Direct Oral Anticoagulants

From Pharmacology to Clinical Practice

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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

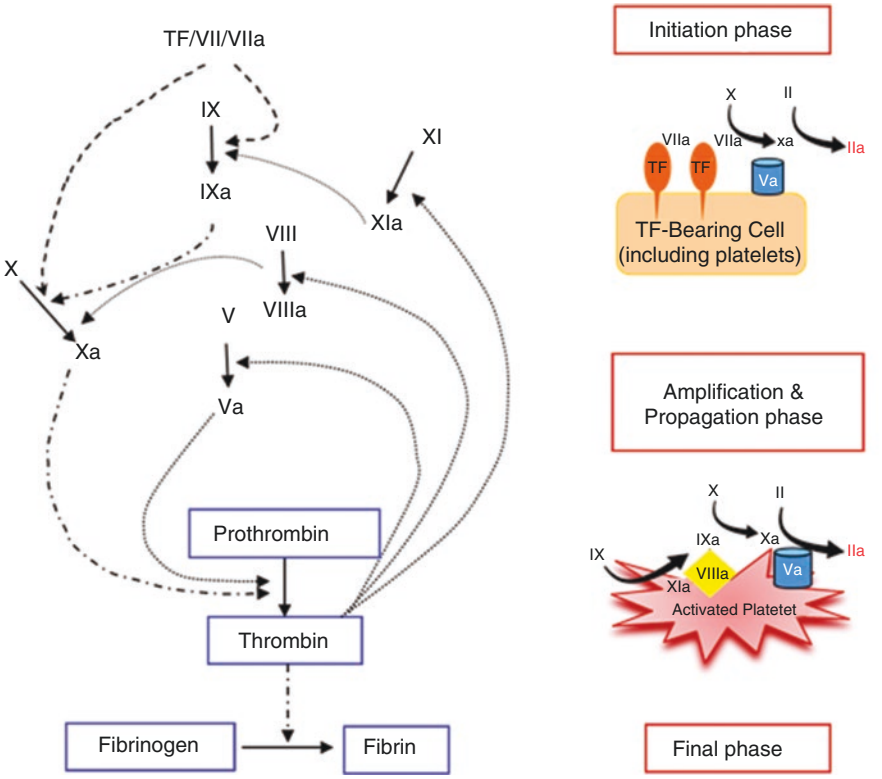

Fig. 1.1 The cell-based model of the blood coagulation cascade

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

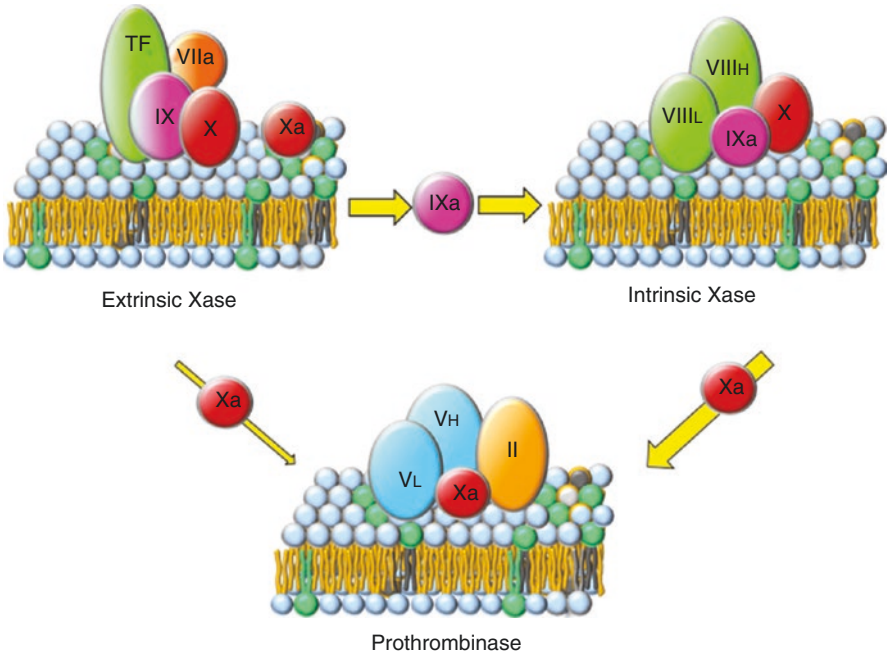

Fig. 1.2 FXa generation through the extrinsic and intrinsic Xase complexes organized on a phosphatidylserine expressing (green phospholipids) plasma membrane. The catalytic efficiency of the intrinsic Xase complex is highlighted by the thicker arrow. FXa assembled into the prothrombinase complex leads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

