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WHITE PAPER

Non–Vitamin K Antagonist Oral Anticoagulants for Mechanical Heart Valves

Is the Door Still Open?

ABSTRACT: The estimated prevalence of mitral or aortic valvular heart disease is ≈2.5% in the general population of Western countries, and is expected to rise with population aging. A substantial proportion of patients with valvular heart disease undergoes surgical valve replacement. Mechanical heart valves are much more durable than bioprostheses, and are thus preferentially implanted in patients with a longer life expectancy, but have the major drawback of requiring lifelong anticoagulation to prevent valve thrombosis because of their higher thrombogenicity. The non–vitamin K antagonist oral anticoagulants (NOACs) are replacing vitamin K antagonists in many settings, including bioprostheses, because of their favorable safety and efficacy profiles. However, mechanical heart valves currently pose an absolute contraindication to NOACs based on the results of a single phase II study comparing dabigatran and warfarin (RE-ALIGN [Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement]). That trial was stopped prematurely because of an excess of both stroke and bleeding with the dabigatran doses tested. Because of such negative findings, research in this area has been halted. We believe that several aspects of both the preclinical studies and the RE-ALIGN trial should be critically reevaluated. In our opinion, 1 single trial with a single NOAC does not represent sufficient evidence for dismissing a therapeutic strategy, anticoagulation with NOACs, that has shown better safety and at least similar efficacy as warfarin in the setting of atrial fibrillation and venous thromboembolism,. Herein, we reevaluate this topic to identify the patient profile that has the greatest likelihood of benefit from some of the NOACs, with a focus on factor Xa inhibitors, thus providing some perspectives for basic and translational research.

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Antithrombotic management of patients with mechanical heart valves (MHVs) continues to be an important medical problem. The estimated prevalence of mitral or aortic valvular heart disease is ≈2.5% in the general population of the United States and Europe, and exceeds 10% in subjects >75 years of age.[1,2] Furthermore, in a recent UK community study, more than half of patients referred to echocardiography for suspected heart failure had at least a mild valvulopathy, 3% of them having a severe disease.[3]

MHVs currently all consist of bileaflet structures mounted on Teflon- or Dacron-covered sewing rings.[4,5] These valves are more durable than bioprostheses,[6] and are thus preferentially implanted in patients with a long life expectancy.[7,8] However, MHVs are much more thrombogenic than bioprostheses, requiring lifelong anticoagulation to avoid subclinical thrombosis[9] and thromboembolic complications. At present, this is achieved with the vitamin K antagonists (VKAs: warfarin, acenocoumarol, phenprocoumon, and phenindione), which are certainly more effective than antiplatelet agents in preventing valve thrombosis and embolization, although thromboembolic events with VKAs still occur at a rate of 1 to 2 per 100 patient-years, and major bleeding still occurs at a rate of 1.4 per 100 patient-years.[10] Well-known drawbacks of the VKAs are interactions with several foods and drugs, and the need for lifelong monitoring through the international normalized ratio (INR).[11] Furthermore, the time in therapeutic range impacts the safety and efficacy of VKA therapy,[12,13] but achieving an optimal time in therapeutic range, above a threshold of 70%, requires "diligence, skill and various therapeutic strategies."[13] This is even more challenging when the target INR exceeds the usual 2 to 3 range most commonly recommended for stroke prevention in atrial fibrillation or for venous thromboembolism.

The well-known limitations of VKAs have prompted the widespread acceptance of non–vitamin K antagonist oral anticoagulants (NOACs). These drugs include dabigatran, which selectively inhibits thrombin, and rivaroxaban, apixaban, edoxaban, and betrixaban, which block factor (F) Xa activity.[14] NOACs can be safely administered in patients with atrial fibrillation, which coexist with most forms of native valvular heart disease. Indeed, a meta-analysis of clinical trials of patients with atrial fibrillation randomly assigned to NOACs or warfarin, the former reduced stroke or systemic embolic events by 19% in comparison with warfarin, mainly because of a 51% reduction in hemorrhagic stroke, with a strong trend toward overall better safety in terms of major bleeding.[15] NOACs also significantly reduced all-cause mortality by 10% and intracranial hemorrhage by 52%.[15] Other well-known advantages of the NOACs include the fact that they do not require coagulation monitoring, and they have much fewer interactions with drugs and foods than VKAs.

NOACs have also been used in a discrete number of patients with bioprostheses >3 months postimplantation. Although dedicated analyses have been performed only for apixaban[16] and edoxaban,[17] it appears reasonable to use NOACs in patients with bioprostheses after 3 months from implantation, although no data are available on the outcomes of earlier treatment.

