases to up to 23.5% (Chatap et al. 2002; Fuster et al. 2001). Vitamin K antagonists (VKAs) reduce the risk of ischemic stroke in patients with AF, especially in the elderly, but increase the bleeding risk and require frequent international normalized ratio monitoring (Perera et al. 2009; Zimetbaum et al. 2010). Furthermore, VKAs have multiple drug and food interactions (Kirchhof et al. 2016). For these reasons, despite the higher risk of ischemic events, anticoagulants are underused in elderly patients (Hylek et al. 2006; Tulner et al. 2010). Elderly may present with multiple comorbidities including dementia, a tendency to falls, chronic kidney disease, anemia, hypertension, diabetes, and cognitive dysfunction (Tulner et al. 2010). Such conditions may limit quality of life, and hepatic and kidney dysfunction, with multiple simultaneous medications, makes drug interactions and adverse drug reactions more likely (Tulner et al. 2010). Integrated AF management and careful adaptation of drug dosing seem reasonable to reduce the complications of AF therapy in such patients (Andreotti et al. 2015). Direct oral

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anticoagulants (DOACs) have emerged as alternatives to VKAs and are gradually increasing their popularity because of their fewer interactions and ease of use. Their effectiveness and safety have been well-established in the general population, but the benefit in the elderly is still unclear. Data about the safety and the effectiveness in patients >75 years old are available, but the management of the DOACs therapy in octogenarians and in frail patients is more challenging. This chapter will focus in detail on patients ≥75 years of age treated for stroke prevention in AF.

Indications for Stroke Prevention in Elderly

The risk scores and the oral anticoagulant (OAC) indications for stroke prevention in elderly with AF are the same as in younger patients. Both the European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) guidelines (UK) recommend assessment of stroke risk using the CHA2DS2-VASc score considering OAC prescription for scores of ≥1 in males and ≥ 2 in females (Hindricks et al. 2020; National Institute for Health and Care Excellence 2014). The American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines differ slightly with OAC being recommended for higher CHA2DS2-VASc scores of ≥2 and ≥ 3 in men and women, respectively (January et al. 2014). For scores of 1, management options include withholding OAC, or treatment either with an OAC or aspirin (January et al. 2014). Therefore, the age ≥ 75 years gives 2 score points and female sex 1 score point, and all patients ≥75 years of age, with AF, are recommended to receive OAC with a class Ia recommendation irrespective of the presence or absence of additional risk factors (Hindricks et al. 2020).

Antithrombotic Strategies in Elderly with AF: Anticoagulant Vs. Antiplatelet Therapy

Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk (Hindricks et al. 2020). In the Birmingham Atrial Fibrillation Treatment of the Aged Study, patients ≥75 years of age on acetylsalicylic acid did not show a lower rate of major bleedings compared with VKA, but VKA was superior to acetylsalicylic acid regarding stroke prevention (Mant et al. 2007). In this study, even very elderly patients had a 50% risk reduction for embolic/ischemic events on VKA with a similar bleeding risk as on acetylsalicylic acid, with well-controlled time in therapeutic range of 67% in the VKAs group (Mant et al. 2007). In the AVERROES trial comparing acetylsalicylic acid and apixaban, bleeding rates in elderly AF patients were similarly increased in the two groups, and for patients ≥85 years, annual rates for stroke or systemic embolism increased to 6.5%, for major bleedings to 4.7%, and for intracranial hemorrhage to 2.9% on acetylsalicylic acid, but anticoagulation with apixaban showed significantly lower rates of stroke or systemic embolism with safety comparable to acetylsalicylic acid (Ng et al. 2016).

Double antiplatelet therapy (DAPT) , for stroke prevention in AF, was studied in two RCTs compared with VKAs. In the ACTIVE W (Atrial Fibrillation Clopidogrel

Trial with Irbesartan for Prevention of Vascular Events) trial (Investigators AWGotA et al. 2006), DAPT with aspirin and clopidogrel was less effective than warfarin for prevention of stroke, systemic embolism, myocardial infarction, and vascular death (the annual risk of events was 5.6% vs. 3.9%, =0.0003; mean age 70.2 ± 9.4 years old), with a similar rate of major bleeding (Investigators AWGotA et al. 2006). Also, in the ACTIVE-A trial (Investigators et al. 2009), patients unsuitable for anticoagulation had a lower rate of thromboembolic complications when clopidogrel was added to aspirin compared with aspirin alone, but with a significant increase in major bleeding (Investigators et al. 2009).

In conclusion, antiplatelet monotherapy was ineffective for stroke prevention and was associated with a higher risk of ischemic stroke and major hemorrhages in elderly patients with AF (Mant et al. 2007; Sjalander et al. 2014; Lip 2011), whereas DAPT is associated with a bleeding risk similar to OAC therapy (Investigators AWGotA et al. 2006; Investigators et al. 2009). In consequence, antiplatelet therapy should not be used for stroke prevention in AF patients (Hindricks et al. 2020).

DOACs in Elderly Patients: Current Evidences

DOACs have been shown to be more effective and safe than VKAs for long-term stroke prevention in patients with non-valvular AF, either in trial (Granger et al. 2011; Patel et al. 2011; Connolly et al. 2011; Giugliano et al. 2013) or in real-life setting (Bando et al. 2018; Deitelzweig et al. 2017; Yao et al. 2016; Shinohara et al. 2018; Kwon et al. 2016; Russo et al. 2015, 2017a, b). In a meta-analysis of randomized controlled trials comparing DOACs (rivaroxaban, apixaban, and dabigatran; insufficient data was available for edoxaban) with VKAs therapy in patients aged ≥75 years, DOACs were associated with equal or greater efficacy than conventional therapy, without causing excessive bleeding (Sardar et al. 2014). Four different randomized controlled trials have evaluated DOACs compared with VKA for stroke prevention in AF with different inclusion and exclusion criteria, and consequently, the DOACs cannot be compared directly (Table 8.1).

Dabigatran

The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial compared the direct thrombin-inhibitor dabigatran to warfarin (Connolly et al. 2009). The study included 3027 patients ≥80 years (16.7%) at baseline (Connolly et al. 2009). In patients ≥75 years of age, the combined risk of stroke or systemic embolism and major bleeding was similar between VKA and both dosages of dabigatran (Eikelboom et al. 2011), with intracranial bleeding risk lower but extracranial bleeding risk similar or higher with both doses of dabigatran compared with warfarin (Eikelboom et al. 2011).

A post hoc simulation of dabigatran usage based on RE-LY trial dataset indicates that "EU label simulated dabigatran treatment" (dabigatran 110 mg bid in one of the following situations: age ≥80 years; increased risk of bleeding or concomitant

Table 8.1 Tabella capitolo Russo trial

	RE-LY (Connolly et al. 2009)	ROCKET-AF (Halperin et al. 2014)	ARISTOTLE (Granger et al. 2011)	ENGAGE (Kato et al. 2016)
Drug (vs. VKA)	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Reduced dose	150 mg bid 110 mg bid	20 mg qd 15 mg qd	5 mg bid 2.5 mg bid	60 mg qd 30 mg qd
Patients (*N*)	18,113	14,264	18,201	14,071
Age (mean in years)	72	73	70	72
Patients ≥75 years, *N* (%)	7258 (40)	6229 (44)	5678 (31)	5668 (40)
Creatinine clearance in ≥75 years at baseline	• ≥80 mL/min: 12% • 50–79 mL/min: 57% • <50 mL/min: 26%	Creatinine clearance, median 55 mL/min (IQR 44, 68)	• >80 mL/min: 10.5% • 51–80 mL/min: 51.5% • 31–50 mL/min: 33.6% • ≤30 mL/min: 3.9%	• >80 mL/min: 12% • 51–80 mL/min: 52% • ≤ 50 mL/min: 37%
Primary safety endpoint	Major bleeding defined as a reduction in the hemoglobin level of at least 2 g/dL, transfusion of at least 2 units of blood or requiring inotropic agents, symptomatic bleeding in a critical area or organ	Composite of major and nonmajor clinically relevant (NMCR) bleeding: • Major bleeding was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability • NMCR bleeding was defined as overt bleeding not meeting criteria for major bleeding but requiring medical intervention, unscheduled contact (visit or telephone) with a physician, temporary interruption of study drug (i.e., delayed dosing), pain, or impairment of daily activities	Major bleeding defined by ISTH criteria: • Fatal bleeding • Symptomatic bleeding in a critical area or organs such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome • Bleeding causing a fall in hemoglobin level ≥2 g/dL or leading to transfusion ≥2 units of whole blood or red cells	Major bleeding defined by ISTH criteria: • Fatal bleeding • Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome • Bleeding causing a fall in hemoglobin level ≥2 g/dL or leading to transfusion ≥2 units of whole blood or red cells

Event rates (DOAC vs. VKA %/years) and hazard ratios (or relative risk for Dabigatran) for stroke or systemic embolism in patients ≥75 years. HR (OR RR) 95% CI	1.9 (110 mg bid) vs. 2.1 1.4 (150 mg bid) vs. 2.1 0.88 (0.66–1.17) (110 bid) 0.67 (0.49–0.90) (150 bid)	2.3 vs. 2.9 0.80 (0.63–1.02)	1.6 vs. 2.2 0.71 (0.53–0.95)	1.9 vs. 2.3 0.83 (0.67–1.04)
Event rates (DOAC vs. VKA %/years) and hazard ratios (or relative risk for Dabigatran) for major bleedings in patients ≥75 years. HR (OR RR) 95% CI	4.4 (110 mg bid) vs. 4.4 5.1 (150 mg bid) vs. 4.4 1.01 (0.83–1.23) (110 bid) 1.18 (0.98–1.42) (150 bid)	4.9 vs. 4.4 1.11 (0.92–1.34)	3.3 vs. 5.2 0.64 (0.52–0.79)	4.0 vs. 4.8 0.83 (0.70–0.89)
Event rates (DOAC vs. VKA %/years) and hazard ratios (or relative risk for Dabigatran) for gastrointestinal bleedings in patients ≥75 years. HR (OR RR) 95% CI	2.2 (110 mg bid) vs. 1.6 2.8 (150 mg bid) vs. 1.6 1.39 (1.03–1.98) (110 bid) 1.79 (1.35–2.37) (150 bid)	2.8 vs. 1.7 1.69 (1.19–2.39)	1.3 vs. 1.3 0.99 (0.69–1.42)	2.2 vs. 1.7 1.32 (1.01–1.72)
Event rates (DOAC vs. VKA %/years) and hazard ratios (or relative risk for Dabigatran) for intracranial bleeding in patients ≥75 years. HR (OR RR) 95% CI	0.37 (110 mg bid) vs. 1 0.41 (150 mg bid) vs. 1 0.37 (0.21–0.64) (110 bid) 0.42 (0.25–0.70) (150 bid)	0.66 vs. 0.83 0.80 (0.50–1.28)	0.43 vs. 1.29 0.34 (0.20–0.57)	0.5 vs. 1.2 0.40 (0.26–0.62)

verapamil use) may be associated with superior efficacy and safety compared to warfarin, presenting a significant reduction in thromboembolic events (HR: 0.74) and major bleedings (HR 0.85), but not gastrointestinal major bleeding (HR: 1.23) (Lip et al. 2014).

A recent subgroup analysis for age of RE-LY trial by Lauw et al. (2017) showed that both doses of dabigatran provide highly consistent protection against stroke and systemic embolism and much lower rates of intracranial bleeding compared with warfarin irrespective of ages. In particular, the effects of dabigatran versus warfarin regarding the stroke/systemic embolism prevention were consistent in patients ≥80 years [dabigatran 110 mg bid (HR = 0.75) and 150 mg bid (HR = 0.67)] and ≥ 85 years [dabigatran 110 mg bid (HR = 0.52) and 150 mg bid (HR = 0.70)] (Sardar et al. 2014). Regarding the intracranial bleeding, there was a lower rate in both patients aged ≥80 years [Dabigatran 110 mg bid (HR = 0.30) and 150 mg bid (HR = 0.55)] and ≥ 85 years [Dabigatran 110 mg bid (HR = 0.13) and 150 mg bid (HR = 0.61)] (Lauw et al. 2017).

A propensity score-matched analysis of 134,414 elderly AF patients (43% aged 75–84 years and 16% aged ≥85 years) enrolled in FDA Medicare study, who initiated anticoagulant treatment with dabigatran, showed the dabigatran use was associated with a significant reduced risk of ischemic stroke (HR 0.80), intracranial hemorrhage (HR 0.34), and mortality (HR 0.86); with a significant increased risk of major gastrointestinal bleeding (HR: 1.28) (Graham et al. 2015). The subgroup analyses stratified by age and gender showed and increased risk of major gastrointestinal bleeding with dabigatran for women aged 75 years and older (HR 1.50) and for men aged 85 years and older (HR 1.55) compared with warfarin. Below these ages, gastrointestinal bleeding risk was comparable for both anticoagulants (Graham et al. 2015). No beneficial effect of dabigatran on mortality was present in women aged 85 years and older (Graham et al. 2015), where there was a trend for a higher risk of death with dabigatran compared with warfarin (HR 1.24) (Graham et al. 2015). This shift in hazard ratio between younger and older aged women represented a statistically significant interaction and suggests that the benefit-risk profile of dabigatran may be less favorable in women aged 85 years and older than in other age-gender groups (Graham et al. 2015).

Rivaroxaban

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism trial in Atrial Fibrillation (ROCKET-AF) study compared the factor Xa-inhibitor rivaroxaban to warfarin (Halperin et al. 2014). The trial included 6229 patients ≥75 years (44%) and 2595 patients (18%) ≥80 years at baseline. A sub-analysis of ROCKET-AF has shown that elderly patients (≥ 75 years old; $n = 6229$) are a particularly high-risk group for thromboembolic events (2.57% versus 2.05%/100 patient-years; $P = 0.0068$) and major bleeding (4.63% versus 2.74%/100 patient-years; $P < 0.0001$) respect to younger; however, the effects of rivaroxaban versus warfarin did not

differ with age. Anticoagulation with rivaroxaban was as effective as warfarin in reducing stroke and systemic embolism (95% CI, HR = 0.88 [0.67–1.16]) in older patients and was associated with less intracranial bleeding (95% CI, HR = 0.80 [0.50–1.28]) (Halperin et al. 2014). Rivaroxaban was associated with a higher risk of this combined bleeding endpoint in elderly patients compared with patients randomized to warfarin, due mainly to more frequent nonmajor bleeding (95% CI, HR 0.70 [0.39–1.25]). This interaction was restricted to extracranial bleeding and driven primarily by gastrointestinal bleeding, which was more frequent among elderly patients in the rivaroxaban group than in the warfarin group (2.81% versus 1.66%/100 patient-years; $P = 0.0002$) (Halperin et al. 2014). Rates of major bleeding were not significantly different between the rivaroxaban and warfarin groups in elderly (4.86% versus 4.40%/100 patient-years; $P = 0.336$). Data about the clinical performance of rivaroxaban in octogenarians enrolled in ROCKET-AF trial are not available.

The Shikoku Rivaroxaban Registry Trial (SRRT) is a retrospective survey of the use of rivaroxaban for stroke prevention in elderly Japanese patients which enrolled 1339 patients divided into control group (886 patients aged <80 years) and extreme elderly group (453 patients aged ≥80 years) (Bando et al. 2018). The incidence of cerebral infarction (0.94%/person-year; HR 1.66; 95% CI 0.45–2.94; $p = 0.450$) and cerebral hemorrhage (0.89%/person-year; HR 2.32; 95% CI 0.51–4.13; $p = 0.274$) did not differ in the extreme elderly group and the control group (Bando et al. 2018). Real-life data about the clinical profile of rivaroxaban in octogenarians Caucasian patients are lacking.

Apixaban

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial compared the factor Xa-inhibitor apixaban to warfarin (Granger et al. 2011). The study included 5642 patients ≥75 years (31%) and 2436 patients (18%) ≥80 years at baseline (Granger et al. 2011). The absolute clinical benefits of apixaban were greater in the older population; in particular, in patients ≥80 years a significant reduction of stroke or systemic embolism (HR 0.81), major bleeding (HR: 0.66), and intracranial hemorrhage (HR 0.36) was showed with apixaban compared to warfarin (Granger et al. 2011).

In a sub-analysis of Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, apixaban was more effective than aspirin for stroke prevention in patients with >85 years old compared to those aged ≥75 years (HR 0.50) (Ng et al. 2016).

In a propensity score-matching short-term observational study, including 7107 AF elderly patients (mean age 78.1 years) in each cohort (apixaban versus warfarin), Deitelzweig et al. (2017) demonstrated that apixaban treatment was associated with a significant lower risk for stroke/systemic embolism (HR: 0.65, $P < 0.001$), ischemic stroke (HR: 0.63, $P < 0.001$), any major bleeding (HR: 0.53, $P < 0.001$),

gastrointestinal major bleeding (HR: 0.53, $P < 0.001$), and other major bleedings (HR: 0.48, $P < 0.001$) respect to VKAs therapy (Deitelzweig et al. 2017). These findings are also consistent with a recent retrospective cohort study conducted by Yao et al., who reported that treatment with apixaban versus warfarin was associated with a 33% lower risk for stroke/systemic embolism (HR = 0.67, $P = 0.04$) and 55% lower risk for major bleeding (HR 0.45, $P < 0.001$) among AF elderly patients (median age: 73 years old) (Yao et al. 2016).

Edoxaban

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial compared the factor Xa-inhibitor edoxaban to warfarin (Kato et al. 2016). It included 8474 patients ≥75 years of age (40.2%) and 1440 patients ≥80 years of age (17%). The rates of stroke/systemic embolic event in patients aged ≥75 years were similar with edoxaban versus warfarin (1.50% per year in warfarin group; 1.18% per year in edoxaban group; hazard ratio vs. warfarin, HR 0.79; $P < 0.001$ for noninferiority, $P = 0.02$ for superiority), while major bleeding was significantly lower with edoxaban (3.43% per year in warfarin group and 2.75% per year in edoxaban group) (Kato et al. 2016). The absolute risk reduction in major bleeding (HR = 0.83) and in intracranial hemorrhage (HR = 0.40) was greater for edoxaban than warfarin as age increased, resulting in a better net clinical benefit with age increase. These benefits relative to warfarin were maintained in patients aged ≥80 and ≥85 years old (Kato et al. 2016; Russo et al. 2019a, 2020a, b), demonstrating the robustness of the findings with edoxaban in octogenarians with AF.

The ELDERCARE-AF (Edoxaban Low-Dose for EldeR CARE AF patients) study is a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study that will compare the safety and efficacy of once-daily edoxaban 15 mg versus placebo in Japanese patients with non-valvular AF ≥80 years of age who are considered ineligible for standard oral anticoagulant therapy (Okumura et al. 2017; Okumura et al. 2020). They showed that once-daily 15-mg dose of edoxaban was superior to placebo in preventing stroke or systemic embolism and did not result in a significantly higher incidence of major bleeding than placebo (Okumura et al. 2020). The results of ELDERCARE-AF may provide clarity as to the efficacy and safety of reduced doses of edoxaban for the prevention of stroke in the Japanese very elderly patients, but data are needed also for the Caucasian population.

VKA Versus DOACs in Elderly

Many studies have compared warfarin vs. DOACs in elderly patients (Russo et al. 2019b, 2020c; Verdecchia et al. 2019). A retrospective analysis of Taiwan National Health Insurance Research Database (NHIRD), including 15,756 AF patients

≥90 years, showed that the risk of ischemic stroke was similar between elderly patients treated with warfarin or DOACs (4.07%/y versus 4.59%/y; HR: 1.16; $P = 0.654$) but the risk of intracranial hemorrhage (ICH) was substantially lower with DOACs (0.42%/year versus 1.63%/year; HR 0.32; $P = 0.044$) (Chao et al. 2018).

Furthermore, Shinohara et al. enrolled 346 AF patients >80 years; 266 (76.9%) received direct DOACs and 80 (23.1%) received warfarin (Shinohara et al. 2018). Low body mass index (BMI) (<18.5 kg/m^2) was demonstrated the most significant factor associated with the bleeding in frail octogenarians with AF who were newly initiated on OACs (Shinohara et al. 2018). The type of OACs was not a risk factor for the development of bleeding whether its dose was appropriately adjusted or not, and the rate of the incidence of bleeding events did not differ significantly between the DOACs and warfarin groups (Shinohara et al. 2018). These findings suggest that DOAC use in non-severe frail octogenarians with AF may be as safe as warfarin therapy (Shinohara et al. 2018). Other data suggest the safety and efficacy use of DOACs in patients aged >80 with low body weight, justified by a reduction in overall mortality over VKAs (Russo et al. 2020d).

A retrospective Asian study analyzed 293 consecutive patients aged ≥80 years with non-valvular AF who had taken either DOACs (148 cases, 50.5%) or warfarin (145 cases, 49.5%) (Shinohara et al. 2018). The incidence of stroke/systemic embolic events were low in both groups with no significant differences (1.16% for DOACs vs. 2.98% for warfarin per 100 patient-years, $P = 0.46$) (Shinohara et al. 2018). However, major bleeding occurred in a significant number of patients with both DOACs (8.96 per 100 patient-years) and warfarin (12.46 per 100 patient-years) treatments, which was not significantly different between the two groups ($P = 0.29$) (Kwon et al. 2016).

Data are needed to identify the difference between the DOACs in terms of safety and benefits and to recognize, "the best anticoagulation" in elderly patients.

Anticoagulation in Frail Elderly

"Frailty" is a clinical condition with an increased vulnerability to pathogens and various types of stress and can lead to addiction and/or death. Fragility can be related to different causes and is mainly observed in the over 80 years old (Clegg et al. 2013). It is more prevalent in those who are >65 years and in females. The prevalence varies from 9% in patients with 75–79 years old to 26% in patients ≥85 years old (Collard et al. 2012).

Frailty represents a condition of high instability that negatively affects both prescription and maintenance of anticoagulation therapy, for many factors such as comorbid conditions (heart failure, dementia, chronic obstructive pulmonary disease, diabetes, chronic kidney disease, etc.), risk of falls, malnutrition, and polypharmacy (Annoni and Mazzola 2016). Older and frail people are less likely to receive OAC despite sufficient evidence supporting the use of OAC in this population (Graham et al. 2015; Biteker et al. 2017; Singh et al. 2011). Frailty, comorbidities, and increased risk of falls do not outweigh the benefits of OAC given the small

absolute risk of bleeding in anticoagulated elderly patients. Evidence from RCTs (Mant et al. 2007; Rash et al. 2007), meta-analyses (Sardar et al. 2014; Ruff et al. 2014), and large registries (Graham et al. 2015; Chao et al. 2018; Lip et al. 2015; Siu and Tse 2014) support the use of OAC in this group. Antiplatelets are neither more effective nor safer than warfarin and may even be harmful (Chao et al. 2018), whereas DOACs appear to have a better overall risk benefit profile compared with warfarin (Mant et al. 2007; Sardar et al. 2014; Chao et al. 2018; Ruff et al. 2014; Mozaffarian et al. 2015; Alnsasra et al. 2019; Dietzel et al. 2018). Prescribing a reduced dose of OAC is less effective in preventing AF adverse outcomes (Steinberg et al. 2013; Gage et al. 2000; Dillinger et al. 2018; Nieuwlaat et al. 2007).

In the ORBIT-AF register, frailty was the third cause of non-prescription of OAC for the high risk and history of bleeding or for the refusal of treatment by the patient (O'Brien et al. 2014). In a small Australian study, only 20% of OAC was prescribed for frail elderly people with AF (Perera et al. 2009). Steinberg et al. (2013) reported that physical frailty represents a barrier to the prescription also for DOACs.

Oqab et al. conducted a systematic review in frail AF patients (Oqab et al. 2018). They found that approximately 40% of adults with AF over the age of 80, admitted in hospital, were diagnosed as frail, and the rate of OAC prescription was lower in frail elderly as compared to non-frail (OR 0.49, 95% CI 0.32–0.74) (Oqab et al. 2018). Geriatric characteristics such as cognitive impairment, malnutrition risk, depression, and falls are frequently cited reasons for under-prescription of oral anticoagulants (Oqab et al. 2018).

In historical studies, the OAC prescription rates were of 35–65%, compared to rate of 70% observed in the FRAIL-AF study (Lefebvre et al. 2016) as it suggested a more judicious use of OAC in older patients, particularly as a significant proportion in the study had diagnoses such as dementia. However, the authors noted that non-frail to moderately frail patients were 3.5 times more likely to receive OAC than severely frail patients, irrespective of their thromboembolic and bleeding risk, highlighting that the impression of severe frailty significantly influenced OAC prescription decisions (Lefebvre et al. 2016).

Studies on which international guidelines was based did not explicitly assess frailty (Granger et al. 2011; Patel et al. 2011; Giugliano et al. 2013; Connolly et al. 2009). Assessment and modification of bleeding risk factors using the HAS-BLED score is recommended, but there may be additional considerations in a population with frailty such as a higher risk of bleeding and falls. The optimal treatment strategy for people with AF and frailty is therefore unclear, and the generalizability of trial evidence across the spectrum of older people may be limited as they excluded people anticipated to be in the last 1–2 years of life and those with several comorbidities.

Fall risk is an important parameter of frailty. In a sub-analysis of the ARISTOTLE trial, a history of fall(s) was associated with an increased intracranial hemorrhage risk (HR 1.96 [95% CI: 1.06–3.61]) (Rao et al. 2018). However, in the ENGAGE AF-TIMI 48 trial and in the Loire Valley AF Project, the presence or absence of fall risk or a history of falls did not increase the incidence of intracranial hemorrhage

(Banerjee et al. 2014; Steffel et al. 2016). The reason for these contradictory results is uncertain.

To evaluate the OAC-associated bleeding risk in AF patients who were at risk of developing falls, Man-Son-Hing et al. (1999) have showed, in analysis of older individuals with an average annual stroke risk of 6% and falls risk of 33%, warfarin was associated with the highest quality-adjusted life expectancy compared to aspirin or no treatment. The study also estimated that an older patient taking warfarin would need to fall 295 times a year to offset the benefits of OAC. Also, for both edoxaban and apixaban, the relative safety and efficacy profile compared with warfarin were consistent in high fall risk patients (Rao et al. 2018; Steffel et al. 2016). Thus, falls or risk of it alone should not be absolute contraindications to OAC (Man-Son-Hing et al. 1999; Steffel et al. 2018).

Dementia is another reason for OAC non-prescription in AF (Bahri et al. 2015; Proietti et al. 2020). However, like falling, dementia should not be a general contraindication for OAC (Steffel et al. 2018; Russo et al. 2020e). Anticoagulation in dementia can be challenging, as therapy adherence and a patients' ability to make decisions are often suboptimal (Steffel et al. 2018). Nonetheless, OAC treatment is correlated with lower ischemic stroke and all-cause mortality rates in these patients (Subic et al. 2018). Moreover, AF is linked to dementia and cognitive decline, and OAC in AF has been associated with a lower risk of dementia (Alonso and Arenas de Larriva 2016; Friberg and Rosenqvist 2018). Anticoagulation treatment is therefore encouraged, but attention to therapy adherence is important.

Practical Choice of DOACs in Older Patients

On the basis of current evidence, it is not possible to recommend one DOAC over another in elderly patients with AF. In general, there are some recommendations to take into consideration. All DOACs are contraindicated in patients with AF and hepatic insufficiency Child-Pugh category C; dabigatran, apixaban, and edoxaban may be used with attention in patients in category B (Steffel et al. 2018). DOACs are associated with lower incidence of major bleeding compared with VKAs in patients with liver disease (Pastori et al. 2018; Lee et al. 2019).

In elderly patients with kidney impairment, apixaban is a reasonable choice (Diener et al. 2017). Dabigatran and rivaroxaban may be used with caution in AF patients aged ≥75 years for the high risk of gastrointestinal bleeding (By the American Geriatrics Society Beers Criteria Update Expert P 2019).

Apixaban seems to be the drug with the most favorable risk/benefit ratio in older patients (Kuhn-Thiel et al. 2014; Pazan et al. 2016).

Furthermore, AF patients should be assessed for DOAC-specific dose-reduction criteria (such as age >80 years, low body weight <60 kg, reduced renal function) and for other factors with potential effect on DOACs plasma level (nonsteroidal anti-inflammatory drugs, drugs interactions with antifungal drugs, quinidine, clarithromycin, erythromycin, verapamil) (Steffel et al. 2018).

Conclusions

The anticoagulant treatment in elderly patients represents a tricky issue in the stroke prevention. Data currently available in literature showed that the better profile of clinical efficacy and safety of DOACs in preventing thromboembolic events, versus VKAs, in AF patients is conserved also in elderly (≥75 year). DOACs showed a particularly high net benefit versus warfarin but, on the basis of current evidence, it is not possible to recommend one DOAC over another, considering only the age. Treatment of elderly patients presents numerous challenges, and an individualized approach should be taken, taking into consideration the risk of bleeding, other comorbidities, and the different characteristics of the individual DOACs.

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The "Obesity Paradox" and the Use of NOAC

9

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Introduction

The World Health Organization defines obesity as a condition of increased adipose tissue up to a body mass index (BMI) > 30 kg/m^2 which affects the state of health (Hales 2017). In the last 40 years, obesity has constantly increased its incidence all over the world (Abarca-Gómez et al. 2017), with a current prevalence of 39.8% of US adults, affecting over 90 million people irrespective of gender, age, or ethnicity (Hales 2017). Obesity, mainly in its abdominal form, is an important cardiovascular (CV) risk factor known to be responsible for increased CV morbidity and mortality (Jensen et al. 2014; Berrington de Gonzalez et al. 2010), including increased rates of venous thromboembolism (VTE) (Ageno et al. 2008; Yang et al. 2012) and atrial fibrillation (AF) (Boriani and Proietti 2018; Lavie et al. 2017) for which oral anticoagulation (OAC) is needed (Hindricks et al. 2020; Konstantinides et al. 2020). To date, for treatment and prevention in non-valvular AF (NVAF) and in VTE patients, major guidelines suggest the use of non-vitamin K anticoagulants (NOACs) over vitamin K oral antagonists (VKAs) (Hindricks et al. 2020; Konstantinides et al. 2020). OAC therapy with NOACs in obese patients can be particularly challenging in consideration of the pharmacokinetic alterations that occur in such subjects (mainly drugs volume distribution and elimination) (Polso et al. 2014; Jain et al. 2011; Morrish et al. 2011; Wurtz et al. 1997). Due to clinical, pharmacokinetic, and pharmacodynamic evidences suggesting drug exposure differences with increased weight and BMI, the International Society on Thrombosis and Haemostasis (ISTH) discourage NOACs use in morbidly obese patients (BMI > 40 kg/m^2 or

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weight > 120 kg) (Martin et al. 2016). Interestingly, in addition to the above, it is important to take into account that evidences in literature support the hypothesis of an inverse relationship between obesity/overweight and CV outcomes which is given the name of "obesity paradox" (Elagizi et al. 2018; Lavie et al. 2009), a phenomenon described in patients with hypertension (Uretsky et al. 2007; Stamler et al. 1991; Tuomilehto 1991; Wassertheil-Smoller et al. 2000), heart failure (Horwich and Fonarow 2002; Fonarow et al. 2007; Powell-Wiley et al. 2018), coronary artery disease (Gruberg et al. 2002; Romero-Corral et al. 2006; Hastie et al. 2010; Oreopoulos et al. 2009), and other CV conditions, including AF (Lavie et al. 2009, 2017) and VTE (Bauer 2019; El-Menyar et al. 2018; Karabay et al. 2019). This chapter aims to review the available evidences of an obesity paradox in NVAF and VTE to examine the current state of the art of the use of NOACs in obese patients suffering from these conditions.

Obesity Paradox in NVAF Patients

Since 2010, several studies focused on the association between NVAF and the obesity paradox.

Three systematic reviews of the literature, of which the most recent published in 2020 (Zhou et al. 2020), investigate the association between obesity and NVAF outcomes (Zhou et al. 2020; Zhu et al. 2016; Proietti et al. 2017).