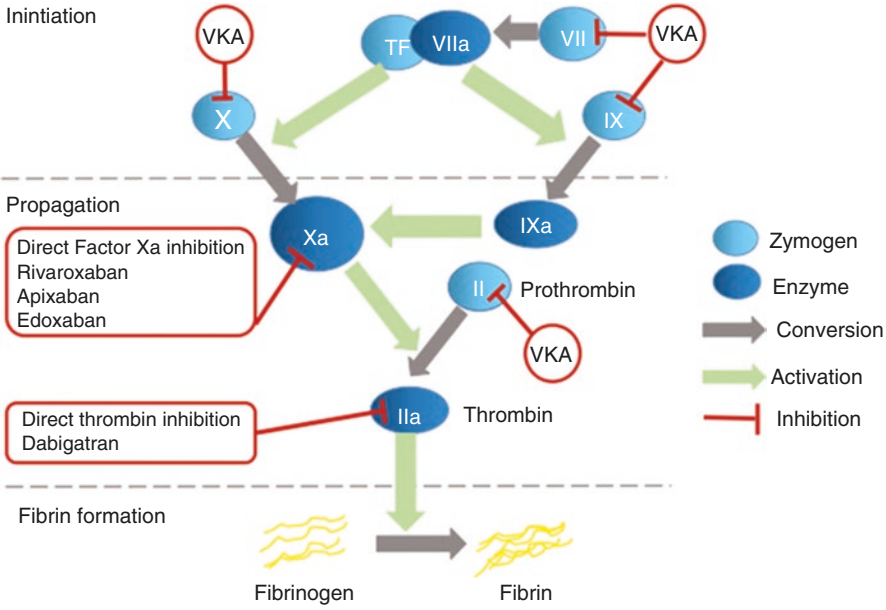

Fig. 1.3 The cell-based model of the blood coagulation cascade and targets of the oral anticoagulant drugs. Targets of direct oral anticoagulant as well as of Vitamin K Antagonists (VKA) are shown

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

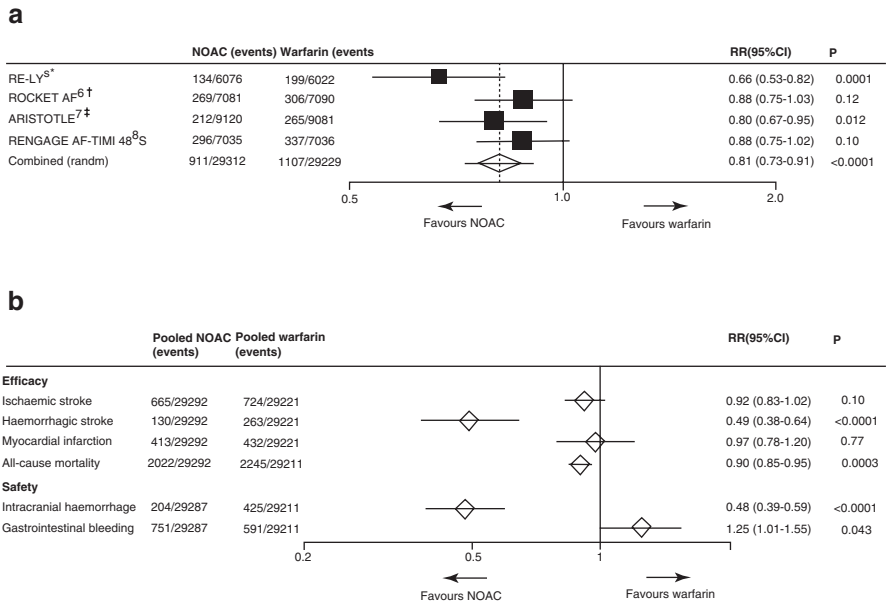

Fig. 2.1 (**a**) Pooled analysis of the landmark clinical trials of atrial fibrillation comparing the incidence of stroke and systemic embolism between those receiving direct oral anticoagulants and those receiving warfarin. (**b**) Combined data from the landmark trials across individual efficacy and 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