All NOACs are currently contraindicated, and thus share a black-box warning, in all patients with MHVs.[7,8,11] This is because of evidence for harm from dabigatran in the RE-ALIGN trial (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement).[18] Does 1 single negative trial with 1 single drug provide sufficient evidence for totally dismissing the possibility of using NOACs, a therapeutic strategy that in the settings of atrial fibrillation and venous thromboembolism has shown better safety and similar or better efficacy than warfarin?[15,19] Probably not. Herein, we will then reevaluate the issue of anticoagulation, and more broadly antithrombotic therapy, for the prevention of thromboembolism in patients with MHVs.

THE PROBLEM: THROMBOEMBOLIC EVENTS IN PATIENTS WITH MHVS

The reported rates of prosthetic valve thrombosis are highly variable, and likely underestimate its true incidence because valve imaging is not performed routinely and may have suboptimal quality.[4] Furthermore, a distinction should be made between the accumulation of small amounts of mural thrombus on the leaflets early after in vivo implantation, which may resolve with the ensuing endothelization, and the progressive leaflet thrombosis, eventually affecting valve hemodynamics.[4] In any case, prosthetic valve thrombosis commonly occurs within months from surgery, and the risk with MHVs is much higher than with bioprostheses.[20,21] The rate of thrombosis on MHVs ranges from 0.1% to 5.7% per year, and is higher with specific valve types, in the early perioperative period, when valves are implanted in the mitral and tricuspid positions, and in association with subtherapeutic anticoagulation.[20] The annual incidence of MHV obstruction ranges from 0.5% to 6.0%.[20] Thromboembolic events in treated populations have an estimated annual incidence of 2.5% to 3.7%.[20]

THE SOLUTION: ANTICOAGULANTS

International guidelines for the management of valvular heart disease recommend lifelong anticoagulation

with VKAs for all patients with MHVs: recommendations are class I, level of evidence A in the latest American Heart Association/American College of Cardiology guidelines[7]; class I, level of evidence B in the European Society of Cardiology guidelines[8]; and class I, level of evidence B in the American College of Chest Physicians guidelines.[11] VKAs block the carboxylation of 4 coagulation proteins, namely FII (prothrombin), FVII, FIX, and FX. The dosage required for optimal anticoagulation displays individual variations according to the diet, drug interactions, disease processes, and gene polymorphisms affecting VKA metabolism.[22] The carboxylation of vitamin K–dependent factors is not blocked to the same speed and to the same extent at the beginning of therapy, and there is considerable interindividual variation in plasma levels of active, carboxylated factors, at any given INR.[23,24] Furthermore, changes in dietary vitamin K intake, poor compliance, drug interactions, or impaired absorption because of gastrointestinal disturbances all increase the intra- and interpatient variability in efficacy.[22–24] For all these reasons, the INR is often unstable, which is a major determinant of thromboembolic or bleeding events,[25] and reduced survival after MHV implantation, as well.[26] Finally, even when the INR remains in the normal range, thromboembolic complications may still occur because of the many different pathogenetic mechanisms involved in thromboembolism after valve surgery.[27]

ATTEMPTS AT USING NOACS WITH PROSTHETIC HEART VALVES

Preclinical Studies: NOACs as a Possible Alternative to VKAs

During early development of the NOACs, their efficacy in preventing thrombosis on MHVs was evaluated in preclinical studies. With a single exception,[28] the only drug with published data is dabigatran, mostly because dabigatran was the earliest drug of this class to approach clinical use.[29]

In an in vitro study, St. Jude Medical 27-mm MHV prostheses were exposed to whole blood anticoagulated with dabigatran, unfractionated heparin (UFH), or low-molecular-weight heparin (LMWH) in a thrombosis tester under pulsatile circulation.[30] In this model, dabigatran proved as effective as both UFH and LMWH in preventing thrombus formation.[30] However, analyses of coagulation parameters revealed that "the lower dabigatran dose (500 nmol/L) did not produce therapeutic anticoagulation conditions."[30] Concentrations of 500 nmol/L (235.8 ng/mL) are almost 5-fold higher than trough dabigatran levels measured in RE-ALIGN (see below), and dabigatran concentrations proven effective in this in vitro study, 1000 nmol/L, are almost 10-fold higher.