The study by Zhu and colleagues included nine studies (Sandhu et al. 2016; Proietti et al. 2016; Kwon et al. 2017; Inoue et al. 2016; Wang et al. 2015; Pandey et al. 2016; Overvad et al. 2013; Hamatani et al. 2015; Ardestani et al. 2010) with 49,364 participants and found that the relative risks (RR) of overweight and obese patients were lower than those of normal weight patients for stroke/systemic embolism (S/SE), all-cause death, and CV death (Zhu et al. 2016) (Table 9.1).

Proietti et al. in a systematic review of 13 studies (5 subgroup analysis of RCTs (Sandhu et al. 2016; Proietti et al. 2016; Ardestani et al. 2010; Badkeha et al. 2010; Senoo and Lip 2016) and 8 observational studies (Kwon et al. 2017; Inoue et al. 2016; Wang et al. 2015; Pandey et al. 2016; Overvad et al. 2013; Bunch et al. 2016; Yanagisawa et al. 2016; Wang et al. 2014)) found an obesity paradox in the overall results of subgroup analysis of RCTs (Table 9.3) but not in observational studies after statistical adjustment (Proietti et al. 2017).

Finally, in 2020, Zhou and coworkers in a systematic review and metanalysis of nine studies (one phase III RCT (Connolly et al. 2009), six post hoc analyses of randomized clinical trials (RCTs) (Sandhu et al. 2016; Proietti et al. 2016; Pandey et al. 2016; Boriani et al. 2019; Balla et al. 2017; Hohnloser et al. 2019), and two retrospective cohort studies (Park et al. 2017; Lee et al. 2019)) confirmed an obesity paradox in overweight and obese anticoagulated AF patients when compared to underweight patients for S/SE (overweight: relative risk [RR] 0.81, 95% CI 0.71–0.91; obesity: RR 0.69, 95% CI 0.61–0.78) and all-cause death (overweight: RR 0.73, 95% CI 0.64–0.83; obesity: RR 0.72, 95% CI 0.66–0.79), while no differences between BMI groups were found for major bleeding (MB) (Table 9.1).

Obesity Paradox in VTE Patients

The concept of obesity paradox can be applied to VTE patients too with controversial results available in literature.

In 2008, Barba et al. investigated the association between BMI and mortality in VTE patients based on the "Registro Informatizado Enfermedad TromboEmbólica" (RIETE) registry data (Barba et al. 2008), an ongoing, international, multicenter, prospective registry of consecutive patients presenting with symptomatic acute VTE confirmed by objective tests (RIETE Registry 2020). At the time, the study included

Table 9.1 Main research on obesity paradox in NVAF patients

References	Study design	Total patients (*n*)	Obese patients (*n*%)	Outcomes	
Zhu et al. (2016)	Meta-analysis and systematic review (9 studies) Underweight, overweight, and obese vs. normal weight patients	49,364	N/A	**S/SE RR (95% CI)**	
				Underweight	1.67 (1.12–2.49) $P = 0.01$
				Overweight	0.91 (0.80–1.04) $P = 0.18$
				Obese	0.84 (0.72–0.98) $P = 0.02$
				All-cause death RR (95% CI)	
				Underweight	2.61 (2.21–3.09) $P < 0.00001$
				Overweight	0.78 (0.62–0.96) $P = 0.02$
				Obese	0.84 (0.64–1.10) $P = 0.21$
				CV death RR (95% CI)	
				Underweight	2.49 (1.38–4.50) $P = 0.003$
				Overweight	0.79 (0.58–1.08) $P = 0.14$
				Obese	0.99 (0.79–1.24) $P = 0.93$

(continued)

Table 9.1 (continued)

References	Study design	Total patients (*n*)	Obese patients (*n*%)	Outcomes	
Zhou et al. (2020; Balla et al. 2017)	Meta-analysis and systematic review	N/A	N/A	**S/SE RR (95% CI)**	
				Underweight	1.98 (1.19–3.28) *P* = 0.008
				Overweight	0.81 (0.71–0.91) *P* = 0.0005
				Obese	0.69 (0.61–0.78) *P* < 0.00001
				All-cause death RR (95% CI)	
				Underweight	4.34 (0.57–32.83) *P* = 0.15
				Overweight	0.73 (0.64–0.83) *P* < 0.00001
				Obese	0.72 (0.66–0.79) *P* < 0.0001
				MB RR (95% CI)	
				Underweight	2.1 (0.89–4.92) *P* = 0.09
				Overweight	0.93 (0.79–1.08) *P* = 0.33
				Obese	1.04 (0.91–1.18) *P* = 0.59

NVAF non-valvular atrial fibrillation, *HR* hazard ratio, *OR* odds ratio, *RR* relative risk, *CI* confidential interval, *N/A* not applicable, *S/SE* stroke/systemic embolism, *CV* cardiovascular, *MB* major bleeding, RR are expressed with normal weight as reference category, except where explicitly reported

10,114 patients divided into BMI category with 43% of patients being overweight (BMI 25–30 kg/m^2) and 27% of patients being obese (BMI >30 kg/m^2). Study results showed that obese patients with acute VTE have less than half the mortality rate when compared with normal BMI patients (Barba et al. 2008). Moreover, overweight and obese patients demonstrated lower risk of fatal pulmonary embolism (PE). These results were recently confirmed and demonstrated separately for cancer and noncancer VTE patients in extreme obese patients (Giorgi-Pierfranceschi et al. 2020).

The association between mortality and BMI was also the field of investigation of Stein and coworkers (Stein et al. 2011). From the Nationwide Inpatient Sample, the

researchers selected obese and nonobese patients diagnosed with PE from short-stay hospitals throughout the United States from 1998 to 2008 (Stein et al. 2011). Final results showed that overall mortality was statistically significantly lower in obese patients with PE compared with nonobese PE patients (4.3% vs. 9.5%, RR = 0.45, $P < 0.0001$).

Conversely, in a retrospective analysis of 345,831 in-hospital PE patients stratified for BMI, Keller and colleagues showed that in-hospital mortality was lower for obesity class I and II patients while underweight and class III obese patients had higher mortality rate when compared to the reference group (normal weight/overweight patients) (Keller et al. 2019) (Table 9.2).

Also, in a retrospective cohort study by El-Menyar and coworkers of 662 DVT patients (49% obese), BMI >30 kg/m^2 was found to be a predictor of survival but recurrent DVT was higher in obese class I patients ($P < 0.01$) (El-Menyar et al. 2018). After statistical adjustment for age, sex, PE, and duration of warfarin treatment, authors found that patients with BMI >40 kg/m^2 had better survival (El-Menyar et al. 2018). See Table 9.2 for details.

Table 9.2 Main research on obesity paradox in VTE patients

References	Study design	Total patients (*n*)	Obese patients (%)	Outcomes	
Barba et al. (2008)	Retrospective analysis of prospective registry Underweight, overweight, and obese vs. normal weight patients	10,114	2752 (27)	**Death RR (95% CI)**	
				Underweight	2.1(1.5–2.7) $P < 0.001$
				Overweight	0.6 (0.5–0.7) $P < 0.001$
				Obese	0.5 (0.4–0.6) $P < 0.001$
				MB OR (95% CI)	
				Underweight	2.7 (1.4–5.1) $P < 0.01$
				Fatal PE OR (95% CI)	
				Overweight	0.6 (0.4–0.8) $P < 0.01$
				Obese	0.4 (0.2–0.6) $P < 0.01$

(continued)

Table 9.2 (continued)

References	Study design	Total patients (*n*)	Obese patients (%)	Outcomes	
Giorgi-Pierfranceschi et al. (2020)	Retrospective analysis of prospective registry Obese NC and WC patients vs. nonobese patients	16,490	1642 (11.1)	**Death HR (95% CI)**	
				Obese NC	0.67 (0.49–0.96) $P < 0.05$
				Obese WC	0.68 (0.50–0.94) $P < 0.05$
				MB HR (95% CI)	
				Obese NC	0.67 (0.57–1.58) $P > 0.05$
				Obese WC	0.99 (0.51–1.93) $P > 0.05$
Stein et al. (2011)	Retrospective cohort study PE/obese vs. PE/nonobese	17,979,200	203,500 (1)	**All-cause death RR (95% CI)**	
				0.45 (0.44–0.46) $P < 0.0001$	
Keller et al. (2019)	Retrospective cohort study of PE patients Obese, underweight, vs. normal weight/overweight	345,831	29,741 (8.6)	**Mortality OR (95% CI)**	
				Underweight	1.15 (1.00–1.31) $P = 0.04$
				Obesity I	0.56 (0.52–0.60) $P < 0.001$
				Obese II	0.63 (0.58–0.69) $P < 0.001$
				Obese III	1.18 (1.10–1.27) $P < 0.001$
El-Menyar et al. (2018)	Retrospective cohort study Association between obesity and DVT	662	324 (49)	**Predictors of survival (95% CI)**	
				BMI ≥ 30	OR 0.52 (0.29–0.92) $P = 0.03$
				BMI ≥ 40	HR 0.18 (0.05–0.69) $P = 0.02$

VTE venous thromboembolism, *HR* hazard ratio, *OR* odds ratio, *RR* relative risk, *CI* confidential interval, *NC* noncancer, *WC* with cancer, *PE* pulmonary embolism, *MB* major bleeding, *BMI* body mass index in kg/m^2. HR, OR, RR are expressed with normal weight as reference category, except where explicitly reported

Body Weight and Use of NOACS: Pharmacological Considerations

Obesity affects the pharmacokinetics of drugs, including the volume of distribution as well as drug clearance. Indeed, renal blood flow and clearance have been shown to be increased in obesity and could increase elimination of NOACs (Chagnac et al. 2000). Several studies have investigated the pharmacological profile of NOACs depending on changes in body weight.

It has been demonstrated that BMI influences the apparent volume of distribution of dabigatran but without impact on the concentration time profiles and overall exposure (Liesenfeld et al. 2011). Also, evidences from the Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY) trial show that weight is not an independent risk factor for bleeding and thrombotic outcomes even in patients with weight > 100 kg (Reilly et al. 2014).

In the randomized, single-blind, placebo-controlled, parallel-group study of Kubitza et al., rivaroxaban 10 mg in extreme body weight patients (≤50 and >120 kg) was well tolerated, showing no significant changes on its pharmacokinetic and pharmacodynamic profile (Kubitza et al. 2007). Similarly, Barsam and colleagues found that the most important covariate impacting rivaroxaban pharmacokinetics is creatinine clearance, and the weight alone has little effect (Barsam et al. 2017). However, extremely obese patients were poorly represented (BMI >40 kg/m^2: $n = 6$).

The open-label, parallel-group study of Upreti et al. (2013) investigated the effect of extremes of body weight on apixaban pharmacokinetics, pharmacodynamics, safety, and tolerability. Following administration of a single oral dose of 10 mg apixaban, high body weight group (>120 kg) had approximately 31% (90% CI: 18–41%) and 23% (90% CI: 9–35%) lower apixaban C_{max} and $AUC_{(0,\infty)}$, respectively, showing a modest change in apixaban exposure in these patients.

No studies directly designed to investigate the pharmacological profile of edoxaban in extremely obese patients are yet available. However, it has been demonstrated that renal function is the most important intrinsic determinant of total edoxaban exposure and that nonrenal clearance values decrease in subjects with lower body weight (Yin et al. 2014).

Finally, a recent study by Piran et al. examined peak plasma concentration of dabigatran, apixaban, and rivaroxaban in 38 extreme obese patients (BMI > 40 kg/m^2 or weight > 120 kg) (Piran et al. 2018). The study reported that 95% of the study population had peak plasma levels of NOACs higher than the median trough level for each of the three NOACs, 79% (95% CI: 63–89%) of patients had levels within the usual on-therapy range, and 21% (95% CI: 11–37%) of patients had a peak NOAC concentration below the expected range (i.e., below the fifth percentile for apixaban and rivaroxaban and below the tenth percentile for dabigatran), which could be interpreted as indicating suboptimal drug exposure (Piran et al. 2018).

NOACs Versus Warfarin Across BMI Groups: Current Clinical Evidences

NVAF Patients

Dabigatran

In a weight-based analysis of the RE-LY trial, BMI subgroups were categorized into an upper 10% (BMI of >36 kg/m^2), a middle 80% (BMI of 22.5 to ≤36 kg/m^2), and a bottom 10% (BMI of ≤22.5 kg/m^2) to compare efficacy (S/SE) and safety (MB) outcomes at 1 year, in relation to BMI and according to treatment assignment (dabigatran 150 mg, 110 mg, or warfarin) (The use of dabigatran according to body mass index 2020). An obesity paradox was confirmed: 1-year bleeding and S/SE rates were higher in patients with the bottom 10% BMI values compared to middle and upper BMI subgroups (all *P*-values <0.001). One-year S/SE rate was significantly lower in the dabigatran 150 mg group in the middle and upper BMI category while bleeding was significantly lower with dabigatran 110 mg in the same BMI groups.

These findings suggest that dabigatran preserves results of the RE-LY trial irrespective of BMI category (Table 9.3).

Rivaroxaban

Peterson and colleagues compared the risks of S/SE and MB in 3563 matched pairs of morbidly obese AF patients (BMI >40 kg/m^2 or >120 kg) treated with rivaroxaban or warfarin recruited from two different US databases (Peterson et al. 2019). Outcomes analyzed were the incidence of S/SE and MB. Final results showed that outcomes were similar for rivaroxaban and warfarin users (S/SE: 1.5% vs. 1.7%; $P = 0.50$; MB: 2.2% vs. 2.7%; $P = 0.14$) but rivaroxaban administration was associated with a lower healthcare resource utilization and costs (Peterson et al. 2019).

Later, in a larger cohort study of 35,613 NVAF patients with BMI >30 kg/m^2 on rivaroxaban 1:1 propensity matched with a same number of warfarin patients, Costa and colleagues could find that compared to warfarin, rivaroxaban was associated with a reduced risk of S/SE and MB. Subanalysis by BMI groups found no statistically significant interaction across BMI categories for S/SE (*P*-interaction = 0.58) or MB (*P*-interaction = 0.44) outcomes (Costa et al. 2020a). However, BMI >40 kg/m^2 accounted for 25% of the total rivaroxaban cohort with the majority of patients having a BMI between 30 and 34.1 kg/m^2.

These findings suggest that rivaroxaban can be at least as effective and safe as warfarin in obese patients (Table 9.3).

Apixaban

Recently, Hohnloser et al. conducted a weight-based post hoc analysis of the "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)" trial to compare efficacy and safety of apixaban versus warfarin across three different body weight group (≤60, >60–120, >120 kg) (Hohnloser et al. 2019). Final cohort study included 18,139 patients of which 1985 (10.9%) were in the low-weight group (≤60 kg), 15,172 (83.6%) were in the

Table 9.3 NOACs in NVAF obese patients

References	Study design	NOAC	Patients (*n*)	Obese patients (%)	Outcomes	
Ezekowitz et al., 2014 (The use of dabigatran according to body mass index 2020)	Post hoc analysis of the RE-LY trial Upper BMI (>36) vs. middle BMI (22.5–36) vs. bottom BMI (≤22.5) and dabigatran 110/150 mg vs. warfarin across BMI groups	Rivaroxaban	18,113	N/A	**One Year S/SE rates (95% Confidence Interval)**	
					Dabigatran 110 mg	BMI bottom 2% (0.9–3.1)
						BMI middle 1.5% (1.2–1.9)
						BMI upper 1.2% (0.3–2.0)
					Dabigatran 150 mg	BMI bottom 1% (0.2–1.8)
						BMI middle 1.2% (0.9–1.5)
						BMI upper 0.9% (0.1–1.6)
					Warfarin	BMI bottom 2.9% (1.6–4.2)
						BMI middle 1.6% (1.2–1.9)
						BMI upper 1.3% (0.4–2.3)
					One Year Major Bleeding Rates (95% CI)	
					Dabigatran 110 mg	BMI bottom 4.1% (2.5–5.6)
						BMI middle 3% (2.5–3.5)
						BMI upper 3% (1.6–4.4)
					Dabigatran 150 mg	BMI bottom 4.7% (3.0–6.4)
						BMI middle 3.9% (3.4–4.5)
						BMI upper 3.7% (2.2–5.2)
					Warfarin	BMI bottom 5.1% (3.3–6.7)
						BMI middle 3.8% (3.3–4.4)
						BMI upper 3.7% (2.2–5.2)

(continued)

Table 9.3 (continued)

References	Study design	NOAC	Patients (*n*)	Obese patients (%)	Outcomes	
Petearson et al. (2019)	Retrospective propensity score match cohort study Rivaroxaban vs. warfarin in obese patients	Rivaroxaban	3563 matched pairs	3563 (100) matched pairs	**S/SE**	
					OR (95% CI)	
					0.88 (0.60–1.28)	
					P = 0.50	
					MB	
					OR (95% CI)	
					0.80 (0.59–1.08)	
					P = 0.14	
Costa et al. (2020a)	Retrospective propensity score match cohort study Rivaroxaban vs. warfarin in obese patients	Rivaroxaban	35,613 matched pairs	35,613 (100) matched pairs	**S/SE**	
					HR (95% CI)	
					0.83 (0.73–0.94)	
					P = N/A	
					MB	
					HR (95% CI)	
					0.82 (0.75–0.89)	
					P = N/A	
Balla et al. (2017)	Post hoc analysis of the ROCKET AF trial Overweight and obese vs. normal weight patients	Rivaroxaban	14,030	5206 (37.1)	**S**	
					HR (95% CI)	
					Obese patients (BMI ≥ 35) on rivaroxaban	0.62 (0.40–0.96) *P* = 0.033
					Obese patients (BMI ≥ 35) on warfarin	0.48 (0.31–0.74) *P* < 0.001
Hohnloser et al. (2019)	Post hoc weight-based analysis of the ARISTOTLE trial Apixaban vs. warfarin	Apixaban	18,139	982 >120 kg (5.4%)	**S/SE**	
					HR (95% CI)	
					≤60 kg	0.63 (0.41–0.96)
					61–120 kg	0.85 (0.70–1.05)
					>120 kg	0.39 (0.12–1.22)
					Interaction *P* = 0.64	
					All-cause death	
					HR (95% CI)	
					≤60 kg	1.10 (0.85–1.43)
					61–120 kg	0.84 (0.74–0.95)
					>120 kg	1.19 (0.69–2.04)
					Interaction *P* = 0.36	
					MB	
					HR (95% CI)	
					≤60 kg	0.55 (0.36–0.82)
					61–120 kg	0.71 (0.61–0.83)
					>120 kg	0.74 (0.37–1.50)
					Interaction *P* = 0.02	

Proietti et al. 2017 (2017)	Metanalysis (3 out of 13 studies included in the original systematic review) Efficacy and safety of NOACs across BMI groups and vs. warfarin	Dabigatran Rivaroxaban Apixaban	50,031	18,632 (37.2%)	**NOACs across BMI groups**	
					S/SE	
					OR (95% CI)	
					Overweight	0.75 (0.66–0.84) $P < 0.00001$
					Obese	0.62(0.54–0.70) $P < 0.00001$
					Overweight vs. Obese	0.83(0.73–0.94) $P < 0.003$
					MB	
					OR (95% CI)	
					Overweight	0.84 (0.7–1.01) $P = 0.06$
					Obese	0.84 (0.72–0.98) $P = 0.03$
					Overweight vs. Obese	(0.92–1.10) $P = 0.95$
					NOACs vs. warfarin	
					S/SE	
					OR (95% CI)	
					Normal weight	0.65 (0.53–0.79) $P < 0.00001$
					Overweight	0.88 (0.74–1.05) $P = 0.14$
					Obese	0.84 (0.70–1.03) $P = 0.09$
					MB	
					OR (95% CI)	
					Normal weight	0.68 (0.47–0.98) $P = 0.04$
					Overweight	0.89 (0.73–1.08) $P = 0.22$
					Obese	1.03(0.9–1.18) $P = 0.7$

(continued)

Table 9.3 (continued)

References	Study design	NOAC	Patients (*n*)	Obese patients (%)	Outcomes	
Kido and Ngorsuraches (2019)	Retrospective cohort study NOACs vs. warfarin in extremely obese patients	Dabigatran Rivaroxaban Apixaban	128 (64 for each treatment group)	128 (100%)	**S/TIA** **RR (95% CI)** 0.84 (0.23–3.14) *P* = 0.80 **MB** **RR (95% CI)** 0.44 (0.15–1.25) *P* = 0.11	
Zhou et al. (2020)	Systematic review and meta-analysis (9 studies) Efficacy and safety of NOACs vs. warfarin across BMI groups	Dabigatran Rivaroxaban Apixaban Edoxaban	N/A	N/A	**S/SE** **RR (95% CI)**	
					Underweight	0.61 (0.46–0.80) *P* = 0.0004
					Normal weight	0.72 (0.58–0.91) *P* = 0.006
					Overweight	0.87 (0.76–0.99) *P* = 0.04
					Obese	0.87 (0.73–1.04) *P* = 0.12
					MB **Risk Ratio (95% CI)**	
					Underweight	0.67 (0.55–0.81) *P* < 0.0001
					Normal weight	0.72 (0.58–0.90) *P* = 0.004
					Overweight	0.83 (0.71–0.96) *P* = 0.01
					Obese	0.90 (0.81–1.01) *P* = 0.08

NOACs non-vitamin K oral anticoagulants, *NVAF* non-valvular atrial fibrillation, *HR* hazard ratio, *OR* odds ratio, *RR* relative risk, *CI* confidential interval, *N/A* not applicable, *S/SE* stroke/systemic embolism, *MB* major bleeding, *S* stroke, *TIA* transient ischemic attack, *BMI* body mass index in kg/m^2. HR, OR, RR are expressed with normal weight or warfarin as reference category, except where explicitly reported

midrange weight group (>60–120 kg), and 982 (5.4%) were in the high-weight group (>120 kg). Efficacy outcomes were S/SE, all-cause death, and myocardial infarction, while safety outcomes included MB, clinically relevant nonmajor bleeding (CRNMB), intracranial bleeding, gastrointestinal bleeding, and any bleeding at 2 years of follow-up. Treatment with apixaban results in lower rate of efficacy and safety outcome; however, no interaction between body weight, efficacy outcome, and randomization treatment (apixaban vs. warfarin) was found (interaction $P > 0.05$) with the exception of MB, suggesting that warfarin was associated with a higher risk of MB in the lower weight range group when compared with the higher weight categories; this was not seen with apixaban use.

These findings suggest that efficacy and safety of apixaban are not affected by BMI and weight. Table 9.3 shows details on results for S/SE, all-cause death, and MB.

Edoxaban

Data on edoxaban in obese AF patients are presented in a post hoc analysis of The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial (Boriani et al. 2019). In this analysis, higher BMI was independently associated with lower adjusted risk of S/SE (hazard ratio (HR) 0.88, $P = 0.0001$) and death (HR 0.91, $P < 0.0001$) in those treated with edoxaban or warfarin, and no significant interaction was observed between BMI analyzed as a categorical variable and the outcomes of S/SE, all-cause mortality, MB, CRNMB, or the net clinical outcome (P for interaction >0.16 for each outcome). However, increasing BMI was independently associated with a greater risk of MB (HR 1.06, 95% CI 1.01–1.12, $P = 0.025$) and of CRNMB (HR 1.05, 95% CI 1.02–1.08, $P = 0.0007$). The effects of edoxaban vs. warfarin on S/SE, MB, and net clinical outcome were similar across BMI groups.

These findings suggest that edoxaban has comparable clinical profile when compared to warfarin in obese patients with safety characteristics worsening in this subset of patients.

NOACs Overview in NVAF Obese Patients

In the abovementioned systematic review of Proietti et al. (2017), it was also conducted a metanalysis of NOACs safety and efficacy in the subgroup analysis of RCTs. Results showed that overweight and obese patients have a significantly lower risk of S/SE when compared to normal weight patients, with obese patients being at lower risk even when compared to overweight patients. MB was statistically significantly lower when comparing obese patients to normal weight ones with lower risk for obese patients. No significant difference for S/SE and MB between NOACs and warfarin was found across BMI groups with exception of normal weight patients as expected (Table 9.3).

Recently, Kido et al. conducted a retrospective, single-center cohort study in AF patients and extreme body weight (BMI > 40 kg/m^2 or weight > 120 kg), treated with warfarin or NOACs (i.e., dabigatran, rivaroxaban, or apixaban). The primary efficacy outcome was the incidence of S or transient ischemic attack (TIA), whereas the primary safety outcome was the incidence of MB. A total of 128 patients were

included in the study with half of them taking a NOAC (dabigatran: 31.3, apixaban: 29.7%, and rivaroxaban: 39.1%). Results show that the incidence rate of S or TIA was 1.75%/year in the NOAC group compared with 2.07%/year in the warfarin group ($P = 0.80$). The incidence rate of MB was 2.18%/year in the NOAC group, compared with 4.97%/year in the warfarin group ($P = 0.11$). Interestingly, compared with apixaban and rivaroxaban, use of dabigatran showed a highest number of ischemic events (dabigatran: 3, rivaroxaban: 1, apixaban: 0). MB rate was numerically lowest in the dabigatran group (dabigatran vs. rivaroxaban vs. apixaban: 1.34% vs. 2.13% vs. 2.82% per year), but there were two events of life-threatening bleeding in the dabigatran group and no such events with rivaroxaban and apixaban. The authors concluded that while apixaban and rivaroxaban seem to be effective and safe in morbidly obese patients, caution is needed with dabigatran in this subset of patients (Kido and Ngorsuraches 2019) (Table 9.3).

In the metanalysis of Zhou and colleagues, use of NOACs was associated to better efficacy and safety outcomes (S/SE and MB) in underweight, normal weight, and overweight patients compared to warfarin (S/SE; underweight: RR 0.61, 95% CI 0.46–0.80; normal weight: RR 0.72, 95% CI 0.58–0.91; overweight: RR 0.87, 95% CI 0.76–0.99; MB; underweight: RR 0.67, 95% CI 0.55–0.81; normal weight: RR 0.72, 95% CI 0.58–0.90; overweight: RR 0.83, 95% CI 0.71–0.96) while in obese patients, NOACs and warfarin demonstrated similar efficacy and safety profile with no statistically significant differences between treatment groups for S/SE and MB (Table 9.3) (Zhou et al. 2020).

VTE Obese Patients

Dabigatran, Apixaban, and Edoxaban

Even if major RCTs comparing dabigatran vs. warfarin for the treatment of VTE included more obese patients than later landmark trials, they were still underpowered to truly evaluate the safety and efficacy of dabigatran in this population. None of the studies reported outcomes in patients with a BMI of ≥40 kg/m^2 (Schulman et al. 2009, 2011, 2013).

The Oral Apixaban for the Treatment of Acute Venous Thromboembolism (AMPLIFY) trial (Agnelli et al. 2015), which demonstrated the noninferior efficacy of apixaban compared to standard therapy as well as its more favorable safety profile in VTE patients, completed a subgroup analysis by BMI and body weight but the study was underpowered for this analysis. In fact, only 19.4% of patients in the apixaban group weighed 100 kg or more, and only 13% had a BMI >30 kg/m^2.

Regarding edoxaban, no high-quality data on its clinical and pharmacological profile are available for VTE treatment in obese and extremely obese patients.

Rivaroxaban

Spyropoulos and colleagues conducted a retrospective 1:1 propensity score matched cohort study addressed to obese VTE patients started with rivaroxaban or warfarin and followed for 3 months after recruitment. Two thousand eight hundred ninety

matched pairs of morbidly obese VTE patients initiating rivaroxaban or warfarin were identified from 2 US claims databases. Results showed that morbidly obese VTE patients receiving rivaroxaban had similar risks of recurrent VTE (odds ratio [OR]: 0.99; 95% CI: 0.85–1.14) and MB (OR: 0.75; 95% CI: 0.47–1.19) versus warfarin (Spyropoulos et al. 2019) (Table 9.4).

Very recently Costa and coworkers published a retrospective cohort study including 6755 rivaroxaban matched with 6755 warfarin users with BMI ≥ 30 kg/m^2 and incident VTE. Rivaroxaban was associated with a reduced hazard of recurrent VTE compared to warfarin (HR 0.61, 95% CI: 0.51–0.72; HR 0.65, 95% CI: 0.55–0.77; HR 0.63, 95% CI: 0.54–0.74) with no difference in MB (HR 0.99, 95% CI: 0.68–1.44; HR 0.90, 95% CI: 0.64–1.26; HR 1.00, 95% CI: 0.73–1.36). No statistical difference was found across BMI categories (30–34.9; 35–39.9; ≥40 kg/m^2) for either recurrent VTE (*P*-interaction ≥0.43) or MB (*P*-interaction ≥0.58) at any time point (3, 6, and 12 months) (Costa et al. 2020b) (Table 9.4).

These findings suggest that rivaroxaban could be at least as effective and safe as warfarin in the treatment of VTE in extreme obese patients.

NOACs Overview in VTE Patients

Apixaban, rivaroxaban, and dabigatran were compared to warfarin in a retrospective study by Coons et al. including 632 patients receiving a NOAC and 1208 patients receiving warfarin for an acute VTE admission and a body weight at the time of inclusion between 100 and 300 kg. No statistically significant differences were found between groups in the primary outcome of VTE ($P = 0.93$), PE ($P = 0.94$), and DVT ($P = 0.56$). Within 12 months of the index event, bleeding occurred in 11 (1.7%) NOAC patients and 14 (1.2%) warfarin patients ($P = 0.31$). The most common types of bleeding in both groups were gastrointestinal and genitourinary (Coons et al. 2020) (Table 9.4).

A systematic review and metanalysis of the literature recently explored the efficacy and safety of NOACs (dabigatran, apixaban, and rivaroxaban) compared to warfarin in VTE treatment in morbidly obese patients (bodyweight of >120 kg or BMI > 40 kg/m^2). The study included five observational studies (Spyropoulos et al. 2019; Kushnir et al. 2019; Sa et al. 2019; Quan et al. 2020; Perales et al. 2020) finding that NOACs are noninferior to warfarin for efficacy (recurrence of VTE) and safety outcome (MB) (Elshafei et al. 2020) (Table 9.4).

NVAF and VTE Obese Patients: Overview of NOACS Use

Several retrospective studies aimed to investigate the role of NOACs in obese patients in both NVAF and VTE.

The Dresden NOAC Registry enrolled 3432 patients on dabigatran ($n = 348$, 10.1%), rivaroxaban ($n = 2104$, 61.3%), apixaban ($n = 685$, 20%), or edoxaban ($n = 285$, 8.6%) treatment both for NVAF and VTE. Of the all cohort, 731 had a BMI of 30.0–34.9 kg/m^2 and 346 had a BMI of ≥35 kg/m^2. Authors found that

Table 9.4 NOACs in VTE obese patients

References	Study design	NOAC	Patients (*n*)	Obese patients (%)	Outcomes	
Spyropoulos et al. (2019)	Retrospective matched cohort study Rivaroxaban vs. warfarin in obese patients	Rivaroxaban	2890 matched pair	2890 matched pair (100%)	**Recurrent VTE OR (95% CI)**	
					0.99 (0.85–1.14) $P = 0.84$	
					MB OR (95% CI)	
					0.75 (0.47–1.19) $P = 0.22$	
Costa et al. (2020b)	Retrospective matched cohort study Rivaroxaban vs. warfarin in obese patients	Rivaroxaban	6755 matched pairs	6755 matched pairs (100%)	**Recurrent VTE HR (95% CI)**	
					3 months	0.61 (0.51–0.72) $P = 0.43$
					6 months	0.65 (0.55–0.77) $P = 0.59$
					12 months	0.63 (0.54–0.74) $P = 0.61$
					MB HR (95% CI)	
					3 months	0.99 (0.68–1.44) $P = 0.71$
					6 months	0.90(0.64–1.26) $P = 0.72$
					12 months	1.00 (0.73–1.36) $P = 0.58$

Coons et al. (2020)	Retrospective 2:1 propensity score match cohort study NOACs vs. warfarin in obese patients (100–300 kg)	Dabigatran Rivaroxaban Apixaban	1840	1840 (100%)	**Recurrent VTE HR (95% CI)**	
					1.03 (0.71–1.50)	
					Bleeding	
					NOACs	11 (1.7%) of 632
					Warfarin	14 (1.2%) of 1208
					$P = 0.31$	
Elshafei et al. (2020)	Systematic review and metanalysis (5 studies) NOACs vs. warfarin in extreme obese patients	Rivaroxaban	6585	6585 (100%)	**Recurrent VTE OR (95% CI)**	
					1.07 (0.93–1.23) $P = 0.69$	
					MB OR (95% CI)	
					0.80 (0.54–1.17) $P = 0.98$	

NOACs non-vitamin K oral anticoagulants, *VTE* venous thromboembolism, *HR* hazard ratio, *OR* odds ratio, *CI* confidential interval, *MB* major bleeding, HR and OR are expressed with warfarin as reference category, except where explicitly reported

on-treatment rates of clinical outcomes (S/SE, TIA, VTE, MB) were lowest in overweight and obese patients (Tittl et al. 2018) (Table 9.5).