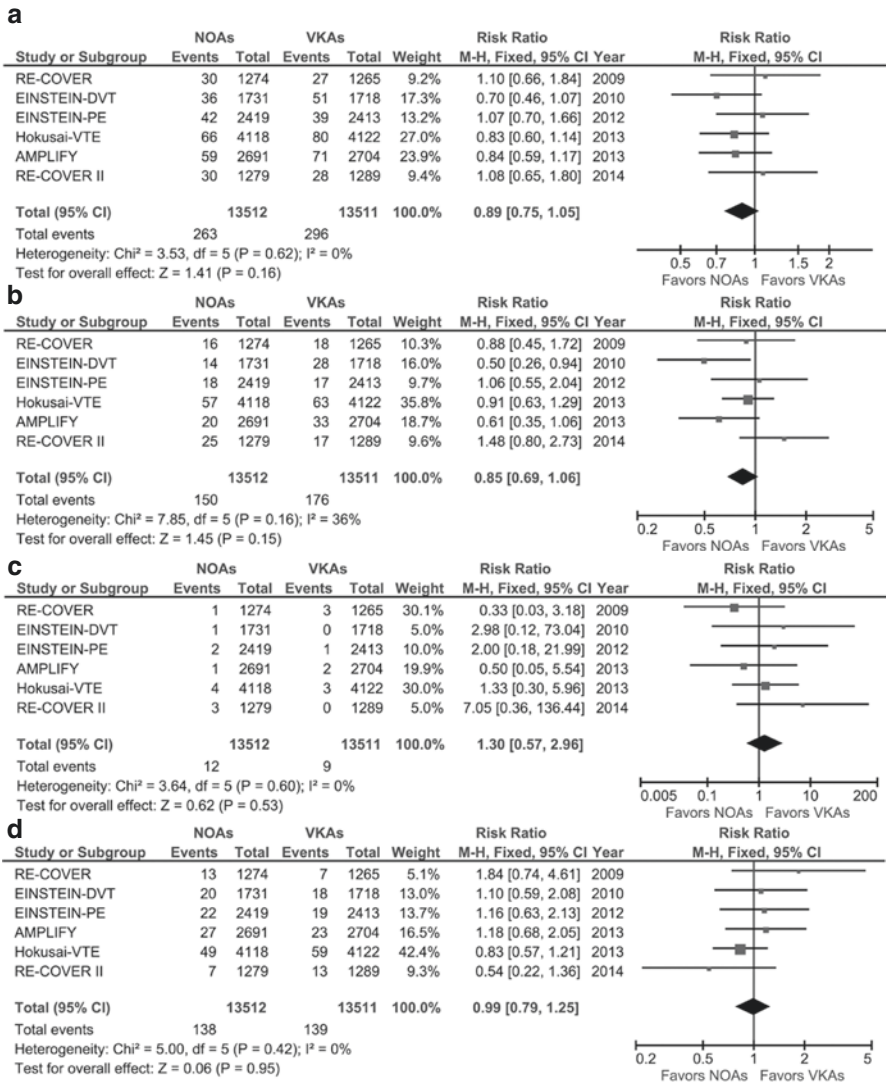

Fig. 2.2 Pooled analysis of the landmark trials comparing direct acting oral anticoagulants and warfarin in patients with venous thromboembolism. (**a**) recurrent venous thromboembolism; (**b**) deep venous thrombosis; (**c**) fatal pulmonary embolism; (**d**) nonfatal pulmonary embolism. (Used with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