Further studies assessed animal models, which were in all cases swine models (Table). In a study, 19 pigs underwent mitral valve replacement with a mechanical valve (27-mm Carbomedics OptiForm).[31] The experimental group consisted of 11 animals receiving dabigatran (20 mg/kg orally twice daily), whereas the 2 control groups consisted of 3 animals receiving no anticoagulation and 5 animals receiving warfarin (1–5 mg once daily, adjusted to maintain an INR from 2.0 to 2.5).[31] Animals on dabigatran had a longer survival (average, 50.3 days) than both control groups (18.7 and 15.6 days for the no anticoagulation and warfarin groups, respectively; P=0.017).[31] Hemorrhagic complications were present in 40% of the warfarin group and 27% of the dabigatran group.[31] The small and heterogeneous sizes of treatment groups may be considered limitations of this study. Furthermore, the warfarin regimen closely recapitulated treatment of human patients,[31] but the animals received 20 mg/kg twice daily of dabigatran, as opposed to the ≈2.1 mg/kg twice daily used for atrial fibrillation at the higher approved dabigatran dose (150 mg twice daily). In another study, 30 swine underwent implantation of a bileaflet mechanical valved conduit (St Jude Masters Series; St Jude Medical) bypassing the ligated, native descending thoracic aorta, a condition mimicking aortic valve replacement.[32] The animals were randomly assigned to no anticoagulation (n=10), the LMWH enoxaparin 2 mg/kg subcutaneously twice daily (n=10), or dabigatran 20 mg/kg orally twice daily. At 30 days, the mean thrombus weight was 638 mg in the no anticoagulation group, 121 mg in the enoxaparin group, and 19 mg in the dabigatran group (P=0.01 enoxaparin versus dabigatran).[32] No major or occult hemorrhagic events were reported.[32] These findings reinforced the rationale of dabigatran use in a clinical trial, but, again, dabigatran was here administered at very high doses (also in comparison with the enoxaparin doses used). Indeed, the animals were exposed to a dabigatran dose that, in a human weighing 70 kg, would correspond, assuming similar intestinal absorption and interspecies ratios of distribution volumes between the intra- and extravascular compartments, to 1400 mg twice daily.

Only 1 study evaluated rivaroxaban, which appeared to be more effective than enoxaparin in preventing MHV thrombosis.[28] Thirty swine were here implanted with a mechanical valved conduit bypassing the ligated descending aorta. The animals were randomy assigned to no anticoagulation (n = 10), enoxaparin at 2 mg/kg subcutaneously twice daily (n = 10), or rivaroxaban at 2 mg/kg orally twice daily (n=10). Mean thrombus weight at day 30 was 760 mg in animals receiving no anticoagulation, 717 mg in those on enoxaparin, and 210 mg in those on rivaroxaban (P=0.05 for enoxaparin versus rivaroxaban).[28] Again, the NOAC dose administered to

Table. **Non–Vitamin K Antagonist Oral Anticoagulants for Mechanical Heart Valves in Animal Studies**

Reference	Setting	Treatment Groups	Non–Vitamin K Antagonist Oral Anticoagulant (Dose)	Results: Efficacy	Results: Safety	Animal Dose/ Full Human Dose
Schomburg et al, 2012[31]	Swine, Mitral valve replacement	No anticoagulation Warfarin Dabigatran	Dabigatran (20 mg/kg twice daily)	Survival: 50.3 days dabigatran, 18.7 days no anticoagulation, 15.6 days warfarin (*P*=0.017)	Hemorrhagic complications: 40% warfarin, 27% dabigatran	9.3
McKellar et al, 2011[32]	Swine, Mechanical valved conduit	No anticoagulation Enoxaparin Dabigatran	Dabigatran (20 mg/kg twice daily)	Mean thrombus weight: 638 mg no anticoagulation, 121 mg enoxaparin, 19 mg dabigatran (*P*=0.01 enoxaparin vs dabigatran)	No major or occult hemorrhagic or embolic events in any groups	9.3
				Platelets deposited: 2.7×108 dabigatran, 1.8×109 enoxaparin (*P*=0.03)		
Greiten et al, 2014[28]	Swine, Mechanical valved conduit	No anticoagulation Enoxaparin Rivaroxaban	Rivaroxaban (2 mg/kg twice daily)	Mean thrombus weight: no anticoagulation 638 mg, enoxaparin 121 mg, dabigatran 19 mg (*P*=0.01 for enoxaparin vs dabigatran)	No hemorrhagic or thrombotic complications in any groups	13.8
				Platelets deposited: 6.13×109 rivaroxaban, 3.03×1010 enoxaparin (*P*=0.03)		

The full human doses are 150 mg twice daily for dabigatran, and 20 mg once per day for rivaroxaban; a 70 kg body weight is considered.

the animals was markedly higher than a full dose tested in humans (as much as 13.8-fold higher; Table).