The retrospective, single-center analysis of Duperreault et al. (2020) compared new or recurrent VTE, stroke, and TIA (major outcomes) and incidence of major or minor bleeding events (minor outcome) between morbidly obese and nonobese patients prescribed apixaban or rivaroxaban for NVAF or VTE. Obese patients with BMI from 30.1 to 39.9 kg/m^2 were excluded to specifically compare nonobese patients with extreme obese ones. The cohort included 291 patients, 153 of whom were morbidly obese and 138 of whom were nonobese. No differences between groups were observed for major outcomes (P = 0.67) but MB occurred less frequently in morbidly obese patients (P = 0.02).

Choi and colleagues collected data on 390 obese patients (BMI >40 kg/m^2) on OAC treatment for NVAF or prior VTE (Choi et al. 2017). In the final cohort of the 182 apixaban-treated patients, 124 had AF and 58 a prior VTE while of the 212 warfarin-treated patients, 124 had AF and 88 a prior VTE. Authors could not demonstrate a statistically significant difference in the rate of recurrent VTE or in the rate of stroke in the apixaban group compared to warfarin group (recurrent VTE: 1.7% vs. 1.1%, OR 1.53, P = 0.76; rate of stroke: 0.8% vs. 2.4%, OR 0.33, P = 0.3) because of the small population size. Regarding bleeding events rate, no statistically significant difference was found between groups (apixaban group: 8.3% vs. warfarin 12.0%, OR 0.67, P = 0.23), but MB was significantly less common in patients on apixaban (0.6% vs. 4.3%, OR 0.12, P = 0.02) (Choi et al. 2017).

Kushnir and coworkers conducted a single-center, retrospective analysis on 795 patients with a BMI of at least 40 kg/m^2 who were prescribed apixaban (150), rivaroxaban (326), or warfarin (319) for VTE (n = 366) or NVAF (n = 429) to compare incidence of recurrence of VTE, stroke, and bleeding between groups. In VTE patients, no significant differences were found between treatment groups in the incidence of recurrent VTE or for bleeding event. In NVAF patients, while incidence of stroke was similar between treatment groups, MB occurred more often in warfarin-treated patients: 3/103 patients on apixaban (29%, 95% CI: 0–6.2), 5/174 on rivaroxaban (29%, 0.4–5.4), and 12/152 on warfarin (79%, 3.6–12.2); P = 0.063 (Kushnir et al. 2019).

Similar results emerged in the retrospective study of 90 obese patients prescribed apixaban (n = 41, 52%), rivaroxaban (n = 33, 37%), dabigatran (n = 11, 12%), or warfarin for NVAF or VTE conducted by Kalani et al. No statistical difference between NOACs and warfarin was found for S/SE (OR 1.11, 95% confidence interval [CI] 0.45–2.78; P = 0.82) and MB events (P = 0.065) (Kalani et al. 2019).

Table 9.5 summarize results from these studies.

Table 9.5 NOACs in both NVAF and VTE obese patients

References	Study design	NOAC	Patients (*n*)	Obese patients (%)	Outcomes	
Tittl et al. (2018)	Retrospective analysis of prospective registry Efficacy and safety of NOACs in obese patients	Dabigatran Rivaroxaban Apixaban Edoxaban	3432	1077 (31.4%)	**Combined Endpoint** **On treatment rate events (%)**	
					VTE (BMI ≤ 30)	24/770 (3.1)
					VTE (BMI ≥ 30)	6/285(2.1)
					NVAF(BMI ≤ 30)	74/1556(4.8)
					NVAF(BMI ≥ 30)	33/778(4.2)
					MB **On treatment rate events (%)**	
					VTE (BMI ≤ 30)	24/770 (3.1)
					VTE (BMI ≥ 30)	9/285 (3.2)
					NVAF(BMI ≤ 30)	104/1556(6.7)
					NVAF(BMI ≥ 30)	44/778(5.7)
Duperreault et al. (2020)	Retrospective matched cohort study Rivaroxaban and apixaban in morbidly obese vs. nonobese	Rivaroxaban Apixaban	291	153 (52.6)	**Thrombotic events** **Number of events (%)**	
					Nonobese	3(1.2)
					Morbidly obese	2(2.2)
					$P = 0.67$	
					MB **Number of events (%)**	
					Nonobese	7 (5.1)
					Morbidly obese	1 (0.7)
					$P = 0.02$	

(continued)

Table 9.5 (continued)

References	Study design	NOAC	Patients (*n*)	Obese patients (%)	Outcomes	
Choi et al. (2017)	Retrospective cohort study Apixaban vs. warfarin in morbidly obese patients	Apixaban	390	1840 (100%)	**Recurrent VTE**	
					Apixaban	1.7%
					Warfarin	1.1
					OR 1.53, $P = 0.76$	
					Stroke	
					Apixaban	0.8%
					Warfarin	2.4%
					OR 0.33 $P = 0.31$	
					MB	
					Apixaban	0.6%
					Warfarin	4.3%
					OR 0.12, $P = 0.02$	

Kushnir et al. (2019)	Retrospective cohort study NOACs vs. warfarin in morbidly obese patients	Rivaroxaban Apixaban	795	6585 (100%)	**Recurrent VTE Incidence rate (95% CI)**	
					Apixaban	2.1% (0.0–6.3)
					Rivaroxaban	2.0% (0.0–4.2)
					Warfarin vs. NOACs	1.2% (0.0–2.9)
					$P = 0.74$	
					MB (VTE patients) Incidence rate (95% CI)	
					Apixaban	2.1% (0.0–6.3)
					Rivaroxaban	1.3% (0.0–3.1)
					Warfarin vs. NOACs	2.4 (0.1–4.7)
					$P = 0.77$	
					Stroke (NVAF patients) Incidence rate (95% CI)	
					Apixaban	1.0% (0.0–2.9)
					Rivaroxaban	2.3% (0.1–4.5)
					Warfarin vs. NOACs	1.3% (0·0–3.1)
					$P = 0.71$	
					MB (NVAF patients) Incidence rate (95% CI)	
					Apixaban	2.9% (0.0–6.2)
					Rivaroxaban	2•9% (0.4–5.4)
					Warfarin vs. NOACs	7•9% (3.6–12.2)
					$P = 0.063$	

(continued)

Table 9.5 (continued)

References	Study design	NOAC	Patients (*n*)	Obese patients (%)	Outcomes
Kalani et al. (2019)	Retrospective cohort study NOACs vs. warfarin in morbidly obese patients	Dabigatran Rivaroxaban Apixaban	180		**S/SE OR (95% CI)**
					1.11 (0.45–2.78) $P = 0.82$
					MB OR (95% CI)
					0.66 (0.11–4.04) $P = 0.65$

NOACs non-vitamin K oral anticoagulants, *NVAF* non-valvular atrial fibrillation, *VTE* venous thromboembolism, *OR* odds ratio, *CI* confidential interval, *S/SE* stroke/systemic embolism, *MB* major bleeding, *BMI* body mass index in kg/m^2. OR are expressed warfarin as reference category, except where explicitly reported

Discussion

Obesity is clearly related to a higher risk of morbidity and mortality in general population (Aune et al. 2016; Di Angelantonio et al. 2016). However, in several CVD (coronary artery disease, hypertension, heart failure), it has been demonstrated an obesity paradox using BMI as an obesity parameter (Uretsky et al. 2007; Fonarow et al. 2007; Gruberg et al. 2002; Oreopoulos et al. 2009). In VTE and NVAF patients and more in NOACs use in obese patients, results from the literature are very controversial.

Although quick and easy to establish, BMI do not take into account the difference in mass composition (fat versus lean) and fat distribution (Nuttall 2015) so that results from available data can be confounded by the use of this parameter to define obesity. To fully understand the association between obesity and CV outcomes, it could be necessary to use other obesity indexes as waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), and waist-to-hip-to-height ratio (WHHR), all of them predictors of all-cause and CV mortality (Coutinho et al. 2011, 2013; Sahakyan et al. 2015). Moreover, obesity paradox demonstrated through BMI has been predominantly observed in overweight an obese I patients, with morbidly obese patients generally poorly represented (Antonopoulos et al. 2016).

Due to these controversial evidences, it is reasonable to hypothesize that a subgroup of obese patients who have a better fitness status (not meeting metabolic syndrome criteria and performing a better exercise test) can show a CV prognosis similar to that of normal weight patients (Ortega et al. 2013).

Even if several studies tried to highlight an obesity paradox in NVAF and VTE, the percentage of extremely obese patients in such studies is generally small and only a few are directly targeted to study this population (El-Menyar et al. 2018; Kubitza et al. 2007; Upreti et al. 2013; Piran et al. 2018; Tittl et al. 2018; Duperreault et al. 2020). Use of NOACs in extremely obese patients is a major concern in clinical practice, and evidences supporting their use are lacking and controversial. On the other hand, NOACs have demonstrated to be as effective and safe as VKAs in several particular settings in which no RCTs are available (Russo et al. 2018a; b, 2019a, b, c; Melillo et al. 2020; Rago et al. 2019) so that even in the obesity field it might be a possibility.

Moreover, NOACs in real-life experiences tend to show good outcomes, maintaining the efficacy and safety profile demonstrated in the main RCTs (Russo et al. 2015, 2017a, b, 2020a;). Anyway, in real-world data too, there are sparse and controversial evidences regarding obese population. In fact, while some real-world registries (ETNA-VTE Europe 2020), subgroup analysis (Deitelzweig et al. 2019), and case report (Russo et al. 2020b, c) found that NOACs have comparable risk of S/SE compared to VKAs, some others report treatment failure in this subset of patients (Breuer et al. 2013; Safouris et al. 2014).

Overall, the available presented data seems to suggest that NOACs are effective and safe used in high-weight/BMI patients especially when compared to low body weight patients who are generally more associated with a poor prognosis (Russo

et al. 2020d). Even so, it is important to note that all studies we have reported are retrospective and the majority relatively small with obvious limits related to their final conclusions.

Conclusion

Obesity paradox is a challenging and new concept in CVD. It can be applied to NVAF and VTE and in anticoagulated patients with NOACs. Emerging data suggests that obese patients on NOACs have similar CV outcomes compared to VKAs users but more extensive and RCTs are necessary to confirm these preliminary observations.

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Direct Oral Anticoagulation in Cancer Patients

10

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Introduction

Thrombosis is the second leading cause of mortality in cancer patients (Prandoni et al. 2005; Noble and Noble 2006). Venous thromboembolism (VTE) , arterial thromboembolism, and disseminated intravascular coagulation are all possible manifestations of cancer-mediated thrombosis (Levi 2014; Eichinger 2016). Atrial fibrillation (AF) and VTE are two common thromboembolic cardiovascular disease (CVD) largely represented in cancer patients. Several studies showed an increased risk of AF after cancer first diagnosis (O'Neal et al. 2015; Hu et al. 2013; Guzzetti et al. 2002) and VTE is estimated to occur in approximately 20% of cases (Blom et al. 2005; Khorana and Francis 2018; Walker et al. 2013) being one of the leading causes of death in cancer patients receiving chemotherapy (Khorana et al. 2007). Anticoagulation is the main prophylactic and treatment regimen in patients suffering thromboembolic events. A number of risk factors (Mandala et al. 2011) and pathogenetic mechanisms (Falanga et al. 2015) are involved in cancer-mediated thrombosis. Anticoagulation exposes cancer patients to an increased risk of bleeding, especially when compared to anticoagulated non-cancer patients (Hull et al. 2006; Hutten et al. 2000; Meyer et al. 2002; Schulman et al. 2013; Prandoni et al. 2002; Palareti et al. 2000). Therefore, the prophylaxis and treatment management of

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thromboembolic events is challenging in this subset of patients. In general population direct acting oral anticoagulants (DOACs) are preferred over Vitamin K antagonists (VKAs) for treatment of VTE and stroke prevention in AF (Hindricks et al. 2020; Konstantinides et al. 2020). Little is still known about use of DOACs in cancer patients with AF with evidences only available from retrospective, observational and subgroup analysis of randomized clinical trial (RCTs) and no available specific guidelines (Russo et al. 2019a; Deng et al. 2019; Yang et al. 2020). More data are available for treatment with DOACs in VTE cancer patients. However, major guidelines still recommend low molecular weight heparin (LMWH) for VTE treatment in this subgroup of patients (Farge et al. 2016; Kearon et al. 2016; Lyman et al. 2015) with the exception of rivaroxaban and edoxaban who were directly compared with LMWH (Khorana et al. 2018). Due to the more favorable pharmacological profile of DOACs over VKAs and LMWH, deepening the knowledge in this field is mandatory. For this reason, we aim to review the available data on the use of DOACs in AF cancer patients for stroke prevention and for treatment of cancer-mediated thrombosis.

Use of DOACs in AF Cancer Patients

Literature data for the use of DOACs in AF cancer patients are generally lacking. The main RCTs of DOACs have included a small number of patients with cancer due to reduced life expectancy or an excessively high risk of bleeding in patients with malignancies (Connolly et al. 2009; Granger et al. 2011; Patel et al. 2011; Giugliano et al. 2013).

Recently several studies have explored the role of DOACs in this subgroup of patients (Russo et al. 2019a; Deng et al. 2019; Yang et al. 2020).

From the observational and metanalytical results obtained, it was possible to conclude that DOACs could be a valid alternative to VKAs for stroke prevention in AF cancer patients (Russo et al. 2019a; Deng et al. 2019; Yang et al. 2020).

From the systematic review including six studies by Russo (Russo et al. 2019a) and colleagues emerged that efficacy and safety profile of DOACs in AF cancer patients are maintained when compared to that of general population. Specifically, some interesting results emerge from this descriptive analysis: (a) the annual incidence of bleedings, ischemic stroke, and thromboembolic events in AF cancer patients on DOAC therapy is generally small compared with VKAs (range for bleedings:1.2–4.4% (Melloni et al. 2017; Laube et al. 2017); range for ischemic stroke and thromboembolic events: 0–4.9% (Ording et al. 2017; Russo et al. 2018)); (b) the risk of thromboembolic and bleeding events in AF cancer patients is similar to that of non-cancer patients, irrespective of the treatment they are prescribed (DOACs vs VKAs) (Ording et al. 2017); (c) in DOACs patients, the risk of stroke, thromboembolic, and bleeding complications is similar between cancer and non-cancer patients (Melloni et al. 2017; Ording et al. 2017); and (d) when gastrointestinal bleedings occur, clinical characteristics are similar between those occurring on dabigatran and those on warfarin (hospitalization rate, mean nights in hospital,

intensive care unit requirement, transfusion requirement, the need for endoscopic, and surgical intervention) (Russo et al. 2019a; Flack et al. 2017). Details of the studies included in Russo et al. analysis are available in Table 10.1.

Deng and Yang's working groups separately conducted a meta-analysis of five studies (Deng et al. 2019; Yang et al. 2020) [three post hoc analyses from three RCTs (Melloni et al. 2017; Fanola et al. 2018; Chen et al. 2019), one retrospective propensity score-matched study (Shah et al. 2018), and one retrospective population-based observational data study (Kim et al. 2018)].

The pooled analysis from the three post hoc analyses of the Apixaban Versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) trial (Melloni et al. 2017), Rivaroxaban Versus Warfarin in Non-valvular Atrial Fibrillation (ROCKET-AF) trial (Chen et al. 2019), and the Edoxaban Versus Warfarin in

Table 10.1 Principal characteristics and results of the studies included in Russo et al. systematic review

References	Study design	Cancer patients on DOACs *n* (%)	Outcomes HR (95% CI)	
Ording et al. (2017)	Restrospective cohort study	1809 (15.2%)	TE events[a,b] *n/N*	**VKA**
				Cancer vs. cancer free
				628/10,046 vs. 2734/49,057 (6.5% vs. 5.8%) HR, 1.0 (0.93–1.1)
				DOACs
				Cancer vs. cancer free
				65/1809 vs. 290/7207 (4.9% vs. 5.1%) HR, 0.80 (0.61–1.1)
			MB[a,c] *n/N*	**VKA**
				Cancer vs. cancer free
				513/10,046 vs. 2025/49,057 (5.4% vs. 4.2%) HR, 1.1 (1.0–1.2)
				DOACs
				Cancer vs. cancer free
				60/10,046 vs. 166/49,057 (4.4% vs. 3.1%) HR, 1.2 (0.92–1.7)

(continued)

Table 10.1 (continued)

References	Study design	Cancer patients on DOACs *n* (%)	Outcomes HR (95% CI)	
Flack et al. (2017)	RE-LY Post hoc analysis	34 (77.2%)	MGIB[d] related to GI cancers (*N* = 44) *n/N*	**Overall** (*N* = 546)
				Dabigatran vs. warfarin
				34/398 vs. W:10/148 (8.5% vs. 6.8%) *P* = 0.6
				Colorectal cancer *N* = 35/44 (79.5%)
				Dabigatran vs. Warfarin
				30/34 vs. 5/10 (88.2% vs. 50.0%) *P* = 0.02
				Gastric cancer *N* = 6
				Dabigatran vs. warfarin
				1/34 vs. 5/10 (2.9% vs. 50%)
Melloni et al. (2017)	ARISTOTLE Post hoc analysis	615 (49.8%)	S/SE[a] *n/N*	**Cancer**
				Apixaban vs. warfarin
				15/615 vs. 14/621 (1.4% vs. 1.2%) HR, 1.09 (0.53–2.26)
				Cancer free
				Apixaban vs. warfarin
				196/8493 vs. 251/8454 (1.3% vs. 1.6%) HR, 0.77 (0.64–0.93)
			MB[a] *n/N*	**Cancer**
				Apixaban vs. warfarin
				24/615 vs. 32/621 (2.4% vs. 3.2%), HR, 0.76 (0.45–1.29)
				Cancer free
				Apixaban vs. warfarin
				303/8493 vs. 430/8454 (2.1% vs. 3.1%) HR, 0.69 (0.59–0.80)

Table 10.1 (continued)

References	Study design	Cancer patients on DOACs *n* (%)	Outcomes HR (95% CI)	
Laube et al. (2017)	Retrospective cohort study	163 (100%)	Stroke	**1 year cumulative incidence (vs. ROCKET-Trial)**
				1.4% (vs. 1.7%) (0–3.4%)
			MB[d]	**1 year cumulative incidence (vs. ROCKET-Trial)**
				1.2% (vs. 3.6%) (0–2.9)
Russo et al. (2018)	Retrospective cohort study	76 (100%)	TE events[e]	0
			MB[d]	**Cumulative incidence**
				3.9%
				Annual incidence
				1.4%
Iannotto et al. (2017)	Case–control study	25 (3.3%)	TE events[f]	**NOACs vs. LDA**
				Incidence rate *n*, (%)
				1 vs. 2 (4–8%)
			MB[d]	**NOACs vs. LDA**
				Incidence rate *n*, (%)
				3 vs. 3 (12% vs. 12%)

DOACs direct oral anticoagulants, *VKA* vitamin K antagonists, *HR* hazard ratio, *CI* confidential interval, *TE* thromboembolic event, *MB* major bleeding, *MGIB* major gastrointestinal bleeding, *GI* gastrointestinal, *S/SE* stroke/systemic embolism, *LDA* low-dose aspirin

[a]Annual incidence

[b]Recurrence of ischemic stroke, VTE, other arterial embolism, or myocardial infarction

[c] Diagnosis of hemorrhagic stroke or GI, lung, or urinary hemorrhage

[d]According to the International Society of Thrombosis and Hemostasis criteria

[e]Ischemic stroke, transient ischemic attack, or systemic embolism

[f]Any documented thrombosis

Patients with Atrial Fibrillation (ENGAGE-TIMI 48) trial (Fanola et al. 2018) in Deng's metanalysis showed that cancer and non-cancer patients have similar efficacy and safety outcome (all $P > 0.05$) (Deng et al. 2019). Moreover, results from the analysis of all studies included showed that cancer patients on DOACs had significantly lower risk of stroke/systemic embolism (S/SE) ($P = 0.04$) and VTE ($P < 0.0001$) with a trend toward a lower rate of ischemic stroke ($P = 0.05$). No significant differences were found in risk of myocardial infarction ($P = 0.26$), all-cause death ($P = 0.39$), and CV death ($P = 0.13$). About safety outcomes, use of DOACs was associated with a decreased risk of intracranial or gastrointestinal bleeding ($P = 0.04$) and a tendency toward statistical significance for a reduced risk of major bleeding (MB) compared with warfarin (RR = 0.73; 95% CI: 0.53–1.00;

$P = 0.05$). Risks of major or clinically relevant nonmajor bleeding (CRNMB) and any bleeding were similar between treatment groups ($P = 0.96$ and $P = 0.39$, respectively) (Deng et al. 2019).

Yang et al. conducted a network meta-analysis (NMA) on the same five studies (Yang et al. 2020; Laube et al. 2017; Fanola et al. 2018; Chen et al. 2019; Shah et al. 2018; Kim et al. 2018) to evaluate and rank anticoagulant strategies in AF cancer patients. The rank score used was the surface under the cumulative ranking area (SUCRA) probabilities: the larger the value, the higher the probability of the endpoint event. The NMA showed no significant differences between DOACs regarding outcome (primary efficacy outcome: S/SE; secondary efficacy outcome: all-cause death; incidental VTE was described too), with all DOACs achieving a better efficacy profile compared with warfarin. Rivaroxaban followed by apixaban ranked the first and second best in lowering risk of S/SE followed by dabigatran and edoxaban and finally warfarin (SUCRAs: 25.2%, 29.3%, 52.3%, 55.8%, 87.4%, respectively) (Yang et al. 2020). In addition, apixaban and dabigatran were associated with the lower probability and the better ranking for VTE occurrence (Yang et al. 2020). Regarding safety outcomes (MB according to the International Society on Hemostasis and Thrombosis (ISTH) criteria (Schulman et al. 2010)), no statistically significant differences were found between treatment groups with the exception of apixaban which was found safer than warfarin (OR 0.39, 95% CI: 0.18–0.79, SUCRA:4.9%) (Yang et al. 2020) .

Table 10.2 shows principal characteristics and results of the five studies included in the abovementioned metanalyses while Table 10.3 summarizes results of Deng and Yang's studies.

Table 10.2 Results on S/SE and MB of the studies included in Deng and Yeng meta-analysis

References	Study design	Cancer patients/DOACs users with cancer DOAC studied	Outcomes HR, (95%CI)	
Chen et al. (2019)	Rocket-AF Post hoc analysis	640/309 Rivaroxaban	S/SE *n/N*	**History of cancer**
				Rivaroxaban vs. warfarin
				8/307 vs. 16/329 (1.36 vs. 2.71)[a] HR, 0.52 (0.22–1.21)
			MB *n/N*	**History of cancer**
				Rivaroxaban vs. warfarin
				97/309 vs. 96/331 (23.63 vs. 21.59) HR, 1.09 (0.82–1.44)

Table 10.2 (continued)

References	Study design	Cancer patients/DOACs users with cancer DOAC studied	Outcomes HR, (95%CI)	
Shah et al. (2018)	Retrospective cohort study	16,096/6075 Dabigatran (2189) Rivaroxaban (2808) Apixaban (1078)	Ischemic stroke *n*/*N*	**Dabigatran vs. warfarin**
				26/2189 vs. 127/8339 HR, 0.89 (0.56–1.42) *P* = 0.63
				Rivaroxaban vs. warfarin
				16/2808 vs. 59/5673 HR, 0.74 (0.40–1.39) *P* = 0.35
				Apixaban vs. warfarin
				4/1078 vs. 18/2775 HR, 0.71 (0.19–2.60) *P* = 0.6
				Dabigatran vs. rivaroxaban
				9/859 vs. 3/922 7.61 (1.52–38.12) *P* = 0.01
				Apixaban vs. rivaroxaban
				3/1126 vs. 13/2016 HR, 0.52 (0.13–2.17) *P* = 0.37
			SB[b] *n*/*N*	**Dabigatran vs. warfarin**
				70/2189 vs. 329/8339 HR, 0.96 (0.72–1.27) *P* = 0.75
				Rivaroxaban vs. warfarin
				68/2808 vs. 181/5673 HR, 1.09 (0.79–1.50) *P* = 0.59
				Apixaban vs. warfarin
				10/1078 vs. 84/2775 HR, 0.37 (0.17–0.79) *P* = 0.01
				Dabigatran vs. rivaroxaban
				22/859 vs. 22/922 HR, 1.07 (0.50–2.32) *P* = 0.86
				Apixaban vs. rivaroxaban
				10/1126 vs. 43/2016 HR, 0.29 (0.13–0.65) *P* = 0.002

(continued)

Table 10.2 (continued)

References	Study design	Cancer patients/DOACs users with cancer DOAC studied	Outcomes HR, (95%CI)	
Fanola et al. (2018)	ENGAGE AF-TIMI 48 Post hoc analysis	1153/395 Edoxaban	S/SE	**Cancer**
				Edoxaban vs. warfarin
				14/390 vs. 24/395 °(1.43 vs. 2.38) HR, 0.60 (0.31–1.15)
				No Cancer
				Edoxaban vs. warfarin
				282/6645 vs. 313/664 °(1.58 vs 1.77) HR, 0.89 (0.76–1.05)
				P-interaction = 0.25
			MB	**Cancer**
				Edoxaban vs. warfarin
				56/390 vs. 63/395 °(7.92 vs. 8.18) HR, 0.98 (0.68–1.4)
				No cancer
				Edoxaban vs. warfarin
				388/6645 vs. 494/6641 °(2.62 vs. 3.34) HR, 0.98 (0.68–1.4)
				P-interaction = 0.31
Melloni et al. (2017)	ARISTOTLE Post hoc analysis	1236/615 Apixaban	S/SE *n*/*N*	**Cancer**
				Apixaban vs. warfarin
				15/615 vs. 14/621 (1.4% vs. 1.2%) HR, 1.09 (0.53–2.26)
				Cancer free
				Apixaban vs. warfarin
				196/8493 vs. 251/8454 (1.3% vs. 1.6%) HR, 0.77 (0.64–0.93)
			MB *n*/*N*	**Cancer**
				Apixaban vs. warfarin
				24 /615 vs. 32/621 (2.4% vs. 3.2%), HR, 0.76 (0.45–1.29)
				Cancer free
				Apixaban vs. warfarin
				303/8493 vs. 430/8454 (2.1% vs. 3.1%) HR, 0.69, (0.59–0.80)

Table 10.2 (continued)

References	Study design	Cancer patients/DOACs users with cancer DOAC studied	Outcomes HR, (95%CI)	
Kim et al. (2018)	Retrospective cohort study	1651/388[d] Dabigatran (140) Apixaban (138) Rivaroxaban (110)	S/SE *n*/*N*	**NOACs vs. warfarin** 9/388 vs. 40/388 (1.3 vs. 5.5)[a] *P* = <0.001
			MB *n*/*N*	**NOACs vs. warfarin** 8/388 vs. 36/388 (1.2 vs. 5.1)[a] *P* = <0.001

DOAC direct oral anticoagulants, *MB* major bleeding, *S/SE* stroke/systemic embolism, *SB* severe bleeding, *CI* confidential interval
[a]Events per 100-patient years
[b]Subarachnoid hemorrhage, intracerebral hemorrhage, gastrointestinal bleeding requiring transfusion and not trauma related
[c]Annualized event rate (100-patient/year)
[d]Propensity scored matched with 388 warfarin users

Table 10.3 Principal results of the metanalysis exploring safety and efficacy of DOACs versus warfarin in cancer patients with AF

References	Studies included (*n*, reference)	Outcomes [a]RR/OR, (95% CI)	
Deng et al. (2019)		Efficacy outcome	**S/SE**
			RR, 0.52 (0.28–0.98)
			Ischemic stroke
			RR, 0.63 (0.4–1.0)
			VTE
			RR, 0.37 (0.22–0.63)
			MI
			RR, 0.75 (0.45–1.25)
			All-cause death
			RR, 0.81 (0.49–1.32)
			CV death
			RR, 0.71 (0.45–1.1)
		Safety outcome	**MB**
			RR, 0.73 (0.53–1.0)
			MB or CRNMB
			RR, 1.00 (0.86–1.17)
			Intracranial or gastrointestinal bleeding
			RR, 0.65 (0.42–0.98)
			Any bleeding
			RR, 0.93 (0.78–1.10)

(continued)

Table 10.3 (continued)

References	Studies included (*n*, reference)	Outcomes [a]RR/OR, (95% CI)		
Yang et al. (2020)		Efficacy outcome	**S/SE**	**Dabigatran**
				0.6 (0.18–1.80)
				Apixaban
				0.48 (0.17–1.30)
				Rivaroxaban
				0.47 (0.18–1.2)
				Edoxaban
				0.71 (0.11–4.5)
			VTE	**Dabigatran**
				0.24 (0.07–1.00)
				Apixaban
				0.12 (0.05–0.52)
				Rivaroxaban
				0.56 (0.25–2.0)
			All-cause death	**Dabigatran**
				0.43 (0.10–1.8)
				Apixaban
				0.72 (0.24–2.00)
				Rivaroxaban
				0.62 (0.21–1.80)
				Edoxaban
				1.1 (0.24–4.8)
		Safety outcome	**MB**	**Dabigatran**
				0.64 (0.25–1.4)
				Apixaban
				0.39 (0.18–0.79)
				Rivaroxaban
				0.65 (0.30–1.20)
				Edoxaban
				0.78 (0.21–2.9)
		SUCRA[b]	**S/SE**	**Rivaroxaban**
				25.2%
				Apixaban
				29.3%
				Dabigatran
				52.3%
				Edoxaban
				55.8%
				Warfarin
				87.4%
			VTE	**Apixaban**
				0.1%
				Dabigatran
				33.3%
				Rivaroxaban
				66.7%
				Warfarin
				100%
			MB	**Apixaban**
				4.9%
				Rivaroxaban
				47.1%
				Dabigatran
				47.3%
				Edoxaban
				62.4%
				Warfarin
				88.4%

Table 10.3 (continued)

References	Studies included (*n*, reference)	Outcomes [a]RR/OR, (95% CI)

DOAC direct oral anticoagulant, *AF* atrial fibrillation, *S/SE* stroke systemic embolism, *VTE* venous thromboembolism, *MB* major bleeding, *CRNMB* clinically relevant non major bleeding, *CV* cardiovascular, *MI* myocardial infarction, *SUCRA* surface under the cumulative ranking area, *CI* confidential interval

[a]RR in Deng's results, OR in Yeng results

[b]NOACs are listed near the corresponding outcome from the better SUCRA to the worst

VTE in Cancer Patients: Are the DOACs Always the Best Choice?

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of cancer, and its prevention and treatment is a challenge because of the drug interactions and varieties of coexisting comorbidities (Khorana 2010). According to a large observational cohort study, the incidence of VTE in active cancer patients is 5.8 per 100 person-years (Cohen et al. 2017). Cancer patients are usually in a state of hypercoagulability that results from various factors, including the type of malignancy, extent of disease, patient age, antitumor treatment, and the presence of coexisting diseases (Zwicker et al. 2007). The highest rate of VTE was observed among patients receiving systemic cancer therapy for tumors of the pancreas, stomach, or lung (Khorana et al. 2007; Blom et al. 2006; Chew et al. 2006; Lyman et al. 2013). VTE is an important cause of death in cancer patients as it is second only to tumor progression (Khorana et al. 2007). VTE can lead to a series of comorbidities, such as longer hospitalization, higher risk of bleeding, and delay or discontinuation of chemotherapy, which may affect patients' quality of life and prognosis (Carrier and Lee 2014). For these reasons, the choice of the best anticoagulation therapy is mandatory for this group of patients.