In all these studies, dose selection relied on current knowledge of interspecies differences in the coagulation profile, as well as the pharmacokinetics and pharmacodynamics of NOACs in swine. Doses selected for the swine models aimed to compensate for significant differences between pigs and humans. Indeed, porcine blood is more coagulable than human blood, with prominent activation of the intrinsic coagulation pathway. For this reason, "the direct application of results obtained from a swine model in the therapy of human diseases may lead to serious disturbances of clotting and fibrinolytic processes, including thromboembolic risk, posing a direct threat to the health or even the life of the patient".[35] Furthermore, dabigatran has a lower affinity for porcine thrombin than for human thrombin, and the half-life of dabigatran in swine is around 5 hours, compared with 11-13 hours in human patients (J. van Ryn, MD, personal communication, 2018). Finally, it may also be noted that in 2 studies,[28,32] the valve was placed in a nonphysiological position, ie, in a conduit bypassing the ligated descending aorta, posing further challenges to the translation of these findings to the human setting. Overall, the difficulty in faithfully reproducing the human phenotype in animals limits the possibility to translate results in the clinical setting, as demonstrated by the sharp contrast between the positive results of animal studies30-32 and the premature discontinuation of the RE-ALIGN trial.[18]

Only Human Study: RE-ALIGN: Dabigatran Is Not an Alternative to VKAs

A phase 2 dose-validation study, RE-ALIGN, was then started in 2011 to compare dabigatran with warfarin.[18] The design and main results of this study are reported in Figure 1. The study population included patients undergoing implantation of a mechanical bileaflet valve in the aortic or mitral position or both (population A), or implanted with a mechanical bileaflet mitral valve (with or without mechanical aortic valve replacement) >3 months before (population B). The patients were randomly assigned in a 2:1 ratio to either dabigatran or warfarin. Exclusion criteria included uncontrolled hypertension, a high risk for bleeding, severe renal impairment, or active liver disease. The initial dabigatran dose was selected based on kidney function (150 mg twice daily for a creatinine clearance <70 mL/min; 220 mg twice daily for 70–109 mL/min; and 300 mg twice daily for a creatinine clearance ≥110 mL/min). Doses were then adjusted after dabigatran dosing: if a patient was found to have a level <50 ng/mL during the first 1 to 2 weeks of treatment, the dose of dabigatran was increased to the next higher dose. The 50 ng/mL value was deemed desirable to prevent valve thrombosis based on pharmacokinetic models. The warfarin dose was adjusted to obtain an INR of 2 to 3 (patients with no additional risk factors) or 2.5 to 3.5 (patients with additional risk factors or a mechanical mitral valve).[18]

The trial was discontinued after the enrollment of 252 patients (199 in population A and 53 in popu-

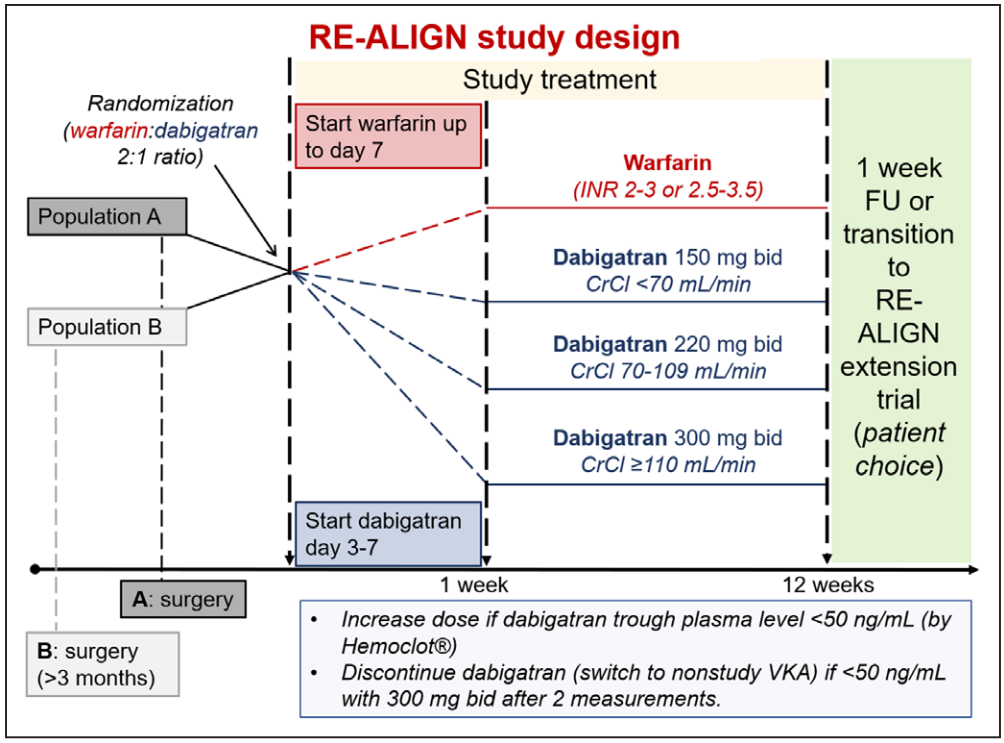

Figure 1. Design and main results of the RE-ALIGN trial (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetic of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement).

The patient numbers for treatment allocation refer to study group assignment. Population A included patients receiving a mechanical heart valve (MHV) in the mitral and aortic position from ≤7 days, whereas patients in population B underwent implantation of a MHV in the mitral position (and possibly also in the aortic position) from >3 months. Mean treatment duration in each study arm is reported. The main outcome measures are provided. The difference in treatment outcomes is much more prominent in population A than in population B, although no formal comparison could be performed. bid indicates twice daily; FU, follow-up; INR, international normalized ratio; and VKA, vitamin K antagonist. Derived from Eikelboom et al.[18]

lation B) because of an excess of both thromboembolic and bleeding events among patients receiving dabigatran. In detail, over a mean follow-up lasting ≈140 days, ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and in no patients in the warfarin group. Major bleeding (with a pericardial location in all cases) occurred in 7 patients (4%) and 2 patients (2%), respectively. It is noteworthy that, in the group that had recently undergone surgery (population A), the majority of thromboem-

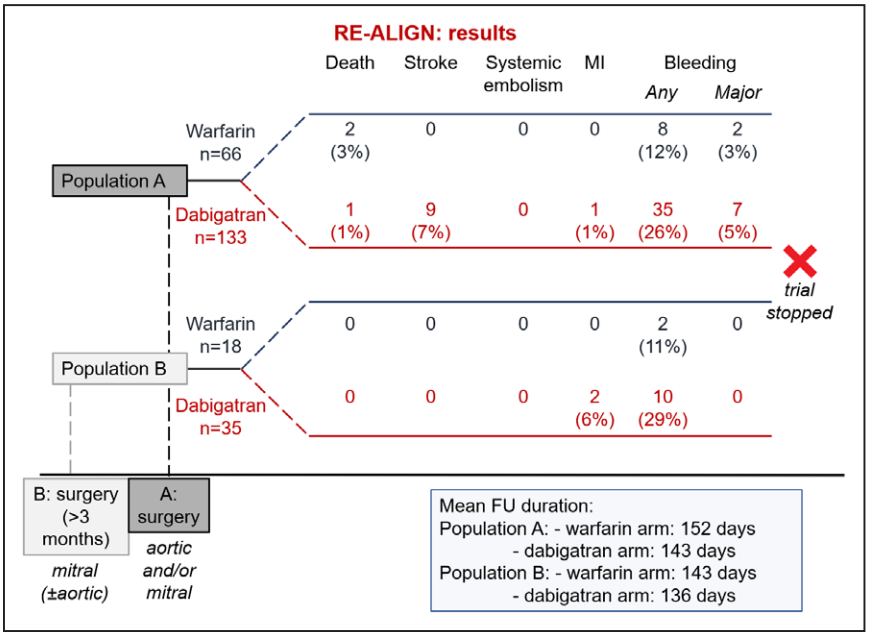

Figure 2. Timing of mechanical heart valve implantation and outcome in the RE-ALIGN trial.

FU indicates follow-up. Derived fom Eikelboom et al.[18]

bolic events occurred within the first 90 days. Furthermore, the differences between the dabigatran and warfarin groups were less prominent in population B; most notably, no patient in either group experienced death, stroke, systemic embolism, or major bleeding, suggesting limited differences between dabigatran and warfarin after 3 months from implantation of a mechanical mitral valve (Figure 2).[18]

These negative findings prompted an intense debate and were variably ascribed to drug-related factors or limitations in study design.[36] For example, it was pointed out that dabigatran is a competitive, reversible inhibitor of a single coagulation factor, with a short half-life and hourly variations in the degree of anticoagulation.[37] Dabigatran also provides a much lower incidence of supratherapeutic anticoagulation than warfarin, and may increase coagulation factor activity during long-term use. Dabigatran excretion is also critically dependent on renal function, which changes over time.[38] In addition, circulating dabigatran levels, as measured in RE-ALIGN, are not tightly associated with the degree of anticoagulation.[39] It has also been noted that the use of antiplatelet therapy in the RE-ALIGN trial was low, although at least 70% of patients had intermediate or high thromboembolic risk,[40] and there was no detailed comparison between patients experiencing complications or not.[41]

Despite the many questions raised by RE-ALIGN, research on this topic stopped completely. A better understanding of thrombosis on MHVs may allow identifying a setting in which NOAC therapy has the greatest likelihood of providing a valuable alternative to VKAs to inform further basic and translational studies.