Primary Prevention of VTE in Cancer Patients

Pharmacological prophylaxis can reduce VTE incidence, but it may also increase the risk of bleeding (Agnelli et al. 2009; Khorana et al. 2017). According to existing research, the most commonly used anticoagulant drugs are LWMH and warfarin. Many large RCTs have demonstrated the efficacy and safety of anticoagulants to reduce the incidence of VTE events in ambulatory cancer patients. The PROTECHT study, involving 1150 patients, has shown that nadroparin reduces the incidence of VTE events without significantly increasing bleeding risks (Agnelli et al. 2009). The SAVE ONCO study involving 3212 patients has shown similar results using the ultra-LMWH semuloparin (Agnelli et al. 2012). However, current guidelines do not recommend the routine thromboprophylaxis in patients receiving chemotherapy (Lyman et al. 2015; https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf) . A systematic review published in the Cochrane Library has indicated some positive results for thromboprophylaxis, but routine thromboprophylaxis is not

indicated in ambulatory cancer patients, and the evaluation of the risks and benefits is necessary before its prescription in high-risk patients (Di Nisio et al. 2016). The risk differs among cancer patients, and the Khorana risk score allows for identification of patients with cancer at increased risk for VTE (Khorana et al. 2008).

In recent years, DOACs have played an increasingly important role in clinical practice (Russo et al. 2015, 2019a, b; Russo et al. 2020a, b, c, d). DOACs have been shown to be safe, effective, and well tolerated for VTE among non-cancer patients (Agnelli et al. 2013; Prins et al. 2013). RCTs comparing DOACs with placebo have been performed for primary prophylaxis in cancer patients with inconstant results for the incidence of VTE events and bleeding complications (Khorana et al. 2019; Carrier et al. 2019). Studies of thromboprophylaxis with LMWH in ambulatory patients with cancer have demonstrated that anticoagulation is associated with a significant relative risk reduction in VTE, but current clinical guidelines do not recommend routine outpatient VTE prophylaxis (except for multiple myeloma and select high-risk solid tumors), because the overall benefit-to-risk profile in an unselected patient population is uncertain (Khorana et al. 2019; Carrier et al. 2019). CASSINI trial (Khorana et al. 2020) is a randomized clinical study that compares the efficacy and safety of rivaroxaban with placebo in the prevention of VTE in high-risk ambulatory patients with cancer receiving systemic cancer therapy, as determined by the validated Khorana risk score. This study confirms the benefit of rivaroxaban in thromboprophylaxis, but only after determining the risk/benefit of anticoagulation in high-risk patients with cancer (Khorana et al. 2020).

Also, apixaban was tested in this setting in the AVERT trial (Carrier et al. 2019). Apixaban therapy resulted in a significantly lower rate of VTE than placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy. The rate of MB episodes was higher with apixaban than with placebo (Carrier et al. 2019).

High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided there are no significant risk factors for bleeding and no drug interactions (Lyman et al. 2015). Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms (Lyman et al. 2015).

At present, no anticoagulant is approved for routinely primary thromboprophylaxis in outpatients with cancer.

Treatment of VTE in Cancer Patients

In the general population, the efficacy and safety of DOACs in the long-term therapy of VTE were demonstrated in six large randomized trials (RECOVER I-II; EINSTEIN-TVP, EINSTEIN-TEP; AMPLIPHY; HOKUSAI TEV). Post hoc analysis and meta-analysis suggested efficacy and safety of DOACs in patients with

cancer, but these patients were underrepresented, not well identified for the type of oncological diagnosis and treatment, and finally the definition of "active cancer" varied greatly from one study to another.

Recent randomized trials have investigated the efficacy of DOACs among cancer patients with VTE (Agnelli et al. 2020; Raskob et al. 2018; Young et al. 2018; McBane et al. 2020). These trials have some limitations: one was a pilot trial (Young et al. 2018), whereas another small trial was prematurely terminated (McBane et al. 2020). Moreover, the two large studies were noninferiority trials and not powered to evaluate the safety of DOACs in this setting (Agnelli et al. 2020; Raskob et al. 2018). The Table 10.4 summarizes the most important characteristics of these studies.

Furthermore, a sub-analysis of the HOKUSAI-VTE cancer study has evaluated the occurrence of the composite outcome, recurrent VTE, or MB in subgroups based on adjudicated cancer diagnoses, including those with gastrointestinal, lung, urogenital, breast, hematological, and gynecological cancer. In the gastrointestinal cancer group, the benefit–risk trade-off requires careful evaluation because edoxaban was associated with an absolute 9.2% increase in MB compared with dalteparin. The absolute risk of recurrent VTE was 3.9% numerically lower with edoxaban. Oral edoxaban is an attractive alternative to subcutaneous dalteparin for the treatment of the majority of patients with cancer-associated VTE, including those with urogenital, lung, breast, hematological, and gynecological cancer (Mulder et al. 2020).

Based on the currently available evidence, the guidelines of European Society of Cardiology and of American Society of Clinical Oncology (Konstantinides et al. 2020; Lyman et al. 2015) recommend that patients with VTE and cancer, particularly those with gastrointestinal cancer, should be encouraged to continue LMWH for 3–6 months. This also applies to patients in whom oral treatment is unfeasible due to problems of intake or absorption, and to those with severe renal disease. In all other cases, the choice between LMWH and edoxaban or rivaroxaban (the publication of the CARAVAGGIO trial on apixaban in this setting is subsequent to the guidelines) is left to the discretion of the physician and the patient's preference. Owing to the high risk for recurrence, patients with cancer should receive indefinite anticoagulation after a first episode of VTE. Renal function and drug–drug interaction should be checked prior to using a DOAC.

Discussion

Compared to warfarin , DOACs have a more predictable anticoagulant effect with a more favorable pharmacological profile, so that they are the first-line anticoagulant treatment proposed in the general population affected by AF and VTE (Hindricks et al. 2020; Konstantinides et al. 2020). Cancer patients are a subgroup of patients with a delicate balance between hemorrhagic and thrombotic risk, so it is essential to choose the right anticoagulation and the time to start it; on the other hand,

Table 10.4 Principal characteristics of the most important RCTs about the treatment of venous thromboembolism (deep venous thrombosis and pulmonary embolism) in cancer patients

	n (DOAC/LMWH groups)	Mean age, years (DOAC/LMWH groups)	Male% (DOAC/LMWH groups)	Type of tumor	Metastasis (DOAC/LMWH groups)	Prior VTE (DOAC/LMWH groups)	DOAC group	Control group	Recurrent VTE (events)			Major bleeding (events)		
									DOAC	LMWH	Risk ratio (95% CI)	DOAC	LMWH	Risk ratio (95% CI)
Young et al. (Meyer et al. 2002) SELECT-D TRIAL	203/203	67/67 (median)	57/48	Colorectal, lung, breast cancer	58/58	NR	Rivaroxaban 15 mg BID for 3 weeks, followed by 20 mg QD for 6 months.	Dalteparin (CLOT protocol) for 6 months.	8/203	18/203	0.44 (0.20–1.00)	11/203	6/203	1.83 (0.69–4.86)
Raskob et al. (Hutten et al. 2000) HOKUSAI-VTE CANCER STUDY	522/524	64.3/63.7	53.1/50.2	Colorectal, lung, breast, gynecologic and hematologic malignancies	52.5/53.4	9.4/12	Edoxaban 60 mg QD (for 6 months) after at least 5 days of concomitant Dalteparin	Dalteparin (CLOT protocol) for 6 months.	41/522	59/524	0.70 (0.48–1.02)	36/522	21/524	1.72 (1.02–2.91)
McBane et al. (Schulman et al. 2013)	150/150	64.4/64.0	72/73	Colorectal, lung, pancreatic and hepatobiliary	65.3/66.0	5.4/8.1	Apixaban 10 mg BID for 7 days followed 5 mg BID for 6 months	Dalteparin (CLOT protocol) for 6 months.	1/145	9/142	0.11 (0.01–0.85)	0/145	2/142	0.20 (0.01–4.04)
Agnelli et al. (Hull et al. 2006) CARAVAGGIO TRIAL	576/579	67.2/67.2	50.7/47.7	Lung, breast, genitourinary	67.5/68.4	7.8/10.5	Apixaban 10 mg BID for 7 days followed 5 mg BID for 6 months	Dalteparin (CLOT protocol) for 6 months.	32/576	46/579	0.70 (0.45–1.08)	22/576	23/579	0.96 (0.54–1.71)

RCT randomized controlled trial, *DOAC* direct oral anticoagulants, *LMWH* low molecular weight heparin, *VTE* venous thromboembolism, *CI* confidence interval, *CLOT* Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant therapy for the prevention of recurrent venous thromboembolism in patients with cancer trial

particular attention is needed for the greater risk of bleeding of the cancer patients during anticoagulant treatment compared to the general population (Hull et al. 2006; Hutten et al. 2000; Meyer et al. 2002; Schulman et al. 2013; Prandoni et al. 2002; Palareti et al. 2000; Hindricks et al. 2020). Especially for AF cancer patients, evidences are rare and sparse. There are no RCTs available that directly compare DOACs to warfarin in this subgroup of patients and results emerge only from retrospective analysis of RCTs (Melloni et al. 2017; Flack et al. 2017; Fanola et al. 2018; Chen et al. 2019) and from very small studies (Russo et al. 2018, 2019a; Deng et al. 2019; Yang et al. 2020; Laube et al. 2017; Shah et al. 2018; Kim et al. 2018; Ianotto et al. 2017). However, in August 2019, the ISTH guidelines recommended the use of DOAC over VKAs and LMWH in cancer patients receiving chemotherapy with newly diagnosed NVAF (Delluc et al. 2019) with the exception of patients with gastrointestinal cancer or the presence of gastrointestinal abnormalities that can lead to gastrointestinal bleeding events. More evidence is currently available on the use of DOACs in VTE cancer patients. Rivaroxaban, edoxaban, and recently apixaban were compared directly with LMWH for the treatment of VTE in cancer patients, demonstrating noninferiority in lowering the rate of VTE recurrence but with some concern for bleeding events (Khorana et al. 2019; Carrier et al. 2019; Raskob et al. 2018). Indeed, a higher risk of CRNMB mainly driven by gastrointestinal bleeding events was evidenced with DOAC in cancer patients and VTE, but such events were almost entirely referable to gastrointestinal cancer patients, which is why guidelines still suggest the use of LMWH in patients with gastrointestinal tumors or gastrointestinal abnormalities that may increase the risk of bleeding events.

Conclusion

DOACs are a revolutionary anticoagulation treatment. Several preliminary evidences suggest their effectiveness and safety in AF cancer patients but RCTs should improve these findings. Currently it is better defined their role in VTE cancer patients even if some concern still remains for their safety profile especially in gastrointestinal malignancies and above all for thromboprophylaxis for which no defined recommendations are available due to the paucity of targeted evidences.

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DOACs and Dementia in Patients with Atrial Fibrillation

11

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Introduction

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice, affecting more than 37 million people worldwide in 2017, and has been increasing in both incidence and prevalence with an aging population (Disease et al. 2018; Chugh et al. 2014). AF is associated with increased morbidity and mortality, including stroke, systemic and venous thromboembolism, heart failure, and myocardial infarction (Wolf et al. 1991; Wang et al. 2003; Violi et al. 2016; Holst et al. 2010; Benjamin et al. 1998). Dementia is another disorder of aging, affecting over 35 million people in 2010 and also increasing worldwide with an aging population (Licher et al. 2019; Wortmann 2012). Dementia is a neurological disorder involving loss of cognition to a degree which affects function, and which also commonly affects memory (Arvanitakis et al. 2019). Alzheimer's dementia is the most common form of dementia and is responsible for up to 75% of cases (Silva et al. 2019).

Direct oral anticoagulants (DOACs) have recently become the standard of care for most patients with non-valvular AF for the prevention of thromboembolic disease (January et al. 2019). In this chapter, we will review the association between

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AF and dementia, as well as the effects of oral anticoagulants (OACs) and specifically DOACs on the risk of dementia in patients with AF.

Atrial Fibrillation and Dementia

The association between AF and dementia has been documented by several large observational studies. Ott and colleagues analyzed data from the Rotterdam study, which included 6584 participants aged between 55 and 106 years. The authors found a significant association of AF with dementia (OR: 2.3, 95% CI: 1.4–3.7) and cognitive impairment (OR: 1.7, 95% CI: 1.2–2.5) (Ott et al. 1997). This association was stronger in women, more pronounced in the young elderly, and independent of a prior history of strokes, which was rigorously adjudicated (Ott et al. 1997). Mielke et al. examined data from a cohort study of 135 elderly patients with incident Alzheimer's disease who were followed for a mean of 3 years with cognitive assessments by clinical dementia rating and mini-mental state examinations scores. The authors reported that participants with AF had a more rapid decline in cognition compared to patients without AF (Mielke et al. 2007). Bunch and colleagues explored the relationship between AF and dementia in a study of 37,025 patients from a large prospective population-based study in Utah, USA using ICD-9 codes to define dementia (Bunch et al. 2010). Participants had no history of dementia and at least 5 years of follow-up data. To provide greater rigor on the diagnosis of dementia, only ICD 9 codes entered by neurology were used. In an age-based analysis, AF independently was significantly associated with all types of dementia with the highest risk was in participants <70 years of age. Interestingly, these younger participants (<70 years) with AF had the highest relative risk of developing Alzheimer's dementia (OR 2.3, $P < 0.001$) suggesting that the observed association went beyond an epiphenomenon due to the common risk factor of advancing age (Bunch et al. 2010). After dementia diagnosis, the presence of AF was associated with a marked increased risk of mortality, around 40%, in all subtypes of dementia.

AF has been identified as an independent risk factor for dementia, including Alzheimer's, vascular, and senile dementia, both in patients with and without a history of stroke (Bunch et al. 2010; Kalantarian et al. 2013; Marzona et al. 2012; Kwok et al. 2011; Santangeli et al. 2012; de Bruijn et al. 2015; Satizabal et al. 2016; Dublin et al. 2011; Singh-Manoux et al. 2017; Saglietto et al. 2019a; Proietti et al. 2020). One meta-analysis, which included eight population-based studies with 77,668 patients, found that in patients without baseline cognitive impairment or history of stroke, AF was associated with increased risk of incident dementia (HR 1.42, 95% CI: 1.17–1.72) (Santangeli et al. 2012). Of the patients included, 15% had AF at baseline; the mean follow-up was 7.7 ± 9.1 years (range 1.8–30 years), and the incidence of dementia was 6.5%. A systematic review by Kalantarian and colleagues, which included 21 studies, demonstrated an increase in relative risk of cognitive impairment in patients with AF and history of stroke (RR 2.7, 95% CI: 1.82–4.00) and independent of stroke history (RR 1.34, 95% CI: 1.13–1.58) (Kalantarian et al. 2013). Kwok et al. performed a meta-analysis of 15 studies which included 46,637 participants with a mean age 71.7 years. This showed that AF was

associated with significant increase in dementia overall (OR 2.0, 95% CI: 1.4–2.7, $P < 0.0001$) (Kwok et al. 2011). Interestingly, one of the included studies showed that conversion of mild cognitive impairment to dementia had a significant association with AF (OR 4.6, 95% CI: 1.7–12.5).

Potential Mechanisms in the Association Between AF and Dementia

The association between AF and dementia is likely multifactorial with numerous possible contributing mechanisms, including stroke, subclinical cerebral infarcts, microvascular bleeds, and cerebral hypoperfusion (Alonso and Arenas de Larriva 2016). These mechanisms are summarized in Fig. 11.1 (Gallinoro et al. 2019). Patients with AF can develop micro thromboembolisms leading to silent infarcts, with about a third of patients with AF being found to have evidence of such on MRI imaging (Hara et al. 1995). Repeated subclinical infarcts are likely the cause of increased risk of vascular dementia in patients with AF.

Over the last 30 years, the incidence of dementia has been declining. (Satizabal et al. 2016) This may be partly attributable to the increased use of anticoagulation in patients with AF. This is supported by a study of patients on long-term warfarin which showed that those with AF were more likely to develop dementia than those on warfarin for other indications (HR 2.42, 95% CI: 1.85–3.18, $P < 0.0001$) and that higher time spent in therapeutic range was associated with reduced risk of developing dementia regardless of AF status (Bunch et al. 2016). However while anticoagulation reduces the

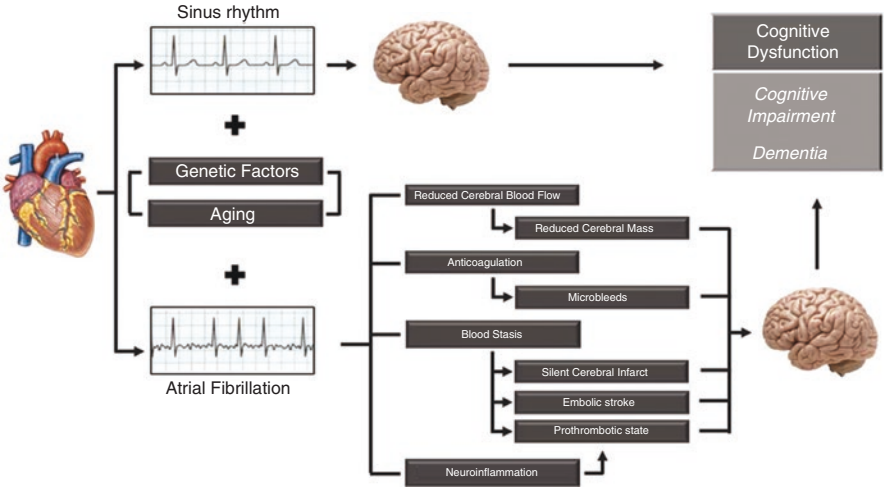

Fig. 11.1 Mechanisms involved in cognitive dysfunction in patients affected by atrial fibrillation. **Gallinoro E, D'Elia S, Prozzo D, Lioncino M, Natale F, Golino P, et al. Cognitive Function and Atrial Fibrillation: From the Strength of Relationship to the Dark Side of Prevention. Is There a Contribution from Sinus Rhythm Restoration and Maintenance? Medicina (Kaunas). 2019;55(9)**

risk of stroke in patients with AF, it also carries the risk of microvascular brain bleeds which may increase the risk of cognitive impairment (Saito et al. 2014). In a study of patients with AF on both warfarin and an antiplatelet agent, patients who had an INR over 3 for more than 25% of the time were 2.40 times more likely to develop dementia ($P = 0.04$), with no difference in risk seen in those who spent less than 25% of the time with an INR over 3. This supports the hypothesis that microvascular bleeds leading to chronic cerebral injury play a role in the association between AF and dementia (Jacobs et al. 2015a). Additionally, in patients on warfarin, the risk of dementia increased with increasing CHADS2 scores, and AF was associated with increased risk of dementia across all CHADS2 score strata. This suggests that the risk of dementia attributed to AF is not solely secondary to OAC use (Graves et al. 2017).

Another possible mechanism relates to AF associated cerebral hypoperfusion (Petersen et al. 1989; Lavy et al. 1980; Anselmino et al. 2016). Gardarsdottir and colleagues assessed the blood flow in the cervical arteries, which was measured with phase contrast MRI and brain perfusion, in 2291 participants who were divided into three groups: persistent AF, paroxysmal AF but were in sinus rhythm at the time of imaging AF, and no history of AF (Gardarsdottir et al. 2017). Those in the persistent AF group had significantly lower total cerebral blood flow, both when compared with the paroxysmal AF group ($P < 0.05$) and the no AF group ($P < 0.001$). Brain perfusion was lowest in the persistent AF group compared with the paroxysmal AF group ($P < 0.05$) and those with no AF ($P < 0.001$) (Gardarsdottir et al. 2017). There is evidence to suggest that higher ventricular rates during AF is associated with higher rates of cerebral hypoperfusion events in a computational model (Saglietto et al. 2019b). One study has shown that AF associated cerebral hypoperfusion is more pronounced in patients under 50, compared to those over 65 (Lavy et al. 1980). This may partly explain the age-dependent risk of developing dementia in patients with AF, as one study showed that incident AF was associated with increased risk of dementia in those aged less than 67 but not in those aged 67 over, with a strong association between the duration of exposure to AF in the younger age group (de Bruijn et al. 2015). It has also been observed that patients with AF who underwent catheter ablation had significantly lower rates of dementia than those with AF who did not undergo ablation and were comparable to the dementia rates in patients without AF (Bunch et al. 2011).

Oral Anticoagulation and Dementia Risk

There have been several observational studies demonstrating that OAC is associated with reduced incidence of dementia in patients with AF. One retrospective study showed that in patients with AF and without dementia at baseline, OAC was associated with a 29% lower risk of dementia (HR 0.71, 95%CI: 0.68–0.74) (Friberg and Rosenqvist 2018). In another analysis using data from the same registry, in patients with AF, low stroke risk (CHADSVASC 1 or 0), and no baseline dementia, OAC was associated with a 38% lower risk of CI (HR 0.62, 95% CI: 0.48–0.81) (Friberg et al. 2019). In a UK registry, OAC was associated with lower risk of dementia when

compared to no treatment (HR 0.90, 95% CI: 0.85–0.95, $P < 0.001$) or antiplatelet therapy alone (HR 0.84, 95% CI: 0.79–0.90, $P < 0.001$). However, in patients on both an OAC and an antiplatelet agent, the risk of dementia was higher than with no treatment (HR 1.17, 95% CI: 1.05–1.31, $P = 0.006$) (Mongkhon et al. 2020). This may be due to an increased risk of cerebral microbleeds.

The association between OAC therapy and a reduction in dementia has been shown in different populations globally. A longitudinal Swedish-based study demonstrated that AF was a risk factor for developing dementia and that use of an OAC in patients with AF was associated with a reduced risk of developing dementia (HR 0.40, 95% CI: 0.18–0.92) (Ding et al. 2018). A Korean-based study showed similar results with AF being associated with increased risk of dementia and those on OAC having lower risk of developing dementia (HR 0.61, 95% CI: 0.54–0.68, $P < 0.001$). The study also showed an increase in the incidence of dementia with increasing CHADSVASc scores independent of AF status (Kim et al. 2019).

The quality of anticoagulation is also important; when using warfarin, this can be assessed via measures such as time in therapeutic range. In a study of patients with AF and no baseline cognitive impairment who were receiving warfarin, longer times spent out of the therapeutic range were associated with increased risk of developing cognitive impairment. Patients who were in the therapeutic range 51–75% of the time had a two-and-a-half-fold increase in risk of cognitive impairment (hazard ratio 2.57, $P = 0.001$), those in therapeutic range between 26% and 50% of the time had a fourfold increase in risk of cognitive impairment (hazard ratio 4.10, $P = 0.001$), and those who were at therapeutic range < 25% of the time had a fivefold increase (hazard ratio 5.34, $P = 0.001$) (Jacobs et al. 2014). This matches the findings of another observational study which showed that both a 10% reduction in time spent in subtherapeutic range (HR 0.71, 95% CI: 0.64–0.79) and time spent in supra therapeutic range (HR 0.67, 95% CI: 0.57–0.79) reduced risk of dementia (Madhavan et al. 2018). Mechanistically, this potentially reflects a reduction in the risk of micro thromboembolisms and microvascular bleeds, respectively. In a recent study, Petroni and colleagues also found similar results: there was a higher risk of dementia in patients who spend less than 60% of time in therapeutic range (OR 21.71, 95% CI: 4.35–108, $P < 0.001$). In addition, the authors found that use of aspirin instead of an OAC (OR 24.74, 95% CI: 1.27–482.12, $P = 0.034$) and the presence of an average daily heart rate over 100 or under 60 (OR 6.04, 95% CI: 1.09–33.29, $P = 0.039$) were independent risk factors for dementia (Petroni et al. 2020).

These findings were confirmed by meta-analyses. One meta-analysis, consisting of one randomized controlled trial and five observational studies found that patients with AF on OAC had reduced risk of developing dementia (RR 0.79, 95% CI: 0.67–0.93) and that the benefit was greatest in those with a high percentage of time spent in therapeutic range (Mongkhon et al. 2019). In another meta-analysis, patients with AF on OAC were 29% less likely to develop dementia (HR 0.71, 95% CI: 0.69–0.74, $P < 0.00001$) (Cheng et al. 2018).

Patient age at the time of initiating anticoagulation may also be an important factor. In one RCT of patients aged 75 and over with AF, warfarin did not show any

significant benefit in reducing dementia compared to aspirin, although the study was limited by the follow-up period of 33 months (Mavaddat et al. 2014).

DOACs and Dementia

As previously mentioned, DOACs are superior or at least noninferior in reducing the risk of stroke compared to warfarin, and all DOACs are also associated with a reduced risk of bleeding. This has been shown in landmark trials of DOACs in patients with non-valvular AF (Ruff et al. 2014). Given the proposed mechanisms for dementia in patients with AF, it is possible that DOACs may be superior to warfarin in preventing dementia. Figure 11.2 depicts the spectrum of cerebral injury which may be reduced by DOAC therapy (Jacobs et al. 2015b).

The current data comparing DOACs to warfarin has been conflicting. In a retrospective analysis of data from a Swedish registry, there appeared to be a lower risk of dementia with DOAC (HR 0.48, 95% CI: 0.40–0.58) than with warfarin (HR 0.62, 95% CI: 0.60–0.64) when compared to no treatment. However, a direct

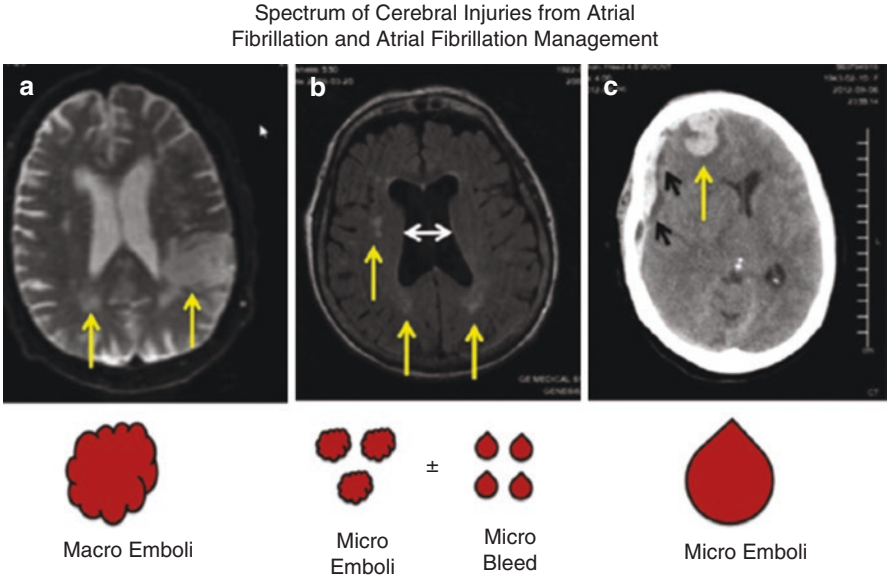

Fig. 11.2 Three separate cranial images with the mechanisms that impact cognition that may be reduced with direct acting oral anticoagulants: (**a**) diffusion-weighted axial magnetic resonance images showing large ischemic injury in the left posterior parietal lobe. Multiple emboli are also seen; (**b**) axial magnetic resonance image in which the ventricles and cortical sulci demonstrate generalized atrophy and resultant enlargement in cerebral spinal fluid spaces as well as white matter disease; (**c**) non-contrast computed tomographic scan showing a subdural hematoma as well as intraparenchymal hemorrhage. Used with permission from Jacobs et al. (2015b). **Jacobs V, Cutler MJ, Day JD, Bunch TJ. Atrial fibrillation and dementia. Trends in Cardiovascular Medicine. 2015;25(1):44–51**

comparison between DOAC and warfarin showed no difference in dementia risk (HR 0.97, 95% CI: 0.67–1.40) (Friberg and Rosenqvist 2018). In another retrospective study, from a UK registry, there was no significant difference in dementia risk for DOACs compared to warfarin (HR 0.89, 95% CI: 0.70–1.14, $P = 0.373$) (Mongkhon et al. 2020). A retrospective study which looked at 39,160 patients on an OAC (with 7.5% using a DOAC) compared patients using a propensity score matching procedure which generated two cohorts with 2528 patients each. Patients on a DOAC had lower incidence of the composite endpoint when compared to warfarin (0.42, CI: 0.19–0.93 compared to 0.74, CI: 0.55–1.00 per 100 years at risk) (Friberg et al. 2019). An observational study of 5254 patients on OAC, over 90% of which had AF, showed that dementia was more likely to occur in those taking warfarin (0.7–0.3%, $P = 0.03$) compared to DOACs with no difference when individual DOACs were compared to each other (Jacobs et al. 2016). Another observational study comparing individual DOACs to warfarin showed that patients on DOACs were less likely to develop dementia, specifically with dabigatran (HR 0.85, 95% CI: 0.71–1.01), rivaroxaban (HR 0.85, 95% CI: 0.76–0.94), and apixaban (HR 0.80, 95% CI: 0.65–0.97). There were no observed differences in dementia rates when comparing DOAC agents to each other (Chen et al. 2018). In a meta-analysis of eight studies that included 471,057 patients with AF, those on DOACs were less likely to develop dementia compared to those on warfarin (HR 0.51, 95% CI: 0.37–0.71, $P < 0.00001$) (Cheng et al. 2018).

Future Directions

There are several pending RCTs which aim to evaluate the efficacy of a DOAC when compared to warfarin for dementia prevention in patients with AF. The Cognitive Decline and Dementia in Atrial Fibrillation Patients (CAF) trial (NCT03061006) is an ongoing clinical trial designed to evaluate whether patients on dabigatran will be less likely to develop dementia when compared to patients on dose-adjusted warfarin (target INR 2.0–3.0). The trial will also examine the effects in serial cognition scores. The study population includes patients with non-valvular AF and a CHADS2 or CHADSVASC score of 2 or more, who were being initiated on OAC. Those with a history of moderate to severe cognitive impairment were excluded (Bunch et al. 2019). Several biomarkers of cerebral neurologic injury have been found to be elevated in patients with AF. These include circulating Tau, GDF15, and GFAP, and these will also be evaluated in the CAF trial to look for correlation with cognition (Galenko et al. 2019). The Anticoagulants and Cognition (ACCOG) trial (NCT04073316) is a randomized controlled trial which aims to compare cognitive performance in patients aged 70 years and older with non-valvular AF, and without baseline dementia, randomized to receive either rivaroxaban or warfarin. The primary outcome will be change in global cognitive performance at 6 months to 1 year. The Trial of Apixaban vs. Warfarin in Reducing Rate of Cognitive Decline, Silent Cerebral Infarcts and Cerebral Microbleeds in Patients with Atrial Fibrillation (ARISTA) (NCT03839355) is a randomized controlled trial

which aims to compare apixaban and warfarin in patients with non-valvular AF, aged 60 and older, and with CHADSVAS 2 and above. The primary outcomes include a standardized neurocognitive function score as well as the incidence of silent cerebral infarcts and microbleed detected by MRI. The Cognitive Impairment Related to Atrial Fibrillation Prevention trial (GIRAF) (NCT01994265) will compare warfarin to dabigatran in patients aged 70 and older with non-valvular AF and CHADSVAS 1 or more in reducing risk of cognitive decline. The Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in AF (BRAIN-AF) (NCT02387229) is an upcoming randomized controlled trial that will enroll 3250 participants aged 30–62 with non-valvular AF and low risk of stroke (CHADS 0). Participants will be randomized to rivaroxaban, when compared to standard of care, with neurocognitive decline as part of a composite primary endpoint, which includes stroke and transient ischemic attack, as well as a secondary endpoint (Rivard et al. 2019).

Conclusions

AF is an independent predictor of dementia in populations with or without a history of stroke. AF is associated with vascular dementia but also Alzheimer's dementia and senile dementia. DOACs may lead to a lower risk of dementia by decreasing the risk of both thromboembolism and microbleeds.

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Non-vitamin K Antagonists and Cardiac Implantable Electronic Devices

12

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Introduction

Cardiac implantable electrophysiological device (CIED) surgeries, which include pacemaker (PM) and implantable cardioverter defibrillator (ICD) implantation, are commonly performed worldwide with approximately 1.5 million procedures per year (Mond and Proclemer 2011). Of patients who undergo such procedures, up to 35% are receiving long-term anticoagulation at the time of implantation (AlTurki et al. 2016). Patients receiving oral anticoagulation require careful perioperative management to avoid the potential significant adverse events of pocket hematoma and pocket infection (Bernard et al. 2012). In addition, the widespread use of CIEDs has led to the recognition of subclinical atrial fibrillation (SCAF); this has been found in a considerable proportion of patients with CIEDs (Healey et al. 2012). Understanding the prevalence of SCAF, associated risk of stroke, and efficacy and safety of oral anticoagulation is imperative in the management of SCAF (AlTurki et al. 2019). The main decision point is whether to start anticoagulation and at what burden of SCAF or in which patient subgroups. In this chapter, we will review the strategies and evidence for the perioperative management of NOACs in patients undergoing CIED surgery. In addition, the management of device detected SCAF will also be reviewed.

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Pocket Hematomas

Device pocket hematomas are an important major adverse event complicating CIED surgery. The incidence of pocket hematomas ranges from 1.2% when no anticoagulant is present, 2.3–6.5% on continued-warfarin therapy, and 7–16% during heparin bridging (Birnie et al. 2013; Sant'anna et al. 2015). Pocket hematomas may lead to significant morbidity, prolong hospitalization, and may require reoperation for evacuation (Birnie et al. 2013; Sridhar et al. 2015; Sticherling et al. 2015). Most importantly, pocket hematomas are associated with a significantly increased risk of device infection (Essebag et al. 2016). A clinically significant hematoma (CSH), which has been defined as a hematoma that required reoperation or resulted in prolongation of hospitalization or required interruption of oral anticoagulation, was associated with an >sevenfold increase in the subsequent risk of serious device infection in BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) (Essebag et al. 2016). Therefore, it is crucial to prevent the occurrence of pocket hematomas, and perioperative antithrombotic management is an integral component of this management.

Vitamin K Antagonists

Vitamin K antagonists (VKAs) were the main therapeutic option for oral anticoagulation prior to the introduction of NOACs. Krahn and colleagues showed that the periprocedural management of VKA anticoagulation varied among electrophysiologists in Canada (Krahn et al. 2009). Most clinicians chose to withhold oral anticoagulation without initiating heparin bridging in those at low risk of thromboembolism and to use a form of heparin bridging in those at medium to high risk of thromboembolism. Observational studies suggested that continued anticoagulation with warfarin was associated with 70% lower odds of a pocket hematoma with a similar risk of thromboembolic events (Sant'anna et al. 2015). The BRUISE CONTROL trial was conducted to resolve the debate whether continued VKA was superior to heparin bridging with regard to CSH in those at moderate or greater risk of thromboembolism (Birnie et al. 2013). This trial randomized 681 patients, with moderate to severe risk of thromboembolism (estimated annual risk of 5% or greater) to either continued-warfarin treatment or bridging therapy with heparin. CSH occurred in 3.5% in the continued-warfarin group, compared to 16.0% in the heparin-bridging group (relative risk, 0.19; 95% confidence interval, 0.10–0.36; $P < 0.001$). Thromboembolic complications were rare and similar in both groups (Healey et al. 2012). Furthermore, continued-warfarin therapy was found to be cost effective compared with bridging-heparin therapy in patients at high risk of thromboembolic events undergoing device surgery, with a cost savings of approximately $1800 per patient treated (Coyle et al. 2015). The BRUISE CONTROL trial led to a change in guideline recommendations and clinical practice (Birnie et al. 2014).

Non-vitamin K Oral Antagonists

The introduction of NOACs, starting in 2009, has transformed the landscape of oral anticoagulation including its perioperative management. The perioperative management of NOACs involves one of the two following approaches: (1) appropriate timing of the cessation and reinitiation of the drug based on the predicted clearance, mainly taking into account patients' renal function; (2) continued anticoagulation based on low patient and surgical risk of bleeding (AlTurki et al. 2016). However, given their relatively recent use, there has been limited data on outcomes in patients undergoing CIED surgery who are receiving NOACs. Prior to the publication of relevant studies on this matter, in a Canadian survey involving 22 centers, which performed approximately 14,971 device implants of which around 10% involved NOACs at the time, NOAC were discontinued in anticipation of device implantation in 82% of centers with 73% of these centers not utilizing heparin bridging (Nascimento et al. 2014). In the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry, among 9129 AF patients, 416 (5%) underwent CIED surgery during a median follow-up of 30 months. Oral anticoagulation therapy was commonly interrupted for CIED surgery in 64% of warfarin patients and 65% of NOAC patients. A substantial proportion of patients, 18% on interrupted warfarin and 10% on interrupted NOAC, received intravenous bridging anticoagulation. Major bleeding or stroke was a very rare occurrence in either group of this analysis (Black-Maier et al. 2017).

The best observational data was derived from secondary analyses of the large landmark randomized trials that compared NOACs to VKAs in patients with non-valvular AF. A sub-analysis of the RELY trial, which compared dabigatran to warfarin, that included 611 patients who underwent CIED surgery offers was the first to be reported (Essebag et al. 2017). Warfarin was interrupted for a median of 144 h with 18.4% of patients undergoing heparin bridging. On the other hand, the duration of dabigatran interruption was a median of 96 h. Pocket hematomas occurred in 2.2% of patients on dabigatran and 4.0% patients on warfarin ($P = 0.218$). Pocket hematoma incidence was lower in those who received dabigatran compared to those who received warfarin with heparin bridging but not when compared with warfarin without bridging. Thromboembolic events were similar between the two groups (Essebag et al. 2017). In data from 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), during a median follow-up of 2.2 years, 453 patients underwent CIED surgery (Leef et al. 2017). Most patients had the study drug interrupted for the procedure without intravenous bridging anticoagulation. The rate of adverse events was low in both groups: 11 patients (4.6%) in the rivaroxaban group experienced bleeding complications compared with 15 (7.1%) in the warfarin group, and thromboembolic complications occurred in 3 patients (1.3%) in the rivaroxaban group and 1 (0.5%) in the warfarin group (Leef et al. 2017). In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AFTIMI 48) trial that compared edoxaban and warfarin, CIED surgeries were performed in

943 patients who were receiving study drug; in the majority (n = 728, 74%), study drug was interrupted >3 days (median 5 days, interquartile range 0–11 days) (Steffel et al. 2019). Again, the event rates were very low: six strokes/systemic embolic events (three each in the lower dose edoxaban arm and warfarin arm) and one major bleeding event (in the lower dose edoxaban arm) occurred; two of the six strokes and the major bleeding event occurred in patients in whom procedures performed with <3 days periprocedural interruption of study drug (Steffel et al. 2019).

The BRUISE CONTROL 2 trial randomized 662 patients with AF and risk of thromboembolism (CHA2DS2-VASc score ≥ 2), to continued vs. interrupted NOAC (Birnie et al. 2018). For the interrupted NOAC approach, rivaroxaban or apixaban was discontinued after the last dose taken 2 days before surgery, while dabigatran was discontinued drug based on a time interval dependent on glomerular filtration rate. All three drugs were resumed at the next regular dose timing ≥24 h after surgery. The median time between pre- and postoperative NOAC doses was 12 h in the continued NOAC arm compared to 72 h in the interrupted NOAC arm. The trial was terminated early due to futility. CSH occurred in 2.1% of patients in the continued NOAC arm and 2.1% of patients in the interrupted NOAC arm (P = 0.97) (Birnie et al. 2018); the incidence of thromboembolic events was also very low with one stroke occurring in each arm. Therefore, either approach is reasonable with the choice dependent on the clinical scenario. This was subsequently confirmed in a systematic review of two trials and three observational studies that showed similar findings: continuing DOAC for device implantation compared to interrupting DOAC resulted in no significant difference in CSH (2.1% vs. 1.8%; RR 1.15; 95%CI: 0.44–3.05) or thromboembolism (0.03% vs. 0.03%; RR 1.02; 95%CI: 0.06–16.21) (Mendoza et al. 2020).

NOAC Interruption for CIED Surgery

The general principle is that CIED surgery is considered a low bleeding risk procedure (AlTurki et al. 2016). Due to the predictable waning anticoagulant effects of NOACs, bridging anticoagulation is not required and has been shown to increase the risk of bleeding in all surgeries (Douketis et al. 2015) as well as CIED surgery specifically (Birnie et al. 2013). Therefore, NOAC interruption involves timing the cessation and reinitiation of the drug based on the predicted clearance, which takes renal function into account (AlTurki et al. 2016; Spinler and Shafir 2012). In patients with normal renal function undergoing a low bleeding risk procedure, the usual practice is to discontinue the NOAC 24 h prior to the procedure and to reinstate the drug 24 h after, provided no significant bleeding has occurred (Sticherling et al. 2015). Figure 12.1 shows the timeframe for NOAC interruption in those undergoing CIED surgery. The specific information for each specific NOAC is provided below (AlTurki et al. 2016; Sticherling et al. 2015; Birnie et al. 2014):

1. Dabigatran
   (a) Twice-daily drug with a half-life of 14 h.

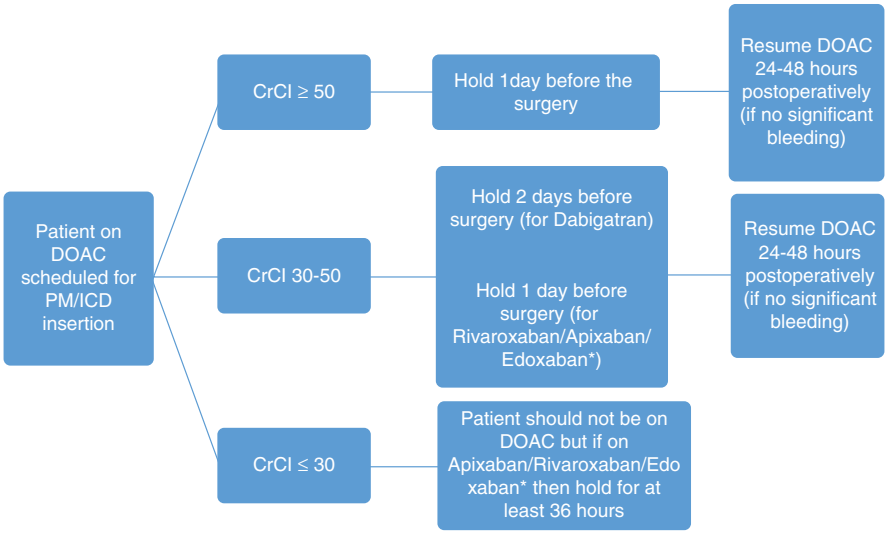

Fig. 12.1 Strategy for NOAC interruption in patients undergoing CIED surgery. **AlTurki A, Proietti R, Birnie DH, et al. Management of antithrombotic therapy during cardiac implantable device surgery. J Arrhythm. 2016; 32:163–169**

   (b) When CrCl is >50 mL/min, hold the day before surgery, i.e., missing 2 doses before the day of surgery (12–25% residual anticoagulant effect at the time of surgery).
   (c) When CrCl is between 30 and 50 mL/min (half-life of 15–18 h), hold 2 days before surgery, i.e., 4 missed doses to give the same residual anticoagulant effect (12–25%).
   (d) Should not be used in patients with a CrCl of ˂30 mL/min.
   (e) Resume 24 h postoperatively.
2. Rivaroxaban
   (a) Once-daily drug with a half-life of 9 h.
   (b) Hold the day before surgery, i.e., missing one dose before the day of surgery (12–25% residual anticoagulant effect at the time of surgery).
   (c) Should not be used in patients with a CrCl less than 30 mL/min.
   (d) If used in patients with a CrCl between 15 and 30 mL/min, at least 36 h of drug interruption is advised.
   (e) Use of the drug should be resumed 24–48 h postoperatively.
3. Apixaban
   (a) Twice-daily drug with half-life of 9 h.
   (b) Hold the day before surgery and resume 24–48 h postoperatively, if renal function is >30 mL/min.
   (c) If apixaban is used in patients with a CrCl between 15 and 30 mL/min, then at least 36 h of drug interruption is advised.
4. Edoxaban
   (a) Once-daily drug with a half-life of 10–14 h.

(b) Hold the day before surgery and resume 24–48 h postoperatively, if renal function is >30 mL/min (Ferretto et al. 2020; Wong et al. 2018).
(c) Should not be used in patients with a CrCl ˂ 30 mL/min.

Concomitant Antiplatelet Therapy

With a substantial proportion of patients receiving antiplatelet therapy in addition to anticoagulation, an understanding of the impact of combined therapy on hematoma development after CIED surgery is important. In a pooled analysis using patient level data from the BRUISE CONTROL trials, antiplatelet use was associated with CSH in 9.8% versus 4.3% of patients ($P < 0.001$) who did not receive concomitant antiplatelet therapy. Furthermore, antiplatelet therapy was a strong independent predictor of CSH after multivariable adjustment (odds ratio, 1.965; 95% CI: 1.202–3.213; $P = 0.0071$) (Essebag et al. 2019a). Unscheduled outpatient visits for wound assessment (15.4% versus 7.5%, $P < 0.001$) also increased if the patient was on an antiplatelet at the time of device surgery. Interestingly, applying current guidelines regarding combination antithrombotic therapy, concomitant antiplatelet therapy is potentially inappropriate or interruptible, and this should be assessed prior to intervention. Of the 681 patients enrolled in the BRUISE CONTROL trial, 280 (41%) received concomitant antiplatelet therapy during CIED surgery. Of the 280 patients receiving antiplatelet therapy, 97 (34.6%) had no indication for concomitant antiplatelet therapy according to current guidelines, and an additional 146 (52.1%) were on antiplatelet therapy that could potentially have been interrupted around CIED surgery (Essebag et al. 2019b).

Predictors of Pocket Hematoma

In patients receiving NOACs, it is important to assess for risk factors that increase the risk of CSH. The presence of these factors should lead to consideration of interruption of NOAC therapy or a greater duration of interruption. Bridging anticoagulation and concomitant antiplatelet therapy have already been discussed. Device type and left ventricular ejection fraction <30% have been shown to be strong predictors of pocket hematoma in single-center studies (Ferretto et al. 2020; Notaristefano et al. 2020). Implantable cardioverter defibrillator implantation carries an increased risk of CSH. In an analysis of the SIMPLE trial which included 2500 patients who received a defibrillator, CSH occurred in 2.2% of patients, of whom 10.7% developed a device-related infection (Masiero et al. 2016). Independent predictors of wound hematoma on multivariable analysis included subpectoral location of the device, older age, previous stroke, and an upgrade from a previous pacemaker.

Anticoagulation of Patients with Subclinical Atrial Fibrillation

Subclinical atrial fibrillation (SCAF) refers to the detection of AF by CIEDs in asymptomatic patients not known to have AF (AlTurki et al. 2019). The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) was a landmark study designed to assess the association between SCAF and stroke and systemic embolism. The trial enrolled 2580 patients who had received a CIED for sinus or atrioventricular nodal dysfunction in the preceding 2 months, had a risk factor for stroke, and were not known to have any history of AF or atrial flutter or require oral anticoagulation for any indication (Healey et al. 2012). After 3 months of monitoring, patients were divided into two groups based on the presence of SCAF and followed for a mean of 30 months. SCAF was associated with a fivefold increased risk of clinical AF (HR 5.56; 95% CI: 3.78–8.17; $P < 0.001$) and a 2.5-fold increased risk of stroke or systemic embolism (HR 2.49; 95% CI: 1.28–4.85; $P = 0.007$). Interestingly, the stroke risk was not as high as that seen with clinical AF, which is fivefold greater than the general population, but is still substantial at two to two-and-a-half times the risk (AlTurki et al. 2019). Two questions remained after the results of ASSERT: which patients with SCAF are at the highest risk of stroke and are anticoagulation beneficial in this population.

Burden of SCAF

The burden of SCAF (i.e., longer and more frequent episodes) is thought to be an important predictor of stroke. Proietti and colleagues assessed this relationship in a systematic review and meta-analysis (Proietti et al. 2016). The analysis was limited by a small number of studies that reported such data and the varying cutoff points used in the studies. The authors concluded that a direct correlation between burden of asymptomatic AF and HR for stroke cannot be confirmed (Proietti et al. 2016). Van Gelder et al. performed an important sub-analysis of the ASSERT study and found that SCAF episodes lasting 24 h and longer were associated with an increased risk of ischemic stroke or systemic embolism (Van Gelder et al. 2017). Patients were divided into one of the following groups on the basis of the duration of the single longest episode of SCAF: >6 min to 6 h (19%), >6 to 24 h (7%), and >24 h (11%), while those who had no SCAF or SCAF for <6 min were excluded from this analysis. There was a threefold increase in the associated risk of stroke (adjusted HR 3.24, 95% CI: 1.51–6.95, $P = 0.003$) in those with episodes of 24 h or more with an absolute stroke risk of around 5% which approximates the risk of stroke seen in clinical AF (AlTurki et al. 2019). In contrast, in those with SCAF between 6 min and 24 h, the risk of stroke was not significantly different from patients without SCAF (Van Gelder et al. 2017). Similar results were reported in another registry; those with SCAF episodes of 24 h or longer had a significantly increased risk of stroke (OR 3.1, 95% CI: 1.1–10.5, $P = 0.044$) (Capucci et al. 2005). While these studies clearly identified a high-risk group, it remains unclear whether those with

episodes lasting between 6 min and 24 h have a significantly increased risk of stroke and in particular those with episodes longer than 6 h (AlTurki et al. 2019).

Progression of SCAF

Another predictor of stroke may be the presence of progression to longer episodes of SCAF. De novo AF with a SCAF burden of ≥5 min was detected in 2244 patients (34%) during a follow-up period of 2.4 ± 1.7 years in a large multicenter registry. Among those with SCAF, 49.8% transitioned to a higher SCAF burden threshold during follow-up, including 24% of patients who transitioned from a lower threshold to a daily SCAF burden of ≥23 h (Boriani et al. 2018). Male gender and a CHADS2 score of 2 or greater predicted the transition to a greater SCAF burden on multivariate analysis (Boriani et al. 2018). In another sub-study of ASSERT, patients in whom the longest SCAF episode was >6 min but <24 h during the first year were included (Wong et al. 2018). The authors assessed the association between progression to SCAF >24 h or the development of clinical AF and heart failure hospitalizations. During a mean follow-up of 2 years, 15.7% of patients progressed and the rate of heart failure hospitalization among patients with SCAF progression was 8.9% per year compared with 2.5% per year for those without progression (Wong et al. 2018). This is consistent with the relationship seen between clinical AF and heart failure in which a vicious cycle can develop (Glotzer 2018); the development of heart failure is another risk factor for stroke.

Predictors of SCAF

Through several studies, predictors of SCAF have been identified. A high proportion of right ventricular pacing predicted SCAF in those with sinus node dysfunction and hypertension predicted SCAF in those with pacemakers for atrioventricular block (Cheung et al. 2006). In ASSERT, sinus node dysfunction and a lower resting heart rate predicted SCAF (Healey et al. 2012). In another study, older age and diastolic blood pressure predicted SCAF (Glotzer et al. 2009). In addition, prior HF, sinus node disease, and increased left atrial volume index independently predicted SCAF (Kim et al. 2016). In a meta-analysis of ten studies, only heart failure reliably predicted SCAF (Belkin et al. 2018). In patients older than 65 years of age with at least two stroke risk factors who received an implantable loop recorder, independent predictors of AF included increased age and increased left atrial size (Healey et al. 2017).

Anticoagulation for SCAF

The treatment of SCAF presents several challenges due to the aforementioned issues, and there are various factors to keep in mind when considering the treatment of SCAF. In clinical AF, oral anticoagulation is recommended regardless of AF subtype and depending on the presence of clinical factors (age, hypertension, diabetes mellitus, heart failure, and stroke) which have consistently been shown to increase stroke risk (Andrade et al. 2018). Given that oral anticoagulation has been shown to significantly decrease stroke risk in clinical AF, this risk reduction should theoretically translate to SCAF. However, in SCAF, the increased risk is of a lower magnitude (2–2.5 times) compared to clinical AF (5 times), and this may reduce the net clinical benefit observed with anticoagulation in SCAF. Patients with SCAF >24 h have an absolute risk profile that is similar to that observed in clinical AF and are the subgroup of SCAF most likely to derive benefit from oral anticoagulation (AlTurki et al. 2019). This is consistent with current guidelines, and NOACs are used preferentially to warfarin similar to the treatment of clinical AF. An algorithm for the management of SCAF is shown in Fig. 12.2. Current guidelines suggest that patients with SCAF greater than 24 h as well as at least one risk factor for stroke should receive oral anticoagulation. In addition, the guidelines also suggest that patients with shorter durations of SCAF but who are at high risk, such as those with cryptogenic stroke, ought to be considered for oral anticoagulation (AlTurki et al. 2019; Macle et al. 2016). Due to the absence of well-defined cutoffs of AF burden in which oral anticoagulation is indicated, a substantial variation in physician attitudes and practice patterns exists (Noseworthy et al. 2019). This is best illustrated in a cohort study that included 10,212 patients who received CIEDs in 2011–2014; 45%, 39%, 32%, and 24% of patients had SCAF lasting ≥6 min, >1 h, >6 h, and >24 h, respectively (Perino et al. 2019). The proportion of patients who were prescribed oral anticoagulation within 90 days of SCAF was relatively low with small increments as the AF burden increased (≥6 min, 13%; >1 h, 16%; >6 h, 21%; >24 h, 27%) (Perino et al. 2019). Clearly, more data is needed to provide clinicians guidance on how to manage SCAF of intermediate duration. Two ongoing trials will hopefully shed some much-needed light.

Ongoing Trials

ARTESIA is a prospective, multicenter, double-blind, randomized controlled trial, enrolling patients with SCAF detected by a CIED who have additional risk factors for stroke (Lopes et al. 2017). Inclusion criteria include: (1) least one episode of SCAF ≥6 min in duration; (2) 55 years of age or older; and (3) have risk factors for stroke. Exclusion criteria are: (1) documented AF on a 12-lead electrocardiogram and (2) an indication for oral anticoagulant therapy. Participants will be randomized to apixaban or aspirin 81 mg daily with appropriate placebo pills accordingly. The primary outcome is the composite of stroke, transient ischemic attack with imaging confirmation, and systemic embolism. The trial is aiming to recruit 4000 patients

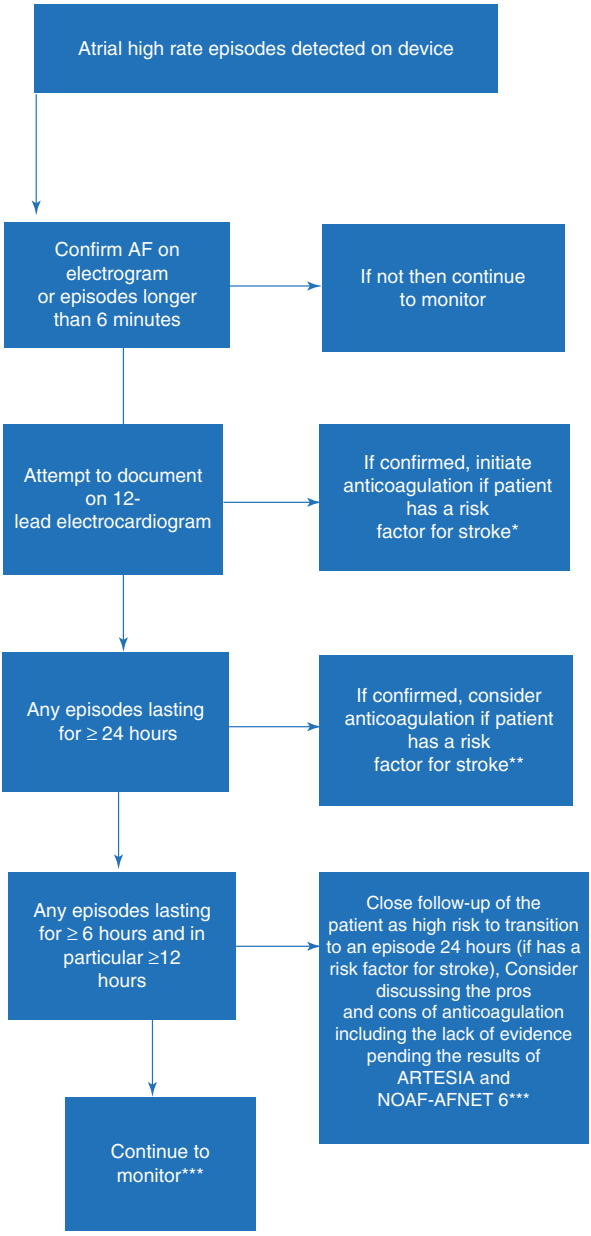

Fig. 12.2 Management algorithm for subclinical atrial fibrillation. **AlTurki A, Marafi M, Russo V, et al. Subclinical Atrial Fibrillation and Risk of Stroke: Past, Present and Future. Medicina (Kaunas). 2019;55**

from 230 international clinical sites and is expected to have 36 months of follow-up until 248 adjudicated primary outcome events have occurred (Lopes et al. 2017).

NOAH-AFNET 6 is an investigator-driven, prospective, randomized trial (Kirchhof et al. 2017). The trial enrolled patients with SCAF and one or more risk factors for stroke. Inclusion criteria include: (1) SCAF; (2) age ≥65 years; and (3)

at least one other stroke risk factor. Exclusion criteria include: (1) documented AF or (2) an indication for oral anticoagulation. Broad inclusion/exclusion criteria used to replicate clinical practice. NOAH-AFNET 6 will randomize 3400 patients to edoxaban or no anticoagulation in a superiority trial; aspirin may be used depending on the clinical indication. The primary efficacy outcome is stroke or cardiovascular death, and the primary safety outcome will be major bleeding and all patients will have follow-up until the intended 222 target primary outcomes are reached. Patients who develop AF will be censored and offered open-label anticoagulation instead (Kirchhof et al. 2017).

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Direct Oral Anticoagulants and Atrial Fibrillation Ablation

13

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Introduction

Catheter ablation (CA) for atrial fibrillation (AF) is increasingly used as a strategy for rhythm control due to expanding indications (AlTurki et al. 2020). Improvements in operator experience, techniques, and equipment have resulted in greater efficacy and safety (Calkins et al. 2017a). The incidence of major adverse events due to CA is low (Samuel et al. 2017); however, thromboembolism remains a major concern with targeted strategies to mitigate that risk. The periprocedural management of anticoagulation is of great import as it impacts the incidence of major bleeding and has a central role in preventing thromboembolism.

In the aftermath of CA, the decision to continue anticoagulation has important implications in the short and longer term. Patients often desire an end to oral anticoagulation. Data from the AFFIRM trial suggested that discontinuing anticoagulation in those receiving rhythm control with an antiarrhythmic drug is ill-advised with a notable increase in the risk of thromboembolism (Sherman et al. 2005). CA is much more efficacious at establishing rhythm control and lowering the burden of AF than AADs (Calkins et al. 2017a; AlTurki et al. 2019a). A lower burden of AF has been suggested to decrease thromboembolism risk (AlTurki et al. 2019b).

In this chapter, we will review the evidence for the periprocedural management of anticoagulation in patients undergoing CA as well as the short and long-term postprocedural management. We will focus on the role of direct acting oral anticoagulants in these contexts.

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Risk of Thromboembolism with AF Ablation

AF ablation increases the risk of thromboembolism during and in the aftermath of the procedure (Page et al. 2014); the mechanisms for this increased risk are through all the components of Virchow's triad. Firstly, endothelial injury caused by the introductions of sheaths and catheters into the left atrium and ablation energy application onto the endothelial surface. In addition, the sheaths and catheters may dislodge any preformed thrombus and can serve as a nidus for thrombus formation. Secondly, hypercoagulability induced by the interaction of ablation hardware with blood as well as thrombogenic debris, which is generated at the site of ablation; and finally, blood flow stasis post conversion of AF into sinus rhythm. This is due to left atrial stunning as well as left atrial dilatation. The fundamental goal of anticoagulation is to minimize the risk of thromboembolism without excessively increasing the risk of clinically significant bleeding, which may involve vascular access complications, the most common complication, and pericardial effusion and tamponade, the most serious complication.

Pre-ablation Anticoagulation Strategies

Many of those who undergo an AF ablation have an elevated risk of thromboembolism, best assessed by using the CHADSVASc score. The presence of even one risk factor, excluding female sex and vascular disease, is enough to indicate chronic oral anticoagulation. Given the risk of thromboembolism associated with the procedure, especially if the patient is in AF at the time, most electrophysiologists would anticoagulate the patient for 3 weeks prior to the scheduled ablation. There are two broad strategies for managing oral anticoagulation in the days prior to the procedure: uninterrupted oral anticoagulation and interrupted oral anticoagulation. In an interrupted strategy, patients have their oral anticoagulant stopped before the CA, with or without bridging with another anticoagulant; while in an uninterrupted strategy, there is continuation of oral anticoagulation throughout the periprocedural period.

Warfarin Management Periprocedurally

Warfarin had been the mainstay for stroke prevention AF. Initially, the standard practice was to interrupt warfarin 5 days prior to the procedure and then bridge patients with low molecular weight heparin. The rationale for this approach was the notion that an uninterrupted anticoagulation strategy would lead to an increased risk of major bleeding especially pericardial tamponade. However, in a prospective multicenter, Di Biase et al. showed that uninterrupted anticoagulation with warfarin periprocedurally was associated with a lower risk of periprocedural stroke (0% vs. 0.9%; $P < 0.05$) (Biase et al. 2010). In addition, there was no observed increase in the risk of bleeding complications. This study was seminal to the concept that an

uninterrupted anticoagulation strategy may be the optimal approach. The results were subsequently corroborated in a large meta-analysis, which included nine studies and 27,402 patients (Santangeli et al. 2012). Uninterrupted warfarin was associated with a decrease of thromboembolic complications (OR, 0.10; 95% CI: 0.05–0.23; $P < 0.001$) and minor bleeding complications (OR, 0.38; 95% CI: 0.21–0.71; $P = 0.002$) compared with interrupted warfarin. Importantly, uninterrupted warfarin was not associated with an increase in the risk of major bleeding (OR, 0.67; 95% CI: 0.31–1.43; $P = 0.30$), including cardiac tamponade (OR, 0.69; 95% CI: 0.19–2.47; $P = 0.57$). A randomized controlled trial, COMPARE, was conducted to more definitively identify the optimal anticoagulation strategy (Biase et al. 2014). The study enrolled 1584 patients: 790 assigned to discontinue warfarin and 794 assigned to continuous warfarin. The primary endpoint of the study was incidence of thromboembolic events in the 48 h after ablation. There were 29 strokes (3.7%) in those who discontinued warfarin compared to only two strokes (0.3%) in those receiving continuous warfarin ($P < 0.001$). Warfarin discontinuation was an important predictor of periprocedural thromboembolism (odds ratio, 13; 95% confidence interval: 3.1–55.6; $P < 0.001$). The incidence of major bleeding did not differ between the two groups ($P = 0.31$) but there was a higher incidence of minor bleeding in the interrupted warfarin group (22.0% vs. 4.1%, $P < 0.001$). On the basis of these results, the current standard of care has become an uninterrupted warfarin strategy.

DOAC Management Periprocedurally

The introduction of DOACs in 2010 has changed the anticoagulant management of patients with AF. Due to a superior safety profile and possible better efficacy compared to warfarin, DOACs have become first-line therapy for anticoagulation of AF and are used in preference to warfarin. The increased use of DOACs has led to a need to identify the optimal anticoagulation strategy in patients undergoing AF ablation.