MECHANISMS OF THROMBOSIS ON MHVS

Surface-Related Factors

Artificial surfaces promote thrombosis through a series of interconnected processes.[42,43] Rapid absorption of plasma proteins seems to occur first, promoting platelet adhesion and activation.[44] Thrombin generation on valve surfaces is attenuated by a FXIIa inhibitor, and reduced in FXII-deficient plasma.[45] This outlines the crucial role of the activation by artificial surfaces, the Dacron and Teflon sewing ring being even more thrombogenic than metal leaflets.[45] Negatively charged and hydrophilic surfaces appear to be powerful promoting stimuli, and activated platelets support the activation of the intrinsic coagulation pathway.[46] This pathway leads to the production of FXa, which activates prothrombin; thrombin then promotes its own generation and platelet aggregation, as well. Finally, thrombin converts fibrinogen into fibrin monomers, which then polymerize into fibrin strands that stabilize platelet aggregates.[47] FXIIa also induces complement activation, which amplifies thrombin generation through a crosstalk between the complement and coagulation pathways.[43] In addi-

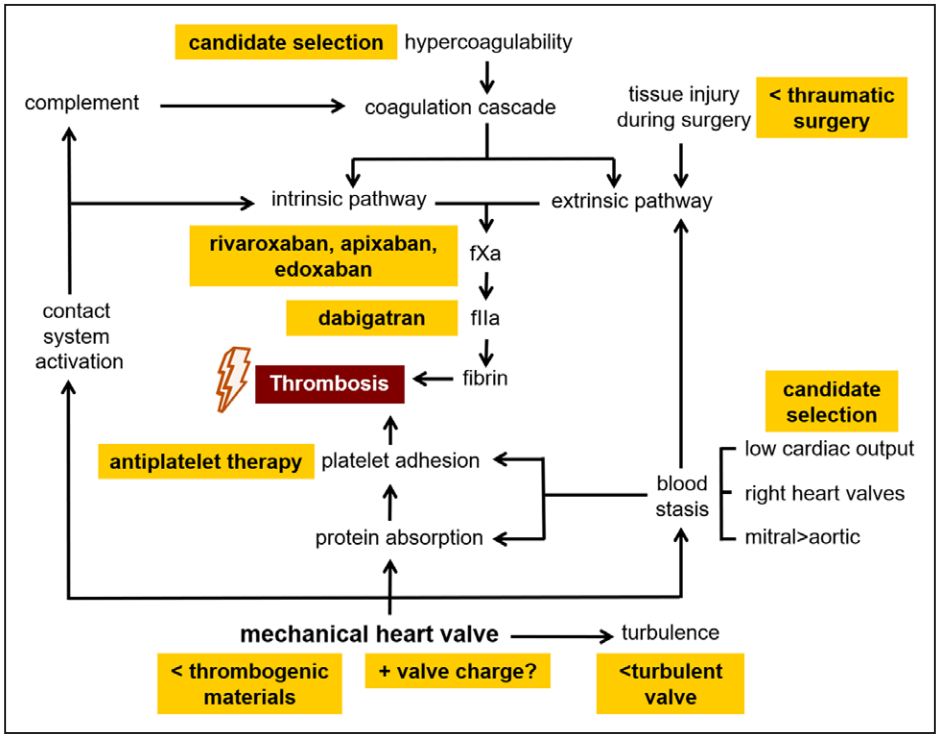

Figure 3. Mechanisms of thrombosis on mechanical heart valves and possible therapeutic approaches.
Mechanical heart valve implantation elicits platelet activation and the coagulation cascade, as discussed in detail in the text. Several therapeutic approaches may contribute to prevent valve thrombosis in patients not taking a vitamin K antagonist. A combination of strategies is probably required, as demonstrated by the negative results of the RE-ALIGN trial comparing dabigatran with warfarin. f indicates factor.