Rivaroxaban is an oral factor Xa inhibitor that was shown to be noninferior to warfarin in the ROCKET-AF trial (Patel et al. 2011). Piccini and colleagues performed a post hoc analysis of the ROCKET-AF trial that examined patients who underwent AF ablation and found that the incidences of stroke or systemic embolism (1.88% vs. 1.86%) and death (1.88% vs. 3.73%) were similar in the rivaroxaban-treated and warfarin-treated groups (Piccini et al. 2013). In a cohort study, 272 patients receiving uninterrupted periprocedural rivaroxaban before an AF catheter ablation procedure were matched by age, sex, and type of rhythm disorder with 272 patients who received uninterrupted phenprocoumon, a vitamin K antagonist (Dillier et al. 2014). No thromboembolic events occurred in either group and there were no deaths. The incidence of major bleeding was low and similar in both groups with one tamponade in the rivaroxaban group and one hematoma requiring transfusion in the phenprocoumon group (Dillier et al. 2014). Similar results were found in a multicenter, observational, prospective study of a registry of patients undergoing

AF ablation in which patients receiving uninterrupted rivaroxaban were matched by age, sex, and AF type to those receiving uninterrupted warfarin (Lakkireddy et al. 2014). No differences were observed in the incidence of major bleeding (1.6% vs. 1.9%, $P = 0.772$), minor bleeding (5.0% vs. 5.9%, $P = 0.602$), or thromboembolic complications (0.3% vs. 0.3%, $P = 1.0$) between the rivaroxaban and warfarin groups, respectively, in the first 30 days (Lakkireddy et al. 2014). In a meta-analysis of seven observational studies involving 3575 patients, thromboembolic events occurred in 0.4% and 0.4% (RR 0.71, 95% CI 0.26–1.96; $P = 0.51$) and major bleeding events occurred in 1.2% and 2.3% (RR 0.49, 95% CI 0.24–1.02; $P = 0.06$) of those receiving rivaroxaban and warfarin, respectively (Aryal et al. 2014). VENTURE-AF (active-controlled multicenter study with blind-adjudication designed to evaluate the safety of uninterrupted rivaroxaban and uninterrupted vitamin K antagonists in subjects undergoing catheter ablation for non-valvular atrial fibrillation) was randomized, open-label trial of patients with AF undergoing catheter ablation (Cappato et al. 2015). The incidences of major bleeding and thromboembolic events were similarly low in both treatment arms; no events in the rivaroxaban arm and one major bleeding as well as two thromboembolic events in the vitamin K arm (0.8%; one ischemic stroke and one vascular death). This highlights the safety of an uninterrupted oral anticoagulation strategy.

Dabigatran is a direct thrombin inhibitor and was the initial DOAC approved for stroke prevention in AF. In an analysis of data from a prospectively collected registry that included 999 patients who received either dabigatran that was minimally interrupted or uninterrupted warfarin, there was no difference in thromboembolic (0.3% vs. 0.2%; $P = 0.78$) or major bleeding (1.1% vs. 1.6%; $P = 0.48$) events in the two groups (Bassiouny et al. 2013). However, observational data also suggested an increased risk of bleeding with dabigatran compared to warfarin. In a prospective registry of 290 patients who received either uninterrupted dabigatran or uninterrupted warfarin, there was no difference in thromboembolic events (2.1% vs. 0%; $P = 0.25$). Those who received dabigatran had a significantly higher risk of major bleeding (6.0% vs. 1.0%; $P = 0.019$), and dabigatran use was an independent predictor of bleeding (Lakkireddy et al. 2012). Meta-analyses on the subject produced conflicting results. Abdulhak and colleagues, in an analysis of nine studies that included 3036 patients, found no difference in thromboembolic events (OR 2.15, 95% CI: 0.58–7.98; $P = 0.54$) or bleeding (Bin Abdulhak et al. 2013). In contrast, Sardar et al. in a meta-analysis of 18 studies that included 5513 patients found that the risk of stroke or transient ischemic attack (OR 5.54, 95% CI: 1.94–10.08), and all thromboembolic events (OR 2.81, 95% CI: 1.23–6.45) were higher in those who received dabigatran (Sardar et al. 2014). There was no difference in the risk of major bleeding between the two groups, and dabigatran use was associated with a lower risk of minor bleeding (OR 0.60, 95% CI: 0.41–0.87). These conflicting results and the need for more definitive data led to the Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy (RECIRCUIT) trial (Calkins et al. 2017b). This was a randomized, open-label trial with blinded adjudicated endpoints in which 635 patients who were undergoing AF catheter-based ablation

received either uninterrupted dabigatran or uninterrupted warfarin for 4–8 weeks prior to the procedure and 8 weeks after. The primary endpoint, which was the incidence of major bleeding events during and up to 8 weeks after ablation, was lower with dabigatran than with warfarin (1.6% vs. 6.9%; $P < 0.001$). In addition, dabigatran was associated with fewer periprocedural pericardial tamponades and groin hematomas than warfarin. Thromboembolic events were also assessed as a key secondary endpoint and had a very low incidence with only one event occurring in the warfarin group (Calkins et al. 2017b).

Apixaban is an oral factor Xa inhibitor and in patients with AF, apixaban was shown to be superior to warfarin with regard to stroke prevention, major bleeding, and all-cause mortality (Granger et al. 2011). In a prospective multicenter registry, Di Biase and colleagues assessed the feasibility of an interrupted apixaban strategy in patients undergoing AF ablation; these patients were matched for age, gender, and type of AF, for an equal number of patients undergoing AF ablation on uninterrupted warfarin (Di Biase et al. 2015). There were no differences in major complications (1% vs. 0.5%, $P =$ or total bleeding complications (4.5% vs. 3%, $P = 0.43$) between the two groups, and there were no symptomatic thromboembolic complications. Another matched cohort study by Kaess et al. and an observational study by Shah et al. showed similar results (Kaess et al. 2015; Shah et al. 2017). In a meta-analysis of six studies with 1691 patients comparing uninterrupted apixaban and uninterrupted warfarin, there was no difference in thromboembolic events (OR = 1.10, 95% CI: 0.24–5.16), major bleedings (OR = 1.56, 95% CI: 0.59–4.13), cardiac tamponade (OR 1.69, 95% CI: 0.52–5.54), minor bleedings (OR 0.96, 95% CI: 0.58–1.59), and the composite endpoint of death, thromboembolic events, and bleedings (OR 1.03, 95% CI: 0.65–1.64) between the two groups (Blandino et al. 2016). Randomized controlled trials were performed to ascertain whether uninterrupted apixaban is similar to uninterrupted warfarin, the standard of care as well as to compare uninterrupted to minimally interrupted apixaban. In an exploratory open-label randomized trial in Japan that randomized 200 patients, those who received uninterrupted apixaban required administration of more heparin to maintain an activated clotting time >300 s than those who received uninterrupted warfarin (apixaban, 14,000 ± 4000 units; warfarin, 9000 ± 3000 units) (Kuwahara et al. 2016). There was no difference in thromboembolic events including silent infarcts as well as major or minor bleeding between the two groups. In the Apixaban Evaluation of Interrupted Or Uninterrupted Anticoagulation for Ablation of Atrial Fibrillation (AEIOU) trial, 300 patients were randomized to uninterrupted versus minimally interrupted (holding one dose) periprocedural apixaban (Reynolds et al. 2018). Clinically significant bleeding did not significantly differ between the two groups, occurring in 11.3% of patients on uninterrupted apixaban and 9.7% patients on interrupted apixaban, and neither did major bleeding with incidence rates of 1.3% with uninterrupted apixaban and 2.1% with interrupted apixaban; there were no thromboembolic events. The Atrial Fibrillation catheter Ablation compared to VKA therapy (AXAFA—AFNET 5) trial was an investigator-initiated, randomized, blinded outcome assessment study comparing continuous apixaban therapy to continuous vitamin K antagonist therapy (Kirchhof et al. 2018). The primary outcome

of death, stroke, or major bleeding was observed in 6.9% patients randomized to apixaban, and in 7.3% randomized to VKA which met the margin for noninferiority. There was no significant difference in major bleeding (6.2% vs. 7.9%), tamponade (0.6% vs. 1.6%), quality of life, or cognitive function between the two groups (Kirchhof et al. 2018).

Edoxaban is also an oral factor Xa inhibitor and was shown to be noninferior to warfarin with respect to the prevention of stroke or systemic embolism and was associated with significantly lower rates of bleeding in patients with non-valvular AF (Giugliano et al. 2013). In an analysis from this trial of patients who underwent AF ablation while receiving edoxaban, with a greater than 3-day interruption of edoxaban in the majority of patients, treatment there associated was a low risk of ischemic (0%) and bleeding (1.3%) events during the first 30 days post ablation (Steffel et al. 2017). Data from small observational studies showed the feasibility of an uninterrupted edoxaban strategy compared to an uninterrupted vitamin K antagonist strategy (Kottmaier et al. 2018; Naito et al. 2020). In a prospective multicenter study in Japan that included 513 patients who received uninterrupted edoxaban for at least 4 weeks prior to AF ablation and at least three after the ablation, no thromboembolism and one major bleeding event (0.2%, cardiac tamponade) were observed (Takahashi et al. 2019). However, this study was limited by the lack of a comparative group. To investigate the efficacy and safety of uninterrupted edoxaban versus warfarin in 553 patients undergoing AF catheter-based ablation, the ELIMINATE-AF trial (a Prospective, Randomized, Open-Label, Blinded Endpoint Evaluation Parallel Group Study Comparing Edoxaban versus VKA in Subjects Undergoing Catheter Ablation of Non-valvular Atrial Fibrillation) was conducted (Hohnloser et al. 2019). There was no difference in major bleeding (2.5% vs. 1.5%), thromboembolic events (0.2% vs. 0%), or death (none) in those who received edoxaban or warfarin, respectively.

Therefore, current guidelines now recommend uninterrupted DOAC therapy as a standard of care for patients undergoing AF catheter ablation (Calkins et al. 2017a). In addition, it is reasonable to hold one to two doses of DOAC therapy prior to AF ablation with reinitiation post ablation. Interestingly, while the individual trials did not show superiority of DOAC compared to warfarin, Romero and colleagues performed a meta-analysis of randomized trials comparing DOAC to warfarin and found that DOAC use was associated with a reduced risk of major bleeding (RR: 0.45; 95% CI: 0.20–0.099 $p = 0.05$) (Romero et al. 2019) (Fig. 13.1).

Intraprocedural Anticoagulation

Intraprocedural anticoagulation with unfractionated heparin is an integral and well-established component of catheter ablation of atrial fibrillation (Calkins et al. 2017a). As mentioned, this is to reduce the effect of endothelial injury, hypercoagulability, and stasis induced by instrumentation of the left atrium. Heparin should be administered prior to transeptal puncture, and this practice has been shown to reduce the incidence of thromboembolism (Di Biase et al. 2014). Current guidelines

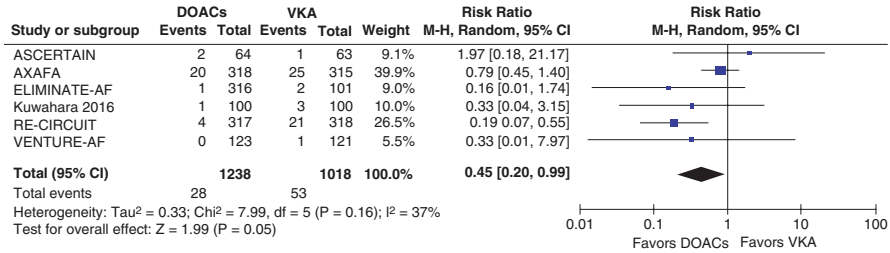

Fig. 13.1 Forest plot comparing the risk of major bleeding with an uninterrupted direct oral anticoagulant strategy versus an uninterrupted vitamin K antagonist strategy. Used with permission from Romero et al. (Elsevier) (Romero et al. 2019)

recommended heparin dosing should be adjusted to achieve and maintain a target activated clotting time of 300 s or greater based upon body weight and preprocedural coagulation profile. However, when using an uninterrupted DOAC strategy as opposed to warfarin, data suggests that higher doses of heparin are required to achieve the targeted clotting time, and the operating electrophysiologist should be aware of this.

Postprocedural Anticoagulation

AF ablation has clearly been shown to improve rhythm control of AF and results in a lower burden of disease (AlTurki et al. 2020). In a recently published trial with 2789 patients that compared early rhythm control including AF ablation to usual care, early rhythm control led to a reduction in the primary endpoint which was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome (hazard ratio, 0.79; 96% CI: 0.66–0.94; $P = 0.005$); there was also a significant reduction in stroke (hazard ratio 0.65; 95% CI: 0.44–0.97) (Kirchhof et al. 2020). The optimal long-term anticoagulation strategy in those who undergo AF ablation is unclear and is an area that is lacking in high-quality data. The current standard of care is to provide at least 8–12 weeks of oral anticoagulation post ablation and then decide on longer term anticoagulation based on the patient's overall stroke risk; this is in keeping with current international AF ablation guidelines (Calkins et al. 2017a). Bunch et al. showed that in select patients with low stroke risk (CHADS2 = 0–1) who undergo AF ablation using an aggressive anticoagulation strategy with heparin as well as an open-irrigated tip catheter scores have a low risk of thromboembolism when discharged on aspirin alone compared to warfarin (Bunch et al. 2009). Saad and colleagues examined a cohort of 327 patients, the majority of whom had a CHADS2 score of 2–3, who underwent AF ablation and discontinued oral anticoagulation 6–12 months post ablation and were then followed up for 46 ± 17 months. There were no symptomatic ischemic cerebrovascular events despite 91% of patients not receiving anticoagulation (Saad et al. 2011). In a large multicenter observational study of

3355 patients that compared those who discontinued anticoagulation versus those who continued, there was a very low risk of thromboembolism in both groups (0.07% off anticoagulation vs. 0.45% on anticoagulation) that was not statistically significant ($P = 0.06$) (Themistoclakis et al. 2010). A major hemorrhage was observed in 0.04% of those off anticoagulation compared to those on anticoagulation (2%; $P < 0.0001$). Proietti et al. performed a meta-analysis of 16 studies that included 25,177 patients (Proietti et al. 2019). There was no significant difference in the incidence of thromboembolic events between patients on and off oral anticoagulants AF ablation (RR 0.66; 95% CI: 0.38–1.15). The Optimal Anti-Coagulation for Enhanced-Risk Patients Post–Catheter Ablation for Atrial Fibrillation (OCEAN) trial is an ongoing study that aims to assess whether using a DOAC (rivaroxaban) is superior to acetylsalicylic acid in reducing the risk of clinically overt stroke, systemic embolism, or covert stroke (primary composite outcome) in patients who have not had an apparent recurrent atrial arrhythmias for a minimum of 1 year after AF ablation (Verma et al. 2018). Major bleeding including intracranial hemorrhage will also be assessed. This trial may help identify the optimal long-term anticoagulation strategy after AF ablation.

Conclusions

Uninterrupted DOAC is the current standard of care for patients undergoing AF catheter-based ablation. Higher doses of heparin are required intra-procedure to maintain activated clotting times at target when using DOAC compared to warfarin. DOAC use must be maintained for at least 8 weeks post ablation, and long-term use depends on overall thromboembolic risk. Observational data suggests that thromboembolic risk is low in patients with low overall risk who undergo ablation. An ongoing trial will evaluate whether cessation of DOAC is safe post ablation.

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DOAC Therapy in Patients Post Left Atrial Appendage Occlusion or Isolation

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T. Jared Bunch

Atrial fibrillation (AF) is the most common encountered sustained arrhythmia in clinical practice. In a cohort of 5201 adults, in people over the age of 65 years, the arrhythmia had an incidence of 19.2 per 1000 patient-years (Psaty et al. 1997). This AF incidence is increasing both in developed and underdeveloped countries as traditional risk factors in these community increase as well as from unknown factors (Go et al. 2001).

Approximately 1 of 6 embolic strokes are associated with AF, and their impact is significant with higher rates of disability, healthcare costs, stroke recurrences, and mortality compared to strokes from other sources (Wolf et al. 1991). Overall, the mechanisms of stroke in patients with AF are multifactorial and represent both embolic and non-embolic sources. In addition, atherosclerotic carotid and cerebral macro- and microvascular diseases are common in patients with AF and enhance stroke risk (Lodder et al. 1990; Chesebro et al. 1990; Bunch et al. 2020).

The left atrial appendage (LAA) has been commonly cited as the source of most embolic events in patients with AF. Most citations refer to a study by Blackshear and Odell(1996), which examined the location of clots in patients with AF compared by the presence or absence of rheumatic heart disease. In 1288 patients with AF, 222 patients were found to have an intra-atrial source, and among these patients, 201 (91%), the intra-atrial source was the LAA. The study promotes two foundational principles; first, that in the vast majority patients with AF, we currently do not know the source of the embolic event, and strategies to prevent stroke must take into consideration this uncertainty. Second, when we do know the location of the source, it is most likely the LAA, and as such, in a minority of patients, LAA therapies are an important consideration to reduce stroke risk.

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Stroke Reduction in Patients with Atrial Fibrillation

Anticoagulation for systemic disease–based risk in patients with AF remains the cornerstone of stroke prevention therapies. Vitamin K antagonists are highly effective in decreasing stroke risk and have been used for nearly seven decades for this purpose (Lip et al. 2012; Ruff et al. 2014). The narrow therapeutic index, need for frequent monitoring, and multiple dietary and drug interactions have resulted in underutilization of these drugs and the need to seek better pharmacologic solutions (Ruff et al. 2014). Direct oral anticoagulants (DOAC) have been widely adopted into contemporary practice with fewer drug and dietary interactions, no need for routine monitoring of drug levels, and equal to superior efficacy and safety compared to vitamin K antagonists (Connolly et al. 2009, 2011; Patel et al. 2011; Giugliano et al. 2013).

Despite the potential ease-of-use advantages with DOAC therapies, compliance rates remain suboptimal. In a large meta-analysis of real-world adherence involving 594,784 unique patients, the pooled proportion of patients with good adherence was 71% for apixaban, 60% for dabigatran, and 70% for rivaroxaban. Adherence with DOAC therapy was superior to that observed with vitamin K antagonists (odds ratio, 1.44 [95% CI: 1.12–0.86). Lack of adherence with DOAC therapies was associated with an increased risk of stroke (hazard ratio (HR), 1.39 [95% CI: 1.06–1.81]) (Ozaki et al. 2020). A persistent challenge with DOAC therapy use is the cost of these medications that impact access and used in both developed and underdeveloped countries.

These limitations with prior and contemporary therapies have provided a very attractive substrate for the development of alternative approaches to reduce stroke rates in patients with AF.

Left Atrial Appendage Occlusion

Multiple technologies for LAA occlusion are available, but for this chapter the focus will be primarily on the Watchman device (Boston Scientific. Marlborough, MA) as the data to date comprise the largest enrolled LAA occlusion populations with the longest follow-up durations.

The PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial included 542 patients and an additional 460 in a continued access protocol registry that underwent attempted LAA occlusion. In 91% of patients, the device was successfully implanted. Procedure- or device-related safety events within 7 days were commonly initially (7.7%) and declined with experience (3.7%), including procedure-related stroke (0.9% and 0%, respectively) (Reddy et al. 2011). The LAA occlusion device compared favorably to warfarin in regard to incident strokes (1.8 versus 4.3 events per 100 patient-years).

In a second randomized trial, PREVAIL AF (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin

Therapy), periprocedural complication rates remained low, and at 18 months, the rate of the composite of stroke, systemic embolism, and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group, which did not achieve the prespecified criteria noninferiority (Holmes et al. 2014).

At 5 years of follow-up, a meta-analysis of these studies showed that ischemic stroke/systemic embolism rate was higher with LAA closure, but did not reach statistical significance (HR: 1.71; $p = 0.080$). Differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAA closure (HR: 0.20; $p = 0.0022$; HR: 0.45; $p = 0.03$; HR: 0.59; $p = 0.027$; HR: 0.73; $p = 0.035$; HR: 0.48; $p = 0.0003$, respectively) (Reddy et al. 2017).

Even when successfully implanted, LAA closure device performance over time has been suboptimal. Device endothelialization has been slower than anticipated and can be incomplete years after implantation, and risk factor-driven device-related thrombus can develop in up to 3.8% of patients. These risk factors elevate stroke risk by four to fivefold (Sivasambu et al. 2019; Alkhouli et al. 2018). Risk factors for device-related thrombus include many of those associated with general stroke risk on patients with AF and include transient ischemic attack or stroke (OR: 2.31; 95% CI: 1.26–4.25; $P = 0.007$), permanent atrial fibrillation (OR, 2.24; 95% CI: 1.19–4.20; $P = 0.012$), vascular disease (OR, 2.06; 95% CI: 1.08–3.91; $P = 0.028$), left atrial appendage diameter (OR, 1.06 per mm increase; 95% CI: 1.01–1.12; $P = 0.019$), and left ventricular ejection fraction (OR, 0.96 per 1% increase; 95% CI: 0.94–0.99; $P = 0.009$) (Dukkipati et al. 2018).

In addition, residual LAA leaks after implantation are common with small leaks present in up to 32% of patients and larger leaks in approximately 1–12% (Saw et al. 2017; Viles-Gonzalez et al. 2012). Leak is more common in patients with a large landing zone diameter, persistent/permanent AF, and an off axis device location (Nguyen et al. 2019). The presence of leaks is associated with stroke and major adverse event rates, but should improve with procedural experience and technology advances.

The persistent long-term stroke events compared to warfarin, which has performed poorly historically, and those event rates observed with DOAC therapies suggest that post-procedure antithrombotic strategies will likely play a key role in the long-term utility observed after LAA closure (Table 14.1).

Antithrombotic Therapy After Percutaneous Left Atrial Appendage Occlusion

Although most patients who receive LAA occlusion have an absolute or relative contraindication to anticoagulation, antithrombotic therapy post-procedure is recommended for a specified period of time to prevent device-associated thrombus. However, the type of therapy, duration of therapy, and in what combination to use are not well defined. In addition, all of these questions may differ as individualized approaches based upon actual or perceived risk are required for long-term management.

Table 14.1 Comparison of clinical data from the PROTECT AF and PREVAIL AF and DOAC trials

	PROTECT AF	PREVAIL AF	PROTECT AF	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
	LAA closure	LAA closure	Warfarin	(ARISTOTLE)	(ROCKET AF)	(ENGAGE AF)	(RELY)
Age, years	72	74	73	70	73	72	72
CHADS2	2.2	2.6	2.3	2.1	3.5	2.8	2.1
Major or minor bleeding (%)	–	–	–	18.1	14.9	16.9	16.4
Major bleeding (%)	3.5	–	4.1	2.1	3.6	2.8	3.1
Stroke/systemic embolism (%)	2.3	2.3	2.7	1.3	1.7	1.6	1.1

Different antithrombotic strategies studied after Watchman device implantation include vitamin K oral anticoagulants, DOACs, dual antiplatelet therapies, aspirin monotherapy across different time duration as well as no additional therapy (Reddy et al. 2017, 2013; Boersma et al. 2017; Bergmann et al. 2017).

For example, in the PREVAIL and the PROTECT AF trials that are widely used for guidance, patients were treated with warfarin for 45 days (INR 2–3) after device placement to allow healing and potential endothelialization . Warfarin was discontinued if transesophageal echocardiography showed complete closure or near closure. After that, patients received aspirin and clopidogrel for 6 months, and then long-term aspirin (Reddy et al. 2017).

In the real-life registry, EWOLUTION (Watchman Outcomes in Real-Life Utilization), strategies were variable and reflected individualized practices. Following LAA closure, patients received dual antiplatelet therapy, vitamin K antagonists, DOAC, single antiplatelet, or no therapy (60.3%, 15.4%, 10.9%, 7%, and 6.5%, respectively). Device thrombus (2.6%), stroke (0.4%), and major bleeding SAE (2.6%) rates were low in general at 3 months and did not vary by postimplantation antithrombotic medication strategy (Bergmann et al. 2017).

In the ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) trial, which was a multicenter, prospective, nonrandomized study of the WATCHMAN device in warfarin ineligible patients postdevice treatment included dual antiplatelet therapy for 6 months followed by aspirin indefinitely. Serious procedure- or device-related safety events occurred in 8.7% of patients (13 of 150 patients). All-cause stroke or systemic embolism incidence was 2.3% per year and ischemic stroke incidence (1.7% per year) (Reddy et al. 2013). Other strategies have been advocated for different LAA closure systems, but the general themes of diversity based upon expert opinion of risk and benefits prevail in these studies.

Recently, PRAGUE-17 (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents) was published. Patients were randomized 1:1 to DOAC therapy versus LAA closure. After LAA closure, the recommended antithrombotic regimen was aspirin 100 mg/day plus clopidogrel 75 mg/day for 3 months. If a transesophageal echocardiogram then showed no device-related thrombus or leak of >5 mm, clopidogrel was withdrawn, and aspirin was continued indefinitely. In patients with a very high thrombotic risk, alternative regimens included DOAC substitution for DAPT for up to 3 months or DOACs for 6 weeks followed by dual antiplatelet therapy for 6 weeks. The primary outcomes of stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or nonmajor relevant bleed, or procedural-related complications were similar at a median follow-up of 19.9 months (10.9% LAA closure group versus 13.4% DOAC group, $p = 0.0004$ for noninferiority) (Osmancik et al. 2020). In the subgroup of high-risk AF patients in which DOAC therapy could be used in the early post LAA closure period, there were also no differences in long-term safety or efficacy outcomes.

The European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions expert consensus statement has issued

Table 14.2 Antithrombotic therapy before and after LAA closure

Clinical situation and therapeutic concept (Adapted from Consensus Statement) (Glikson et al. 2020)
"Should do this"—Green Heart Recommendation
• After WATCHMAN implantation, warfarin (INR 2–3) should be given for 45 days, followed by clopidogrel for 6 months after the procedure in low bleeding risk group of patients; while in high bleeding risk group, oral anticoagulation should not be applied
"May do this"—Yellow Heart Recommendation
• DOAC is a possible alternative to warfarin after WATCHMAN implantation
• After WATCHMAN implantation in patients not suitable for oral anticoagulation, dual antiplatelet therapy including clopidogrel 75 mg/day for 1–6 months after the procedure (load 300–600 mg prior to procedure if not previously on clopidogrel)
• After AMPLATZER Cardiac Plug or Amulet implantation, dual anticoagulation therapy including clopidogrel 75 mg/day for 1–6 months after the procedure (load 300–600 mg prior to procedure if not previously on clopidogrel)
• Other options that may be considered on a case-by-case basis include a single antiplatelet therapy (acetylsalicylic acid or clopidogrel) for short periods of time, as long as approved by a team consensus

recommendations for antithrombotic treatment approach after left atrial appendage closure (Table 14.2) that reflect many of the trials and their post closure management approaches (Glikson et al. 2020).

Left Atrial Appendage Isolation

Pulmonary vein isolation is the cornerstone of ablation strategies for patients with atrial fibrillation (Calkins et al. 2017). However, in some patients, particularly those with advanced AF subtypes, the left atrial appendage can serve as a trigger for recurrent arrhythmias. The BELIEF trial was a randomized trial in longstanding persistent AF patients between a standard "extensive" ablation versus standard ablation with LAA isolation. At 12-month follow-up, 48 (56%) patients in LAA isolation group vs. 25 (28%) in extensive ablation alone group were recurrence free of atrial arrhythmias after a single procedure (HR1.92; 95% CI: 1.3–2.9; $p = 0.001$) (Di Biase et al. 2016).

Despite a potential value in rhythm control with LAA isolation, the mechanisms surrounding thrombus formation in the LAA, hemostasis, hypercoagulability, and endothelial injury are augmented in patients that undergo persistent electrical isolation of the LAA with mechanical uncoupling. As such it was not surprising to find patients such as the one illustrated in Fig. 14.1 that presented with stroke, despite adequate anticoagulation. In a registry study of 50 patients that underwent LAA isolation, transesophageal echocardiography was performed during follow-up in 47/50 (94%) patients independent of symptoms. LAA thrombus was identified on transesophageal echocardiography in 10 (21%) patients (on oral anticoagulation = 9; no oral anticoagulation = 1) (Rillig et al. 2016). Among these nine patients, three were on vitamin K antagonists, one on dabigatran (200 mg/day), four on

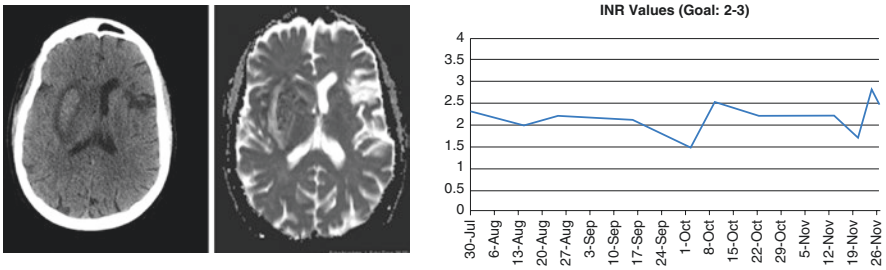

Fig. 14.1 The figure shows the CT images at the time of admission for an acute stroke. The INR findings show the values recorded 4 months prior to admission. The case is of 56-year-old female with hypertension, grade ¾ diastolic dysfunction, two prior ablations, the second with extensive substrate modification for non-PV triggers (4 months prior) with left atrial appendage isolation

rivaroxaban (20 mg/day), and one on apixaban (10 mg/day). If a thrombus was found on DOAC therapy, these patients were transitioned to a vitamin K antagonist with a goal INR of 2.5–3.5. Among the 50 patients that underwent LAA isolation, three (6%) suffered a stroke.

A second larger study examined the impact of post LAA isolation occlusion or long-term oral anticoagulation on risk of LAA thrombus at 6 months post LAA isolation (Di Biase et al. 2019). In this study, 1854 consecutive post-LAA isolation patients with follow-up transesophageal echocardiography (TEE) performed in sinus rhythm at 6 months to assess LAA function was included. In the post-ablation period, 336 patients with preserved LAA function were off oral anticoagulation with very low stroke events. In the 1518 patients with abnormal LAA contractility, 1086 remained on oral anticoagulation with incident stroke/transient ischemic attack rate of 1.7% versus 16.7% in those off oral anticoagulation ($p < 0.001$). In 81 patients with impaired LAA function, an LAA closure device was placed with standard post device anticoagulation with no observed strokes.

This second study highlights the significant iatrogenic stroke risk with LAA isolation that results in impaired LAA function. In the group without impaired LAA function, it is unclear if there was durable isolation, if the flow measurements were reproducible, or if there was some benefit to the enhanced mechanical atrial function. What is very concerning about the observed strokes in this population is that they often occurred rapidly, within 1–10 days, of a held or missed dosed of anticoagulation, highlighting the potential challenges with long-term anticoagulation use in patients that undergo LAA isolation and the likely value of LAA occlusion despite the limitations discussed previously.

Future Directions with Left Atrial Appendage Closure and Anticoagulation

There are a number of trials actively recruiting in this space that will provide additional clarity regarding the role of LAA occlusion in patients with AF compared to DOACs, but there are none to compare postimplantation anticoagulation strategies.

The Left Atrial Appendage Occlusion versus Novel Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation (Occlusion-AF, ClinicalTrials.gov: NCT03642509) is a randomized (1:1) trial of 750 patients that will compare outcomes between the Amulet or Watchman devices and DOACs. The primary outcome is a composite of stroke (hemorrhagic or ischemic), systemic embolism, major bleeding, or all-cause mortality assessed after at least 2 years follow-up for the last enrolled patient.

Comparison of Anticoagulation with Left Atrial Appendage Closure After AF Ablation (OPTION, ClinicalTrials.gov Identifier: NCT03795298) is a randomized (1:1) trial of 1600 patients that will compare outcomes post atrial fibrillation between patients treated with the Watchman FLX device sequential or planned at the time of ablation and DOACs. The primary endpoints are noninferiority for stroke, all-cause death, and systemic embolism and then for superiority for nonprocedural bleeding over 36 months of follow-up.