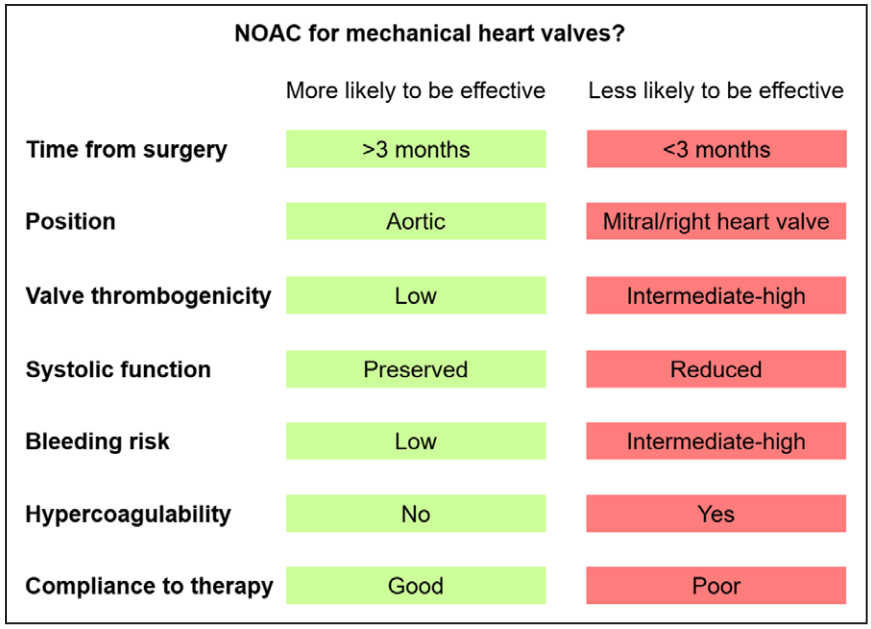

Figure 4. Characteristics of the optimal candidate for mechanical heart valve implantation.
Based on preclinical studies and the RE-ALIGN trial, the characteristics of the ideal candidate for non–vitamin K antagonist oral anticoagulants (NOACs) are proposed.

tion, both local tissue injury during surgical valve replacement[4] and the release of heme because of hemolysis[48] may activate the extrinsic coagulation pathway, which nonetheless is not essential for MHV thrombosis.[30] These mechanisms are schematized in Figure 3.

After ≈3 months, a neointima composed of smooth muscle cells, elastic extracellular matrix, and endothelial cells covers most of the frame struts, whereas areas of high-velocity blood flow remain bare.[49] Over time, the neointimal layer becomes more fibrotic and less thrombogenic.[49] This could be crucial for interpreting the findings of RE-ALIGN, which, as discussed above, showed a clustering of thrombotic events in patients with valves implanted <3 months before enrollment.

Hemodynamic Factors

Blood stasis reduces the washout and dilution of activated clotting factors, while limiting the action of coagulation inhibitors. Furthermore, regional turbulence disrupts laminar flow and creates zones of rapidly varying shear stress, favoring thrombosis. Turbulence may also delay endothelization or cause itself neointimal injury or dysfunction, further activating hemostatic mechanisms.[50] Accordingly, valve thrombosis occurs 20-fold more often in the tricuspid than in the mitral position,[21] and 2- to 3-fold more often on mitral than on aortic mechanical prostheses.[9] States of low cardiac output, as occur in heart failure, further increase the risk of valve thrombosis.[9]

Hemostasis-Related Factors

Several congenital or acquired conditions increase the likelihood of thromboembolic complications on MHVs. Such are FV Leiden and prothrombin gene mutations, antithrombin, protein C or protein S deficiencies, atrial fibrillation, malignancies, the antiphospholipid antibody and the nephrotic syndromes, high estrogen hormonal states, smoking, and obesity. Although evidence in the specific setting of MHVs is quite limited, it is reasonable to assume that all such conditions increase the risk on thrombosis in such conditions.[4,9,50]

LESSONS FROM THE RE-ALIGN FAILURE AND FUTURE PERSPECTIVES

In the coagulation cascade, each factor activates multiple downstream effectors, and several positive feedback systems are in place. For this reason, a procoagulant stimulus elicits an amplified response in terms of thrombin generation. MHVs activate the intrinsic coagulation pathway starting from contact phase activation, eliciting a sustained thrombin generation. As a result, it is conceivable that local concentrations of thrombin exceed those achievable by dabigatran, which inhibits thrombin in a 1:1 ratio, overcoming dabigatran effects.[45] By contrast, VKAs block the production of several factors of the intrinsic and common pathways, namely FIX, FX, and prothrombin, in addition to FVII in the extrinsic pathway, thus being effective also when thrombin generation is triggered by MHVs.[45] As a proof of this, in an in vitro study, thrombin generation on MHV was blunted by the plasma of warfarin-treated patients already with an INR >1.5, whereas dabigatran concentrations <200 ng/mL had minimal effects.[45] Dose-equivalency plots revealed that dabigatran concentrations of 254 and 488 ng/mL were required to suppress thrombin generation to the same extent as warfarin at INR values of 2.0 and 3.5, respectively.[45] Therefore, one could