Left Atrial Appendage Closure in Patients with Atrial Fibrillation Compared to Medical Therapy (CLOSURE-AF, ClinicalTrials.gov: NCT03463317) is a randomized trial of 1512 patient to CE-mark–approved LAA closure devices followed by post-procedure treatment (antiplatelet therapy with acetylsalicylic acid and clopidogrel) versus DOAC or vitamin K antagonist therapies. The primary endpoints are sought at 24 months, but the trial is designed to be an event driven with a noninferiority test, if significant, followed by superiority test. The primary endpoint is a composite of stroke, systemic embolism, major bleeding, and cardiovascular or unexplained death.

Amplatzer Amulet LAAO vs. NOAC (CATALYST, ClinicalTrials.gov: NCT04226547) randomized trial (1:1) of 2650 patients randomized to the Amplatzer Amulet LAA Occluder versus DOAC therapy with follow-up of 2 years. The endpoints are that the device will be noninferior for the composite of ischemic stroke, systemic embolism, or cardiovascular mortality and superior for major bleeding or clinically relevant nonmajor bleeding.

In consideration of these trials, most are anticipating low stroke event rates and are focused on a noninferior design to show noninferiority to anticoagulation approaches. The follow-up periods when considering the score and duration of management of a patient with AF are brief. However, many of these trials are designed not to answer the way to manage patients with AF long term, but to try to answer the prevalent question can LAA closure approach the benefit shown by DOAC therapies alone in a scientifically acceptable manner for therapy adoption into practice.

Next, the field of electrophysiology remains plagued by the continued use of clinical stroke, often with disability, as the primary endpoint for brain health. This endpoint provides a myopic understanding of the actual impact of atrial fibrillation on brain health and function and relies for the most part on a clinical presentation of a frequently clinically silent event, whose true impact may become apparent years later.

Finally, there remains a critical need to explore the role of different long-term antithrombotic strategies in patients that receive an LAA closure device. The reliance on long-term antiplatelet strategies is not supported by quality data, and these agents are far from benign for both macro- and micro-brain injuries.

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Use of Direct Oral Anticoagulants After Transcatheter Aortic Valve Replacement

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Introduction

Transcatheter aortic valve replacement (TAVR) has emerged as the standard of care for patients with symptomatic severe, aortic stenosis (Nishimura et al. 2021; Baumgartner et al. 2017). Since the completion of large randomized clinical trials on low-risk patients treated with transfemoral TAVR, a number of approximately 270,000 candidates may benefit from this procedure in European Union and North America annually (Durko et al. 2018). Similarly to percutaneous coronary intervention (PCI), a balance between bleeding and thrombotic complications has to be taken into consideration. The optimal antithrombotic therapy is determined by procedural and clinical considerations. Current evidence and the future perspectives on the use of anticoagulants after TAVR will be presented.

Technical Aspects of Transcatheter Bioprosthetic Heart Valves

The available transcatheter bioprosthetic heart valves (BHVs) consist of three leaflets of bovine or porcine pericardium attached to a stent frame. Despite some common features, BHVs differ from their surgical counterparts due to some unique features that must be considered for appropriate selection of antithrombotic therapy.

The stents are uncoated and are directly exposed to blood flow. Comparisons among different materials are not available but, extrapolating knowledge from coronary stent research, nitinol frames (self-expandable BHVs) might offer better hemocompatibility and lower thrombogenicity potential compared to stainless steel

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(Mangieri et al. 2019). Various grades of endothelization have been reported in struts in direct contact with native endocardium. On the contrary, some concerns have been raised regarding thrombus development on bare-metal structures in ascending aorta lumen (van Kesteren et al. 2017).

In the absence of outcome studies on bovine and porcine leaflets in transcatheter BHVs, the experience derived from cardiac surgery suggests that no significant differences should be expected between these two types of leaflet tissues (Hickey et al. 2015). Animal models demonstrated how crimping forces can lead to structural changes (e.g., leaflet tears) which can represent the primum movens of thrombosis (Kiefer et al. 2011).

Finally, the implanted BHVs are responsible of altered hemodynamic conditions in the space between the valve leaflets and the sinus of Valsalva (Ducci et al. 2016). The decreased turbulence, flow velocity, and shear rate found in this region might account for increased thrombogenicity after TAVR leading to hypoattenuating leaflet thickening (HALT) development and reduced motion.

Thrombotic vs. Bleeding Risk

Antithrombotic therapy in TAVR is particularly challenging because of the risk of both ischemic and bleeding events (Saito et al. 2020). These complications are associated with conspicuous high mortality rates (Saito et al. 2020). Therefore, a correct balance between these opposing adverse outcomes is fundamental in the choice of antithrombotic therapy and may vary depending on the clinical context.

Recent Percutaneous Coronary Intervention

In case of recent percutaneous coronary intervention (PCI), management of medical therapy is mainly driven by the need for dual antiplatelet therapy (DAPT). The clinical syndrome (stable coronary artery disease vs. acute coronary syndrome), rather than the stent type, determines the duration of such therapy. Therefore, for obvious reasons, in the absence of preexisting indications, there is no room for anticoagulation in this setting.

Atrial Fibrillation

Atrial fibrillation (AF) is the most common rhythm disorder associated with severe aortic stenosis; the STS/ACC TVT Registry reported a prevalence of 40% in patients undergoing TAVR (Holmes et al. 2015). An additional 10% of new onset AF cases has been detected (Mojoli et al. 2017). Therefore, up to half of the patients undergoing TAVR potentially need oral anticoagulation (OAC) as part of the antithrombotic therapy. A recent study investigated the impact of OAC type on 1-year clinical outcome after TAVR (Jochheim et al. 2019). Although bleeding risk was

comparable, a higher ischemic event rate was found among patients taking non-vitamin K OAC (NOAC) compared to those on vitamin K antagonists (VKAs); composite outcome of all-cause mortality, myocardial infarction, and cerebrovascular event at 1-year was 21.2% with NOAC vs. 15.0% with VKAs (hazard ratio [HR] 1.44, $p = 0.050$). Opposite results emerged from an analysis of the PARTNER (Placement of AoRTic TraNscathetER Valve) II registries where patients discharged on NOAC did not differ from those on VKAs in the following outcomes: overall death 21% vs. 27.6%, stroke or TIA 11.6% vs. 8.8%, bleeding 23.1% vs. 22.4%, in NOAC vs. VKAs, respectively (Kosmidou et al. 2019). However, when OAC was added to a minimum 6 months regime of DAPT, a significant reduction in strokes was observed. This finding was maintained after analyzing only acute/subacute (procedure related) and late events (diffuse inflammatory and atherosclerotic process). For this reason, Kosmidou et al. (2019) suggest the use of OAC (regardless of type) in conjunction with APT for at least 6 months in patients with AF undergoing TAVR. The absence of a significant difference between NOAC and VKAs in term of bleeding could be attributed to the aetiology of post-TAVR hemorrhages that are mostly mechanically provoked. Another possible explanation may be found in the advanced age of patients undergoing TAVR. The reduction of major bleeds with NOAC becomes nonsignificant when analyzing patients with AF and ≥75 years old (Ruff et al. 2014).

Cerebrovascular Complications

Stroke is the most feared complication after TAVR. In the first year, it can occur in up to 7% of intermediate or high-risk patients, similarly to what is observed in the surgical counterpart (Vranckx et al. 2017). This 1-year time window can be further divided into three parts, classifying stroke occurrence as acute, subacute, or late. Acute stroke (on the first day) results from the mechanical deployment of the device which interacts with the calcified aorta and degenerated valve. The consequence of the embolization of tissue-derived debris is the finding of new cerebral emboli on neuroimaging. This phenomenon has been observed in two-thirds of the patients but does not correlate with clinical events (Giustino et al. 2016). A careful advancement of the TAVR system and the use of embolic protection devices can attenuate this complication. After the procedure and up to 30 days, we can define stroke occurrence as subacute. It is mainly caused by new-onset AF, which, as previously mentioned, can be detected in up to 10% of the patients (Mojoli et al. 2017). Finally, late strokes are those reported in the 30 days–1 year period after the procedure. These events are mainly related to systemic atherosclerosis with peripheral arterial disease and preexisting AF. In some series, the role of anticoagulants in protecting from late strokes caused by AF has been reported (Chopard et al. 2015).

Subclinical Leaflet Thrombosis

Subclinical leaflet thrombosis is a phenomenon already described in surgical bioprosthetic valves. It has been recently investigated in TAVR where its occurrence has been found to be higher compared to the surgical counterpart (101 of 752 [13%] vs. 5 of 138 [4%], TAVR vs. SAVR, respectively; $P = 0.001$) (Chakravarty et al. 2017). The diagnosis can be made identifying hypoattenuating lesions with the use of four-dimensional multidetector computed tomography angiography. These lesions have been associated with increased stroke risk and trans valvular gradients 1–9 months after TAVR and can potentially result in decreased long-term valve durability (Hansson et al. 2016). The PARTNER 3 Cardiac Computed Tomography (CT) sub-study described the dynamic nature of subclinical leaflet thrombosis: spontaneous resolution (50%), new appearance (20%), and increased frequency with time (24% at 1 year) (Makkar et al. 2020). Given these findings, the authors question the utility of routine CT scanning at a single time point; a clinic-guided CT imaging would be more prudent. Both DOACs and VKAs were associated with lower rates of subclinical leaflet thrombosis compared to placebo, single, or DAPT (4% vs. 15%, 16%, and 15%, respectively; all $p < 0.0001$) (Chakravarty et al. 2017). A short-term (90 days) duration of anticoagulation led to resolution of leaflet thrombosis and improved function, while OAC discontinuation was associated with 50% risk of recurrence (Hansson et al. 2016). An anticoagulation treatment strategy in patients without an established indication for oral anticoagulation after successful TAVR has not yet proven to be of clinical benefit. The extension of TAVR to younger and low-risk patients, whose frequency of subclinical leaflet thrombosis reaches 1 in 4 patients, represents a strong argument for further clinical trials. Indeed, this type of patient could benefit most from an oral anticoagulant therapy; the healthier status could lead to a more favorable risk–benefit ratio for anticoagulation, and the longer life expectancy makes valve durability even more relevant.

Current Evidence and Future Perspectives

Current guideline recommendations are largely derived from expert consensus extrapolating experience from PCI and open-heart aortic valve replacement and are summarized in Table 15.1.

Intraprocedural antithrombotic treatment is mainly based on the use of parenteral anticoagulation with unfractioned heparin (UFH) at doses of 50–70 IU/kg with a target activated clotting time between 250 and 300 s. This practice is favored in order to address the risk of thrombotic complications due to catheter manipulations, guidewire insertion, balloon aortic valvuloplasty, and valve implantation and to avoid bleedings from vascular access sites. Bivalirudin can be considered as a valid alternative in case of contraindications to UFH .

After TAVR, until recently it was widely prescribed a DAPT with aspirin and clopidogrel for 3–6 months, followed by aspirin alone lifelong. However, these indications are not well supported by current evidence and may be applied only in

Table 15.1 Current society guidelines for antithrombotic therapy after transcatheter aortic valve replacement

Society guidelines	Timing	Indication for OAC	
		NO	YES
ACC/AHA 2020	Short term	– DAPT for 3–6 months (IIb/B) if low bleeding risk – VKAs (INR 2.5) for 3 months (IIb/B-NR) if low bleeding risk – Rivaroxaban (10 mg daily) plus aspirin (75–100 mg) is contraindicated (III/B)	– VKAs in new-onset (≤ 3 months) AF (IIa/B)
	Long term	Aspirin 75/100 mg (IIa/B)	– NOAC or VKAs after 3 months (I/A)
ESC/EACTS 2017	Short term	– DAPT for 3–6 months (IIa/C) – SAPT if high bleeding risk (IIb/C)	– OAC + aspirin/ thienopyridine for 3 months (IIa/C) – OAC if high bleeding risk (I/C)
	Long term	Aspirin/thienopyridine (IIb/C)	OAC (I/C)

OAC oral anticoagulation, *ACC/AHA* American College of Cardiology/American Heart Association, *NOAC* non-vitamin K OAC, *DAPT* dual antiplatelet therapy, *VKAs* vitamin K antagonists, *INR* international normalized ratio, *ESC/EACTS* European Society of Cardiology/European Association of Cardio-Thoracic Surgery, *SAPT* single antiplatelet therapy

patients with low-bleeding risk. In fact, a recent randomized clinical trial demonstrated an advantage of single antiplatelet therapy (SAPT) over DAPT in reducing the risk for major or life-threatening events while not increasing the risk for myocardial infarction or stroke (Rodés-Cabau et al. 2017). Therefore, provided that larger studies support this approach, a single antiplatelet agent could be a safer alternative to DAPT in patients without an indication to OAC.

The issue of bleeding complications was not addressed by clinical trials on transcatheter procedures until the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2) trial. Bleeding was found to be a predictor of death at 1 year that was as powerful as myocardial infarction (Feit et al. 2007). This strong evidence impacted all subsequent studies that considered this complication worthy of being a primary outcome. The Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antiplatelet-based Strategy after Transcatheter aortic vaLve rEplacement to Optimize Clinical Outcome (Galileo, $n = 1520$) study randomized TAVR patients *who did not have indications for OAC* in receiving 10 mg of rivaroxaban up to 25 months plus low-dose aspirin during the first 3 months vs. 3 months DAPT followed by aspirin alone (NCT02556203). Addition of OAC was found to be associated with increased risk of death, thromboembolic as well as bleeding complications and resulted in premature termination of the study (Dangas et al. 2020). The Anti-Thrombotic Strategy after Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS, $n = 1509$) trial will provide

more data on the use of NOAC comparing the standard of care (DAPT or VKAs) with an anticoagulant-based strategy with apixaban 5 mg bid, stratifying for the need or not for OAC other than TAVI (NCT02664649).

In the setting of *preexisting OAC indication*, The Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular TAVI, $n = 1000$) trial was designed to provide randomized data on OAC vs. OAC plus clopidogrel for 3 months (NCT02247128). The investigators of this study reported a lower incidence of serious bleeding over a period of 1 month or 1 year with OAC alone than with OAC plus clopidogrel (Nijenhuis et al. 2020). In the same context of OAC indication but with the use of different NOAC, the Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR) trial will report on the net clinical benefit of OAC alone (VKAs or Apixaban/Edoxaban) vs. OAC plus aspirin at 1 year (NCT02735902).

While the use of OAC is undisputed among patients with AF, the need to add an antiplatelet agent is still debatable. As previously mentioned, conflicting evidence complicate the final selection. Therefore, the choice of appropriate therapy needs to be characterized by an approach that will favor OAC alone in case of enhanced bleeding risk and, on the contrary, will suggest OAC plus aspirin if the thrombotic risk prevails. Triple antithrombotic therapy (OAC plus DAPT) is not addressed by current guidelines and should be considered only in special situations (e.g., recent PCI and concomitant AF). In addition to the previously mentioned ATLANTIS trial, the Edoxaban Compared to Standard Care after Heart Valve Replacement Using a Catheter in Patients with Atrial Fibrillation (ENVISAGE-TAVI AF; NCT02943785; $n = 1400$) and the Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement (ADAPT-TAVR; NCT03284827; $n = 220$) trial will provide more evidence on the efficacy and safety of NOAC (edoxaban) vs. VKAs or vs. DAPT, respectively.

At the moment, subclinical leaflet thrombosis is not addressed by current guidelines. Particular attention must be paid to this complication which can be effectively treated with the use of anticoagulation therapy.

To conclude, we can affirm that, to date, there are several gaps that need to be filled. In the absence of risk prediction models, a careful clinical judgement has to guide the choice of the appropriate antithrombotic therapy. Ongoing studies will provide better knowledge and more robust recommendations.

Conflict of Interest The authors have no conflicts of interest to **declare.**

Disclaimer None.

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Use of Direct Oral Anticoagulants After Percutaneous Coronary Intervention

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Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder with an estimated prevalence of 1.5–2% in the general population (Moti et al. 2015). The burden of this emerging arrhythmia is predicted to further expand in the next years due to growing ageing population, with a major increase in healthcare cost (Virani et al. 2020). The cornerstone of AF-related thromboembolic prevention is represented by oral anticoagulation (OAC) with vitamin K antagonists (VKA) and more recently with direct oral anticoagulants (DOAC) (Steffel et al. 2018). In this setting, OAC is essential for preventing cerebral and systemic embolization arising from left atrial appendage thrombus, where blood stasis and low shear-stress promote formation of less platelet-rich thrombi.

However, about 30% of AF patients present with concomitant coronary artery disease (CAD), often requiring percutaneous coronary intervention (PCI) (Michniewicz et al. 2018; Nieuwlaat et al. 2005). Moreover, indications for lifelong OAC occur in up to 10% of patients undergoing coronary angiography (Michniewicz et al. 2018). In this context, dual antiplatelet therapy (DAPT) is needed to prevent stent thrombosis (ST) and coronary events due to platelet-rich thrombi in high shear-stress regions.

A sizeable proportion of patients presents with multiple comorbidities, which may require the combination of OAC and DAPT, a treatment also known as triple antithrombotic therapy (TAT). On one hand, this regimen is "theoretically" required in order to prevent ischemic complications with different pathophysiological mechanisms (systemic, cerebral, and coronary ischemic events); on the other hand, the

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risk of major and fatal bleedings is markedly increased in patients on TAT, in particular in those patients with high bleeding risk at baseline. The growing interest of the scientific community has led to several randomized controlled trials (RCTs), evaluating different strategies of combining OAC and antiplatelet therapy. However, the optimal management of AF patients requiring PCI is still debated, and ongoing studies and meta-analyses will probably change the landscape in the near future (Capodanno and Angiolillo 2014; Capodanno et al. 2019).

In this chapter, we summarize current evidence coming from large RCTs and recent recommendations about management of antithrombotic therapy in AF patients undergoing PCI. We also discuss the pivotal role of personalized ischemic and bleeding risk assessment in order to offer a tailor-made treatment for those patients. Finally, we will present emerging interventional strategies in high bleeding risk patients, such as left atrial appendage occlusion (LAAO) and newer generation drug-eluting stents (DES).

In the Middle of Ischemic and Bleeding Risk

The advent of DOAC in clinical practice and evidences from landmark trials has brought about a paradigm shift in the optimal treatment strategies in AF patients undergoing PCI.

An antithrombotic regimen consisting of OAC, aspirin, and $P2Y_{12}$ inhibitors (TAT) has been initially endorsed by international guidelines to ensure a comprehensive protection against ischemic events (thromboembolism and coronary thrombosis). However, TAT is associated with a higher risk of bleeding, particularly in protracted administration. Sørensen et al. have clearly outlined that TAT fourfold increases the risk of fatal and nonfatal bleedings in patients with myocardial infarction (MI) when compared to treatment with aspirin alone (Sørensen et al. 2009). Moreover, it is important to emphasize that high bleeding risk (HBR) patients are excluded or underrepresented in clinical trials, and the reported rates of major and minor bleeding represent only the tip of the iceberg. Indeed, in major DAPT trials, 1-year major bleeding rates range from 0.3 to 2.8% (Fig. 16.1). Thus, the recognition of HBR patients is of paramount importance in daily clinical practice as well as its impact on prognosis, which is emerging as a major issue. Data from ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial demonstrated that major bleedings occurrence 12-fold increases the risk of death, stroke, and MI within 30 days (Held et al. 2014).

This increased bleeding risk associated with TAT and its impact on clinical outcomes has generated great interest in this complex clinical scenario, and main research initiatives aim to identify alternative antithrombotic strategies and determine their optimal duration. Indeed, antithrombotic treatment and its duration should take into account the dynamic nature of ischemic hazard (thromboembolism and coronary thrombosis) and the individualized stratification of ischemic and bleeding risk.

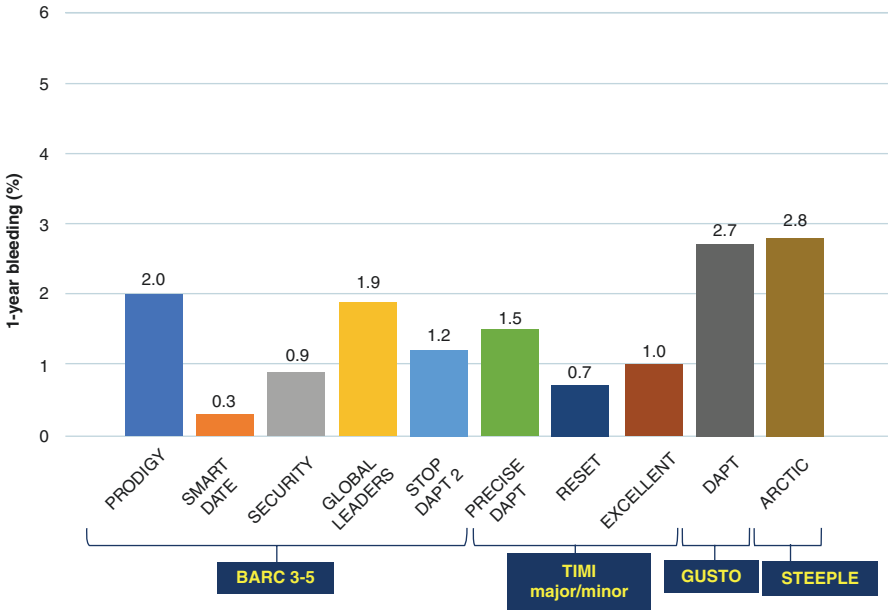

Fig. 16.1 One-year bleeding rates in dual antiplatelet therapy (DAPT) trials according to different bleeding scores. As we can see from the bar chart, high bleeding risk patients are excluded or underrepresented in DAPT trials. Bleeding events were evaluated according to different risk scores. *BARC* Bleeding Academic Research Consortium, *TIMI* thrombolysis in myocardial infarction, *GUSTO* Global Use of Strategies to Open Occluded Arteries, *STEEPLE* Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation

Temporal evolution of ischemic risk represents a key point and different trends, and pathophysiological mechanisms are recognized in the context of thromboembolic and coronary events. Indeed, in AF patients requiring OAC, it has been well established that stroke risk continues to increase over time. This continuous increase may be related to structural remodeling of left atrium, which undergoes progressive enlargement and loss of contractile function, with consequent increase of AF burden, blood stasis, and thromboembolic risk. On the other hand, pathophysiological mechanisms of ST are quite different and its risk seems to follow a more predictable temporal pattern. Indeed, the majority of ST events occurs in the early phases after coronary stenting, a temporal window of high thrombotic hazard in which a more aggressive antiplatelet therapy is needed. Following this vulnerable period, lowering the intensity of antiplatelet treatment has been demonstrated to be a safe option in patients at high bleeding risk.

Current guidelines and consensus documents underline the importance of individual stratification of ischemic and bleeding hazard (Angiolillo et al. 2018; Neumann et al. 2018; Valgimigli et al. 2017). In recent years, several scores have been proposed to predict the risk of ischemic or bleeding events in AF patients or those undergoing PCI. For instance, in AF patients, $CHADS_2$ and CHA_2DS_2-Vasc

are well-established scores for ischemic risk assessment, while HAS-BLED, ABC, and ATRIA are used for bleeding risk stratification. On the other hand, in patients undergoing PCI, DAPT and PRECISE-DAPT scores have been proposed for ischemic and bleeding risk stratification, respectively (Saito and Kobayashi 2019). However, no scoring system has been validated in AF patients undergoing PCI and tested in RCT. Moreover, some of these scores are limited by considerable overlap among risk factors for ischemic and bleeding events. Initial evidence seems to support the predictive ability of CHA_2DS_2-Vasc (with cutoff value of 5) and HAS-BLED scores towards ischemic and bleeding events, respectively, in anticoagulated patients undergoing PCI (Fauchier et al. 2016; Yoshida et al. 2019).

Currently, antithrombotic therapy, its composition and duration, is left to clinician's discretion and should take into consideration not only scoring systems and clinical factors but also anatomical and PCI features (Giustino et al. 2016). Further studies are warranted to develop or validate novel scoring systems, aiming to guide antithrombotic therapy in AF patients undergoing PCI.

Lessons from Randomized Clinical Trials

VKA in Triple Versus Dual Antithrombotic Therapy

Two randomized trials attempted to explore novel antithrombotic strategies to improve safety of TAT by withdrawing aspirin (WOEST trial [What is the Optimal antiplatelet & Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary StenTing] (Dewilde et al. 2013)) or reducing its duration (ISAR-TRIPLE trial [Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation] (Fiedler et al. 2015)).

The WOEST trial was the first RCT enrolling 573 patients (28% with acute coronary syndromes [ACS]) treated with PCI and randomized to TAT (VKA, aspirin and clopidogrel) versus dual antithrombotic therapy (DAT) (VKA and clopidogrel) (Dewilde et al. 2013). The primary endpoint was 1-year minor and major bleedings. The study demonstrated a 64% relative reduction of bleeding in patients randomized to DAT versus TAT (19.4% versus 44.4%, hazard ratio [HR] 0.36; 95% CI: 0.26–0.5, $p < 0.0001$), driven by a reduction in minor bleedings. Although thrombotic events were also reduced in DAT group, the study was underpowered for efficacy endpoints. Prolonged duration of TAT, the low sample size, and proportion of ACS patients represent the main limitations of this study, which however paved the way to several aspirin-free trials.

The ISAR TRIPLE trial enrolled 614 PCI patients (one-third with ACS) with any indications for OAC and randomized to 6 weeks versus 6 months of DAPT (Fiedler et al. 2015). The primary endpoint, a composite of death, MI, definite ST, stroke, or TIMI major bleeding at 9-month, did not differ between the two groups. Of note, a landmark analysis of events between 6 weeks and 6 months showed an increased risk of bleeding in patients randomized to TAT versus DAT. Despite the low sample size and lack of power to detect significant differences in ischemic endpoints,

WOEST and ISAR TRIPLE trials outlined that TAT should be as short as possible, and a less intensive antithrombotic regimen is a safe option in patient requiring OAC and antiplatelet therapy.

DOAC in Triple Versus Dual Antithrombotic Therapy

The introduction of DOACs represented a major breakthrough in antithrombotic management of AF patients, on the basis of evidence coming from four pivotal studies: RE-LY (Connolly et al. 2009), ROCKET-AF (Patel et al. 2011), ARISTOTLE (Granger et al. 2011), and ENGAGE AF-TIMI 48 trials (Giugliano et al. 2013). Although post hoc analysis of these trials demonstrated the relative safety and efficacy of DOAC in AF patients undergoing PCI, definite conclusions could not be drawn due to low proportion of patients treated with concomitant antiplatelet therapy; moreover, patients on DAPT were mostly excluded from these studies (Fig. 16.2).

Thus, four large RCTs have been conducted to investigate the safety and efficacy of different DOACs in AF patients undergoing PCI (Table 16.1): PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) (Gibson et al. 2016), RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) (Cannon et al. 2017), AUGUSTUS (An Open-label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention) (Lopes et al. 2019a), and ENTRUST-AF PCI (Edoxaban-based Versus Vitamin K Antagonist-based Antithrombotic Regimen After Successful Coronary Stenting in Patients with Atrial Fibrillation) (Vranckx et al. 2019).

	RE-LY Dabigatran	ROCKET-AF Rivaroxaban	ARISTOTLE Apixaban	ENGAGE AF-TIMI 48 Edoxaban
Concomitant ASA	32%	37%	24%	29%
Concomitant Clopidogrel	2%	<2%	2%	2%
Concomitant DAPT	5%	Excluded	Excluded	Excluded

Fig. 16.2 Antiplatelet therapy in direct oral anticoagulants (DOAC) trials. In DOAC trials, patients receiving $P2Y_{12}$ inhibitors or DAPT are excluded or underrepresented. *ASA* acetylsalicylic acid, *DAPT* dual antiplatelet therapy

Table 16.1 Study design and key outcomes of trials investigating DOAC in atrial fibrillation (AF) patients undergoing percutaneous coronary intervention (PCI)

	PIONEER AF-PCI (Gibson et al. 2016)	RE-DUAL PCI (Cannon et al. 2017)	AUGUSTUS (Lopes et al. 2019b)	ENTRUST-AF PCI (Vranckx et al. 2019)
Year	2016	2017	2019	2019
Design	Open label RCT	Open label RCT	RCT, 2 × 2 factorial design	Open label RCT
Size (no. of patients)	2.124	2.725	4.614	1.506
Time to randomization (days)	≤3	≤5	≤14	≤5
ACS (%)	52	51	61	52
DOAC dose	• Low-dose RIVAROXABAN (15 mg od)	Both doses of DABIGATRAN approved for thromboembolic prevention in AF	APIXABAN 5 mg bid; 2.5 mg bid with ≥2 of the following criteria:	EDOXABAN 60 mg od; 30 mg if one or more factors:
			• Age ≥ 80 years	• Creatinine clearance 15–50 mL/min
	• Very-low-dose RIVAROXABAN (2.5 mg bid)		• Weight ≤ 60 kg	• Body weight ≤ 60 kg
			• Creatinine ≥ 1.5 mg/dL	• Concomitant use of specific potent P-GPI
Comparison	1. Low-dose RIVAROXABAN + $P2Y_{12}i$	1. DABIGATRAN 110 mg + $P2Y_{12}i$	1. APIXABAN + $P2Y_{12}i$ + placebo	1. EDOXABAN + $P2Y_{12}i$
	2. Very-low-dose RIVAROXABAN + DAPT	2. DABIGATRAN 150 mg + $P2Y_{12}i$	2. VKA +$P2Y_{12}i$ + placebo	
	3. VKA + DAPT	3. VKA + DAPT	3. APIXABAN + $P2Y_{12}i$ + ASA	2. VKA + $P2Y_{12}i$ + ASA
			4. VKA + $P2Y_{12}i$ + ASA	
Primary End-point	Major or minor TIMI bleeding or bleeding requiring medical attention	Major or clinically relevant minor bleeding	Major or clinically relevant minor bleeding	Major or clinically relevant non-major bleeding

Duration of DAPT in the triple therapy group	1, 6 or 12 months	1 month after BMS 3 months after DES	6 months	1–12 months
Follow-up duration	12 months	>12 months	6 months	12 months

RCT randomized controlled trial, *ACS* acute coronary syndrome, *VKA* vitamin K antagonist, *P-GPI* P-glycoprotein inhibitors, *od* once daily, *bid* twice daily, *BMS* bare metal stent, *DES* drug-eluted stent; other abbreviations as in Figs. 16.1 and 16.2

PIONEER AF-PCI Trial

PIONEER AF-PCI trial compared three treatment strategies in 2124 anticoagulated patients undergoing PCI: low-dose rivaroxaban (15 mg once daily [od]) plus $P2Y_{12}$ inhibitor (DAT, group 1), very low-dose rivaroxaban (2.5 mg twice daily [bid]) plus DAPT followed by rivaroxaban 15 mg od at the time of $P2Y_{12}$ discontinuation (group 2), and standard triple therapy (VKA plus DAPT, group 3) (Gibson et al. 2016). To put the evidences into perspective, it is important to underline that the dosage in both rivaroxaban regimens is lower than that approved for thromboembolism prevention in AF patients. Moreover, DAPT duration (1, 6, 12 months) was left to clinician's discretion in group 2 and 3, and clopidogrel was chosen in the majority of patients (93%). The primary endpoint, a composite of TIMI major or minor bleeding and bleeding requiring medical attention, was significantly higher at 1-year in the standard TAT arm compared to other two groups, driven by a significant reduction in bleeding requiring medical attention. There were no differences in major adverse cardiovascular events (a composite endpoint of cardiovascular death, MI, or stroke) in line with the results of WOEST and ISAR-TRIPLE trial, even though they were underpowered for efficacy endpoints.

RE-DUAL PCI Trial

RE-DUAL PCI randomized 2725 PCI patients with AF (51% with ACS) to two different DAT regimens (dabigatran 110 mg or 150 mg bid plus clopidogrel or ticagrelor in 12% of patients) *versus* standard TAT (VKA plus DAPT with clopidogrel or ticagrelor) (Cannon et al. 2017). In the TAT arm, aspirin was administered for 1 month in patients who received bare metal stents (BMS) and 3 months for patients with DES. At 14-month follow-up, the rate of major or clinically relevant nonmajor bleeding was lower for patients in DAT arms for either the two regimens compared to TAT group (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 both 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). There were no statistically significant differences in thromboembolic complications between two DAT arms and TAT group. Of note, patients randomized to the 110 mg dabigatran dose had an increased absolute risk (although nonsignificant) of thromboembolic events or death (11.0% versus 8.5%, HR 1.30, 95% CI: 0.98–1.73, $p = 0.07$) and ST (15 versus 8 ST events, HR 1.86, 95% CI: 0.79–4.40, $p = 0.15$) when compared with TAT group.

The results of RE-DUAL PCI trial, as well as PIONEER AF-PCI, support the take-home message arising from WOEST trial, i.e., that DAT is associated to less bleeding events compared to TAT. However, it has not yet been elucidated if the lower bleeding risk is related to use of DOAC (instead of VKA) or to early discontinuation of aspirin.

AUGUSTUS Trial

In the AUGUSTUS trial, 4614 patients (61% with ACS, of whom 24% medically treated) were first randomized (2 × 2 factorial design) to receive apixaban or VKA (first randomization) and, then, randomized again to receive aspirin or placebo

(second randomization) (Lopes et al. 2019a). The study was designed to compare safety of apixaban versus VKA and to assess the effect of aspirin withdrawal. Median time from index event to randomization was 6.6 days. At 6-month follow-up, the results may be summarized as follows: (1) apixaban was associated with lower risk of major or clinically relevant nonmajor bleeding events compared to VKA (HR 0.69; 95% CI: 0.58–0.81; $p < 0.001$); (2) additional aspirin resulted in higher risk of bleeding (HR 1.89; 95% CI: 1.59–2.24; $p < 0.001$); (3) the rate of death or ischemic events did not significantly differ between placebo and aspirin group (HR 1.12; 95% CI: 0.9–1.41). Although definite conclusions on efficacy endpoints could not be drawn, AUGUSTUS trial provide interesting insights into the effect of aspirin removal. It should be noted that in all three previous trials, there is a temporal window to randomization from 3 to 14 days (Table 16.1), during which patients were treated with TAT. Thus, it remains debatable if aspirin could be withdrawn in the early period after PCI, when the risk of coronary events is higher.

ENTRUST-AF PCI Trial

In ENTRUST-AF PCI trial, 1506 AF patients undergoing PCI were randomized to edoxaban 60 mg (or 30 mg according to labeling indications) plus a $P2Y_{12}$ inhibitor for 12 months or VKA in combination with a $P2Y_{12}$ inhibitor and aspirin (100 mg once daily, for 1–12 months) (Vranckx et al. 2019). Time to randomization was up to 5 days (median time 45 h). During 12 months of follow-up, DOAC strategy was found noninferior to VKA regimen with regard to the primary endpoint, a composite of major or clinically relevant nonmajor bleeding (17% versus 20%; HR 0.83; 95% CI: 0.65–1.05). No significant differences were detected in ischemic endpoints between the two strategies, although the study was underpowered to detect significant differences in efficacy outcomes.

Meta-analysis

In order to further explore this relevant issue, Lopes et al. conducted a network meta-analysis involving more than 10,000 patients from four RCTs (WOEST, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS) (Lopes et al. 2019b). They found that DAT (consisting of DOAC and a $P2Y_{12}$ inhibitor) significantly reduced bleeding events (odds ratio 0.49; 95% CI: 0.30–0.82) with a similar rate of ischemic outcomes (odds ratio 1.02; 95% CI: 0.71–1.97).

Another recent meta-analysis pooled aggregate data from four DOAC-based RCTs (PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI), showing that DAT and in particular DOAC instead of VKA is associated with less bleeding events, including minor and intracranial hemorrhages (Gargiulo et al. 2019). However, there was a trend toward increased risk of MI with a statistically significant increase in ST with DAT.

Finally, evidence coming from RCT and meta-analysis provided interesting pathophysiological and clinical implications. First, DOAC use should be preferred over VKA in all AF patients undergoing PCI, since the superior safety profile in terms of bleeding seems to be a class effect. Second, efficacy profile of DAT for ischemic outcomes has been evaluated in all RCTs as secondary endpoint, and a

careful evaluation of study population is essential in order to apply these findings into the appropriate clinical setting. Indeed, in RE-DUAL PCI (Cannon et al. 2017) and AUGUSTUS trial (Lopes et al. 2019a), nearly 60% of patients underwent PCI for stable angina, positive stress test, or were medically managed ACS. So, ischemic outcomes—mainly stent-related—should be interpreted and extrapolated to ACS patients with caution due to the "low-risk" CAD. Of note, only up to 30% of patients included in these studies were female, an additional risk factor for thromboembolism and bleeding. Thus, further studies are warranted to evaluate ischemic outcomes in these particular populations. Third, these findings highlight that a one-size-fits-all strategy cannot be applied, and a tailored approach should guide the complex management of these patients, in terms of timing and composition of antithrombotic treatments. In other words, an individual ischemic and bleeding risk assessment should be formulated prior to initiation or early discontinuation TAT.

Current Recommendations

Current guidelines and consensus documents by European and American expert bodies on antithrombotic management of anticoagulated patients undergoing PCI do not include recent evidences on DOAC (Angiolillo et al. 2018; Neumann et al. 2018). Both guidelines endorse DOAC use over VKA, unless contraindicated. However, North American consensus document recommends TAT only during peri-PCI period, and DAT immediately after hospital discharge should be considered in most patients (Angiolillo et al. 2018).

On the other hand, current 2018 ESC guidelines on myocardial revascularization (Neumann et al. 2018) and recent focus update on DAPT (Valgimigli et al. 2017) recommend TAT for at least 1 month and up to 6 months in patients with high ischemic risk due to ACS or other anatomical and procedural features (Table 16.2) which outweigh the bleeding risk. After this TAT period, dual therapy with OAC and aspirin or clopidogrel is recommended up to 12 months, followed by OAC alone. In patients in whom the bleeding risk outweighs the ischemic risk, dual therapy (clopidogrel and an OAC) is an alternative to 1-month TAT. When a DOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose

Table 16.2 High ischemic risk: anatomical and procedural characteristics

Prior ST on adequate antiplatelet therapy
Stenting of the last patent vessel
Multivessel disease (DM)
CKD
≥3 implanter stent
≥3 treated lesions
2-Stent bifurcation technique
Total stent length > 60 mm
CTO treatment

ST stent thrombosis, *DM* diabetes mellitus, *CKD* chronic kidney disease, *CTO* chronic total occlusion

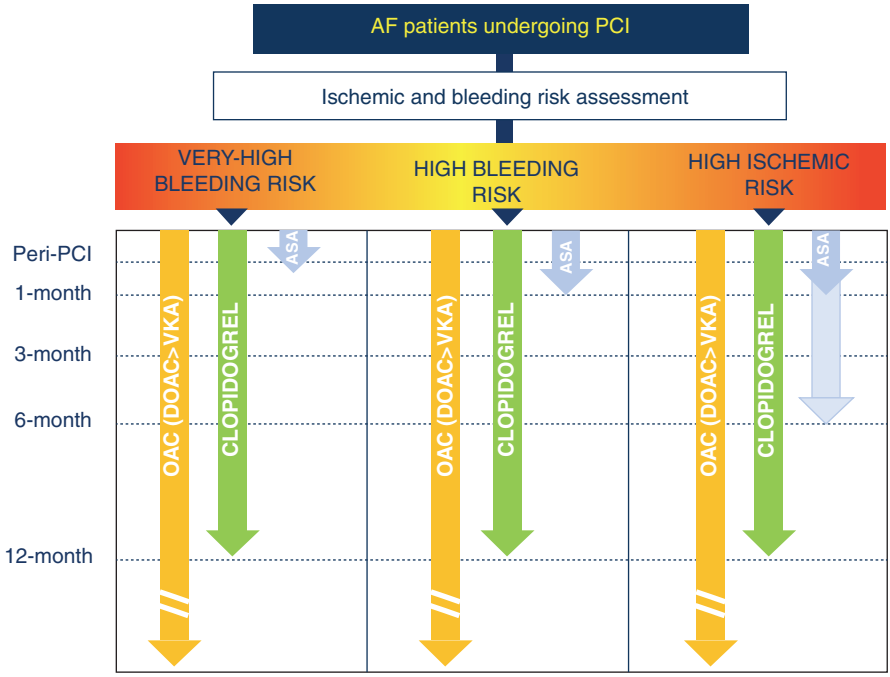

Fig. 16.3 Antithrombotic management of AF patients undergoing PCI, according to European perspective. *OAC* oral anticoagulation, other abbreviations as in Fig. 16.2 and Table 16.1

effective for stroke prevention should be considered. All the above recommendations are class IIa with varying level of evidence. When rivaroxaban is used in combination with aspirin and/or clopidogrel, rivaroxaban 15 mg od may be used instead of rivaroxaban 20 mg od (class IIb, Level of evidence B). Ticagrelor or prasugrel should be avoided as part of TAT because of lack of data and high bleeding risk (class III, level of evidence C) (Sarafoff et al. 2013). Figure 16.3 provides a practical algorithm of antithrombotic management in AF patients undergoing PCI, based on European recommendations.

In summary, European perspective highlights the importance of: (1) keeping TAT duration as short as possible and DAT after PCI should be considered as an option only in very selected patients; (2) ischemic and bleeding risk assessment using validated risk predictors (e.g., CHA_2DS_2-VASc, ABC, and HAS-BLED); (3) considering a target INR in the lower part of the recommended target range when a VKA is used, in order to avoid bleeding complications; (4) using low-dose aspirin; and (5) using routinely proton pomp inhibitors.

Practical Management of AF Patients Undergoing PCI

Procedural and Peri-PCI Management

Nowadays, PCI has become a safe and well-established procedure, with widely adopted use of radial access and very low rates of stent-related complications with contemporary DES, such as ST. Moreover, an appropriate risk and benefit stratification and the increasingly standardized management of OAC in patients undergoing elective or urgent PCI, together with selected use of glycoprotein IIb/IIIa inhibitors only for bailout indications, have contributed to consistent reduction in bleeding events in current clinical practice.

According to guidelines and consensus documents (Neumann et al. 2018; Valgimigli et al. 2017), DAPT duration should be irrespective of stent type, opting for contemporary DES over BMS. However, as mentioned above, the management of aspirin removal represents a major issue. Based on ISAR-TRIPLE trial and other observational studies, many clinically relevant bleeding events occurred during the early period after PCI due to the use of multiple periprocedural antithrombotic medications (Fiedler et al. 2015). All DOAC trials investigating safety of DAT versus TAT randomized AF patients undergoing PCI to an aspirin-free strategy with a time (from index procedure to randomization) of up to 3 days in PIONEER AF-PCI (Gibson et al. 2016), 5 days in RE-DUAL PCI (Cannon et al. 2017) and ENTRUST AF-PCI (Vranckx et al. 2019) trials, and 6 days in AUGUSTUS trial (Lopes et al. 2019a). Consequently, North American guidelines suggest DAT as default strategy (Angiolillo et al. 2018; January et al. 2019), whereas European guidelines recommend DAT (keeping aspirin in the peri-PCI period or until hospital discharge) only for patients at very-high bleeding risk (Neumann et al. 2018).

Choice and Duration of Antithrombotic Therapy After PCI

European and American guidelines strongly recommend preferring DOAC use over VKA, due to the lower bleeding risk. Moreover, in case of VKA use, the dose intensity should be carefully modulated with a target INR in the lower part of the target range aiming for a time in the therapeutic range (TTR)>65–70%. It should be noted that, in the AUGUSTUS trial, median percentage of time of INR <2 was nearly 25% and TTR was only 59% (Lopes et al. 2019a).

When a DOAC is used in TAT regimen, the lowest approved dose effective for stroke prophylaxis should be considered (i.e., dabigatran 110 mg bid, rivaroxaban 15 mg od, according to 2018 ESC guidelines on myocardial revascularization (Neumann et al. 2018)). After antiplatelets discontinuation, OAC should be continued at full dosage approved for stroke prophylaxis.

The duration of TAT should be as short as possible and up to 1 month. Indeed, ISAR-TRIPLE trial showed no significant differences between 6-week and 6-month TAT in anticoagulated patients undergoing PCI in terms of ischemic and bleeding complications. Moreover, a landmark analysis of this study has clearly outlined a

40% reduction of clinically relevant bleeding events in patients randomized to 6-week compared to 6-month group (Fiedler et al. 2015). It has been well established that DAPT is superior to aspirin plus OAC in terms of reduction of ischemic complications for a period of 1-month post-PCI (Leon et al. 1998). On the other hand, recent evidence have demonstrated that adding antiplatelet therapy to OAC increases bleeding events with no added benefit on ischemic protection in stable CAD (Lamberts et al. 2014; Hamon et al. 2014). Accordingly, current guidelines suggest that TAT duration should be up to 1 month, based on individualized bleeding and ischemic risk stratification. Indeed, TAT should be shortened to the peri-PCI period (until hospital discharge) in patients at very-high bleeding risk or prolonged up to 6 months in case of high ischemic risk due to ACS or other anatomical/procedural characteristics that outweigh the bleeding risk (Neumann et al. 2018; Valgimigli et al. 2017).

VKA in Triple Therapy in the DOAC Era: Is There Still Room?

DOAC use should be preferred over VKA in patients treated with TAT. However, there is still room for VKA in selected patients requiring triple therapy; in particular, patients with:

- Moderate to severe mitral stenosis or mechanical prosthetic valves;
- Cancer-associated thromboembolism or other hypercoagulable states (antiphospholipid syndrome, nephrotic syndrome, and congenital coagulopathies);
- Drugs interactions;
- Advanced renal insufficiency, end-stage renal disease, or hepatic dysfunction; and
- High body weight and patients with obesity who undergo bariatric surgery.

Other Interventional Strategies

According to current guidelines, among strategies of bleeding prevention, LAAO may be considered in patients with high stroke risk and contraindications for long-term OAC (class IIb, Level of evidence B) (Kirchhof et al. 2016). Furthermore, several clinical trials are ongoing to evaluate shorter duration of antiplatelet therapy in HBR patients undergoing PCI and will provide further insights into the role of dual antithrombotic therapy in anticoagulated patients.

Conclusions

The optimal management of AF patients following PCI represents a complex clinical scenario, requiring a challenging balance between ischemic and bleeding risk. Recent literature data from large RCT demonstrated the safety of dual (DOAC and

single antiplatelet agent) versus triple antithrombotic therapy. However, the efficacy profile of these strategies for reduction of ischemic events has been evaluated as secondary endpoints and no definite conclusions can be drawn in this regard. Nevertheless, based on current evidence, the protection against ischemic complications offered by TAT seems to be outweighed by an increased bleeding rate, suggesting keeping on TAT as short as possible and for no longer than 6 months (in patients with high ischemic risk). In conclusion, a one-size-fits-all strategy cannot be applied, and an individualized approach should guide the complex management of these patients in a fine balance between ischemic and bleeding complications.

Conflict of Interest The authors have no conflicts of interest to declare.

Disclaimer None.

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Direct Oral Anticoagulants and Left Ventricular Thrombosis: The Evidence for a Good Therapeutic Approach

17

Mauro Massussi, Andrea Scotti, Antonio Landi, and George Besis

Introduction

The formation of thrombus in the left ventricle represents a serious condition leading to significant risk of stroke and systemic embolization. In the thrombolytic era, intraventricular thrombus has been reported in up to 40% of patients after anterior myocardial infarction (Nihoyannopoulos et al. 1989). Along with the improvement of the revascularization technique (primary percutaneous coronary intervention (PCI)) and wide introduction of dual antiplatelet therapy (DAPT), the occurrence of left ventricular thrombosis (LVT) has substantially decreased. However, a prevalence ranging between 4 and 9% after acute myocardial infarction (MI) is still described (Robinson et al. 2016). A marked prevalence of LVT has also been recorded among patients affected by heart failure with reduced ejection fraction. While conspicuous data are available regarding the prevalence of LVT among patients with ischemic cardiomyopathy, only a few have been published regarding nonischemic cardiomyopathies (Zabczyk et al. 2019).

Numerous pathophysiological mechanisms contribute to the genesis of LVT and can be classified among the three components of Virchow's triad: blood stasis, hypercoagulability, and tissue injury. While many of these factors have been well-extensively described, others derive from contradictory studies and need further investigation.

The management of LVT poses unique challenges; though current recommendations indicate anticoagulation as the mainstay treatment, in this specific clinical setting direct oral anticoagulants (DOACs) are not a plausible alternative to warfarin due to the paucity of evidence available, thus more evidence is needed to justify

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their use in clinical practice. The aim of this chapter is to describe the epidemiology and the factors exposing to increased risk of LVT along with a review of the current clinical evidences and the new pharmacological perspectives.

Epidemiology

In clinical practice, the vast majority of left ventricular thrombi are diagnosed after MI. In older series, LVT was described in almost 30% of patients after acute anterior transmural MI (Johannessen et al. 1984; Lamas et al. 1988; Asinger et al. 1981); while in the current era of PCI, there still remains a wide distribution of the prevalence, ranging from 0.4% reported by Ram et al. (2018) up to 26% recorded by Meurin et al. (2015) (Fig. 17.1). These epidemiological observations are mostly explained by patient selection criteria and chosen diagnostic techniques.

LVT in Dilated Cardiomyopathy

Limited evidence are available on the epidemiology of LVT in patients affected by dilated cardiomyopathy; however, according to a recent retrospective investigation by McCarthy and colleagues, heart failure with a reduced ejection fraction is the most common etiology of LVT in the contemporary era (McCarthy et al. 2019). Hypertrophic cardiomyopathy may associate with LVT, especially if apical aneurysm is present. Also, the acute phase of Takotsubo syndrome can be complicated by LVT since apical ballooning is a predisposing condition to thrombi development. Santoro and colleagues reported a 14% rate of LVT in the presence of apical ballooning while a large retrospective observational study on 1676 patients from the International Takotsubo Registry recorded a lower (3.3%) prevalence of left ventricular thrombus and embolism in the acute phase of the disease (Santoro et al.

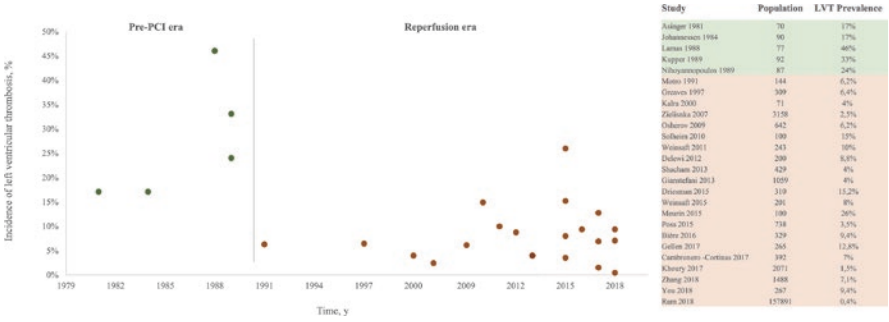

Fig. 17.1 Incidence of left ventricular thrombus after ST-elevation myocardial infarction. On the left side of the graph are reported older studies, accomplished during pre-PCI era while on the right side there are more recent studies

2017). Other phenotypes of Takotsubo syndromes (midventricular and the basal types) are rarely complicated by LVT.

LVT has been sporadically described in the setting of amyloidosis, hypereosinophilic syndrome, and Chagas' disease.

High-Risk Patients

The formation of LVT is mostly influenced by the location and the size of the ischemic injury, and patients with the highest risk are those with anterior-apical MI associated with severe wall motion abnormality (Greaves et al. 1997). There are extensive evidence pointing out that the main risk factors related with LVT after AMI are both the presence of an anterior-apical scar and the reduction of systolic function (Shacham et al. 2013; Gianstefani et al. 2014). According to many authors, LV dysfunction has the strongest impact on LVT formation, and this finding is supported by the LVEF, which is significantly lower in the subgroup of LVT patients. Furthermore, the apex of the left ventricle is largely considered as the region where more likely thrombi occur. The formation of LVT is strongly associated with apical LV dysfunction, thus underlining the role of blood stasis due to regional myocardial dysfunction as an important cause of development of cardiac thrombus (Weinsaft et al. 2016). In addition to the main clinical predictors of LVT, numerous studies have emphasized the impact of mitral regurgitation (MR) on the formation of thrombi within the left heart chambers proposing a protective effect of MR in LVT formation as a consequence of the decreased blood stasis (Kalaria et al. 1998), although clinical results are discordant.

Intriguingly researches have explored the link between CHF and pro-inflammatory and hypercoagulability state (Serebruany et al. 2002).

Diagnostic Modalities

Transthoracic echocardiography (TTE) is widely used to assess post-MI LV function and structure, as well as to exclude early postinfarction mechanical complications. LVT presents as an echo-dense mass distinct from the cardiac muscle, frequently contiguous to an abnormally contracting LV segment or a myocardial aneurysm (Weinsaft et al. 2016) (Fig. 17.2). Based on their appearance, thrombi can be categorized; protuberant thrombi have borders which extrude into LV cavity and may be pedunculated or sessile, while mural thrombi are flat. Protuberant thrombi are often mobile masses, thus they are associated with a higher risk of ischemic stroke.

TTE has reported sensitivity ranging from 21 up to 35% with a specificity greater than 90% (Weinsaft et al. 2011). The major obstacle to LVT detection by TTE is a poor TTE acoustic window.

Transesophageal echocardiography (TEE) is rarely applicable for LVT detection because the left ventricular apex is foreshortened and in the far field. Both TEE and

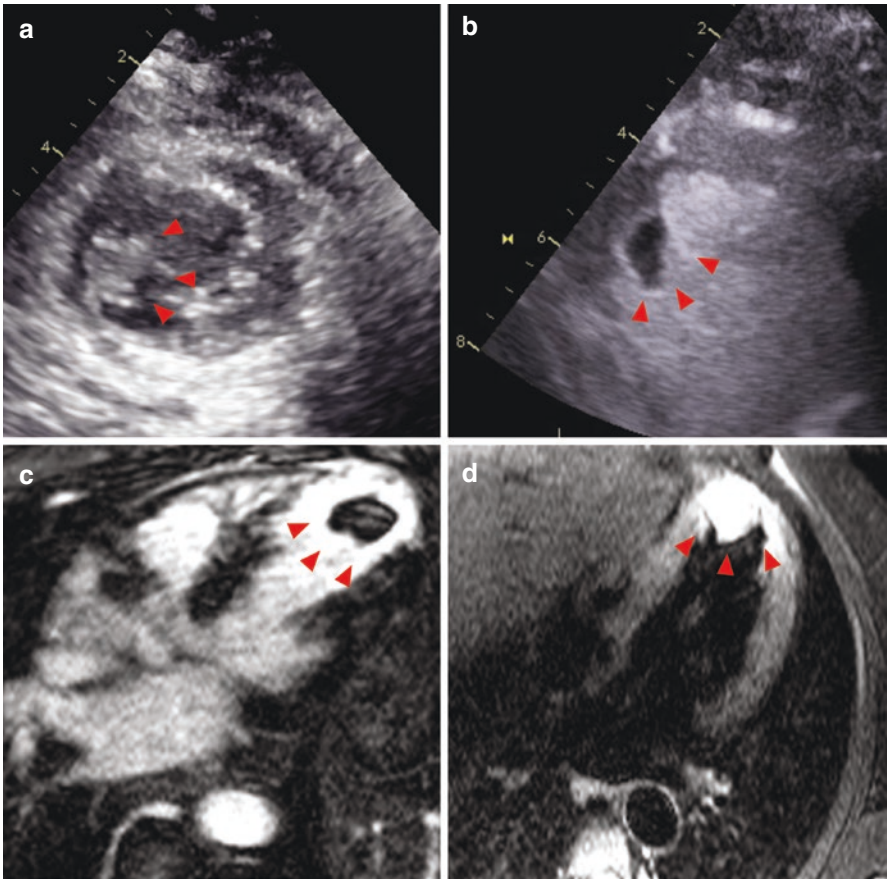

Fig. 17.2 Left ventricular thrombus with different diagnostic tools. Small-size apical LVT appears as an echo-dense mass on transthoracic echocardiography (**a**) and more delineated after intravenous contrast medium (**b**). Cardiac magnetic resonance imaging: LVT on delayed-enhancement image, four-chamber view (**c**), and turbo inversion recovery magnitude (TIRM) sequence of the same view on showing high signal in the apical segments of the left ventricle consistent with myocardial edema and apical thrombus (**d**)

TTE detection rate of LVT correlate with thrombus size, and overall sensitivity may vary according to the thrombus size and to the clinical pretest probability.

If the acoustic window is suboptimal, the addition of intravenous contrast medium improves endocardial border delineation and has a documented higher diagnostic accuracy for LVT (Weinsaft et al. 2016) (Fig. 17.2).

CMR is considered the gold standard imaging modality for assessing the presence, size, and location of intracardiac thrombi. LVT is identified as low-signal intensity intraventricular filling defects, generally sticking to areas of hyper-enhanced LV myocardial scarring (Fig. 17.2).

Treatment Options

LVT provides a substrate for systemic embolism; however, the true incidence of embolic events is still to be unequivocally defined. A recent study, aimed at determining the incidence of systemic embolism linked to LVT, proved that patients had a 3.7% annual for the composite endpoint of transitory ischemic attack, stroke, and systemic arterial embolism over a median follow-up of 3 years, four times higher when compared with matched non-LVT patients (Velangi et al. 2019). Older studies documented a particularly elevated range of embolic risk up to 22%, proving that thrombus mobility and thrombus protrusion were the main risk factors for embolization with a reported sensitivity in predicting embolism of 58% and 88%, respectively (Visser et al. 1985). Of note, studies that included few patients with a relatively short-term follow-up (<12 months) recorded almost no embolic events (Table 17.1).

Prevention of Embolic Events

All decisions regarding anticoagulant therapy in patients at risk of developing LVT must consider the concurrent risk of bleeding, which is a particularly important issue, as many of these patients need to be on DAPT in addition to warfarin therapy. The role of prophylactic anticoagulation for patients without a definite LVT is still unclear. The 2012 ESC guidelines for the management of ST-elevation AMI suggested that anticoagulant therapy will also be of benefit to those at high risk for LVT and low bleeding risk, defined as patients with an LVEF less than 30% or a severe anteroapical wall motion abnormality with apical aneurysm (Steg et al. 2012). It is worth to note that the abovementioned recommendation is based on relatively old trials and is not supported by more recent data (Turpie et al. 1989). Results from observational retrospective studies do not favor the prophylactic OAC with warfarin after primary PCI for patients with anteroapical akinesia (Le May et al. 2015;

Table 17.1 Embolic events rate in published studies of LV thrombus detected by late gadolinium enhancement CMR

	Patients with LVT, *n*	Follow-up, years	Embolic events, *n*	Annualized rate of embolism (%)
Weinsaft et al.	55	0.5	3	–
Weir et al.	15	0.5	0	–
Meurin et al.	19	0.7	1	–
Delewi et al.	17	2	0	–
Poss et al.	26	1	1	3.8
Cambronero-Cortinas et al.	27	3.5	0	–
Merkel et al.	33	In-hospital	3	–
Velangi et al.	155	3.3	19	3.7
Robinson et al.	514	0.9	54	10.9

CMR cardiac magnetic resonance, *LVT* left ventricular thrombosis

Shavadia et al. 2017). Also, the COMMANDER-HF trial failed to demonstrate the benefit of low-dose oral anticoagulation in patients with severe HF in sinus rhythm, but a post hoc analysis of the same trial with an outcome measure more specific for thromboembolic events supported the hypothesis that low-dose rivaroxaban may reduce the risk of myocardial infarction, ischemic stroke, sudden death, and symptomatic pulmonary embolism/deep vein thrombosis (Greenberg et al. 2019).

The introduction of potent platelet $P2Y_{12}$ receptor inhibitors in clinical practice may have contributed to a reduction of LVT incidence after AMI, as suggested by a retrospective analysis comparing ticagrelor to clopidogrel (Altıntaş et al. 2019). Despite being biologically plausible, there is no trial in literature confirming that DAPT plays a protective role against the formation of LVT and subsequent embolization, thus antiplatelet therapy cannot be considered as a substitute for anticoagulation to prevent embolization of LV thrombus.

Treatment of Definite LVT

Current International Guidelines

International guidelines agreed on recommend anticoagulation therapy for patient affected by definite LVT. The 2013 guidelines by the American Heart Association (ACCF/AHA) and the 2017 ESC guidelines both suggested oral anticoagulation with vitamin K antagonists as a first-line therapy (O'Gara et al. 2012; Ibanez et al. 2018). The AHA/American Stroke Association 2014 guidelines on stroke prevention considered DOACs (dabigatran, rivaroxaban, or apixaban) as an alternative to warfarin for post-MI LVT in case of vitamin K antagonists intolerance (Class IIb; Level of Evidence: C) (Kernan et al. 2014).

Surprisingly, the vast majority of the studies cited by guidelines are dated from the era before the routine introduction of DOACs in clinical practice, thus emphasizing only on the efficacy of parenteral therapy with heparin for the treatment of LVT patients with high embolic risk (Kernan et al. 2014). Early studies found that parenteral anticoagulation with heparin, continued for more than 48 h, was effective in preventing systemic embolization (Vaitkus and Barnathan 1993). However, given the fact that oral warfarin therapy in appropriate patients is likely to be as effective and more practical than anticoagulation with heparin, prolonged parenteral therapy is seldom recommended. There are actually no studies that have evaluated the optimal timing of parenteral anticoagulation in patients being started on warfarin, the consensus is that oral anticoagulation therapy should start as soon a definite LVT is identified, and parenteral anticoagulation therapy should be discontinued when effective anticoagulation with warfarin has been achieved (INR of 2–3) (Massussi et al. 2021). Since most events occur within the first 3–4 months, patients with documented LVT should undergo anticoagulant therapy with warfarin starting early after myocardial infarction for at least 3 months to lower the risk of thrombus formation and embolization.

It is well-known that triple antithrombotic therapy with warfarin is associated with an increased risk of bleeding, and the result of landmark approval trials

enrolling patients affected by AF confirmed that all DOACs are superior to warfarin in terms of safety and are not inferior in terms of effectiveness. All the studies evaluating triple therapy with warfarin reported an increased elevated rate of clinically significant bleeding (major bleedings and clinically relevant nonmajor bleedings). Even though contemporary trials evaluating triple vs. double antithrombotic regimens (RE-DUAL PCI (Cannon et al. 2017), PIONEER AF (Gibson et al. 2016), AUGUSTUS (Lopes et al. 2019), and ENTRUST AF PCI (Vranckx et al. 2019)) were not powered to definitively assess these ischemic efficacy endpoints, since it would require much larger samples followed for prolonged duration, double therapy was associated with similar rates of composite thromboembolic events (unplanned revascularization, MI/stent thrombosis, and death) compared with triple therapy.

Direct Oral Anticoagulants

Limited data are available on the use of DOACs to replace warfarin in patients with LVT, and high-quality large prospective studies or randomized trials are missing. Two reviews of published case reports of 36 and 41 patients treated with different molecules confirmed thrombus resolution in almost all the subjects with a median treatment duration of 30 days and with no embolic events reported (Leow et al. 2018; Kajy et al. 2019). Recently, the results of three retrospective studies on the topic were published (Fleddermann et al. 2019; Lattuca et al. 2020; Robinson et al. 2020). Despite not being designed for a direct comparison between VKA and DOACs, the analysis by Lattuca and colleagues on 159 patients with LVT suggested a similar rate of LVT resolution with both anticoagulant strategies (Lattuca et al. 2020). A recent multicentric retrospective investigation by Robinson and colleagues on the risk of stroke and systemic embolism (SSE) with different anticoagulation regimens evidencing that VKA therapy was associated with a lower SSE risk compared to DOACs treatment (Robinson et al. 2020). Only prospective randomized trials could provide more lights on the equivalence of DOACs and warfarin for the treatment of LVT.

Conflict of Interest The authors have no conflicts of interest to declare.

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