calculate that dabigatran doses in the order of 620 mg twice daily would be required to maintain the trough concentration of the drug ≥250 ng/mL.[45] Such doses are more than double the 300 mg twice daily maximum dabigatran dose used in RE-ALIGN,[18] a dose that was already twice as high as the higher one approved for atrial fibrillation,[51] and which caused substantially, actually prohibitively, more bleeding than warfarin.[18] It thus seems unlikely that coagulation activation on MHVs can be suppressed by clinically relevant dabigatran doses. Upstream inhibition through FXa inhibitors might, conversely, prove more effective, because each molecule of FXa generates ≈1000 molecules of thrombin,[52,53] thus more closely resembling the upstream inhibition occurring with warfarin.

A proof-of-concept for the efficacy of FXa inhibition in preventing thrombosis on MHVs is the routine use of LMWHs (which inhibit FXa more than thrombin) in cases when absolute contraindications to VKAs exist, such as during the first and last trimesters of pregnancy.[54] Conclusions on this point rely mostly on observational data, with only 1 small randomized clinical trial supporting it.[55] However, a comprehensive meta-analysis compiling data from 1042 patients recruited in 9 studies (including 95 women from 4 cohorts) found no differences between LMWHs/UFH and VKAs with regard to the risk of thromboembolic events (odds ratio, 0.67; 95% CI, 0.27–1.68), or major bleeding (odds ratio, 0.66; 95% CI, 0.36–1.19), with similar outcomes in pregnancy and other conditions.[56] Since then, however, LMWH therapy instead of VKAs has been associated with higher rates of maternal thromboembolic complications during pregnancy, allegedly because of a combination of factors, including dose requirement changes, the lower reliability of heparin monitoring during pregnancy, and patients' compliance.[57] Further caution is also needed because the fully selective parenteral FXa inhibitor fondaparinux has been shown inadequate to prevent thromboembolic events triggered by foreign surfaces, such as catheters, in contrast to UFH (which inhibits both thrombin and FXa equally), and also to LMWHs (which inhibit FXa, but also, although to a lower extent, thrombin).[58,59]

Inhibitors of contact phase activation, such as FXIIa inhibitors, have been reported to be quite effective in preventing MHV thrombosis in vitro,[45] and further research on such compounds, or other upstream blockers of the intrinsic coagulation pathway, such as FXIa inhibitors, is thus warranted.[60] Activated platelets also seem to play an important role in FXII activation,[44] and aspirin appears to be useful to avoid the need of uptitrating VKAs in patients with MHVs.[7,61] The combination of an antiplatelet agent and a NOAC may thus contribute to better inhibiting the upstream phase of coagulation triggering MHV thrombosis.

In parallel, the quest for approaches complementary to antithrombotic therapy should also focus on newer MHVs with the lowest possible thrombogenic potential,[8] most notably, the On-X valve (On-X Life Technologies).[62] Further advances in the design of mechanical prostheses are also warranted, with the use of less thrombogenic materials, more favorable flow dynamics,[63] and possibly even positively charged surfaces to prevent FXII activation (US patent: https://www.google.com/patents/US200500211344). Finally, less traumatic valve implantation should be pursued, and conditions of lower thrombotic risk should be targeted first. These considerations are recapitulated in Figure 3, prospecting the favorable or unfavorable conditions for a new first-set human experimentation. Profiles of the ideal MHV patient candidate to a new trial of antithrombotic prophylaxis with a NOAC would be patients with MHV implanted in the aortic position >3 months before, with preserved systolic function, a low bleeding risk, no causes of hypercoagulability, including atrial fibrillation, and a prospective good compliance to treatment (Figure 4). Regardless of these considerations, the premature interruption of RE-ALIGN stands as a reminder of the need for acquiring robust preclinical evidence before reconsidering a clinical trial. In animal studies, species differences should be taken into account, and the human setting should be reproduced as close as possible in terms of realistic anticoagulation intensity and valve position. To achieve this goal, a possible approach would be to measure FXa activity in animals receiving warfarin (target INR, 2–3 or 2.5–3.5), and then to search for the anti-FXa dosing able to achieve similar trough-and-peak FXa activity levels. The chosen drug regimen should then be preferably assessed after 3 months from aortic valve replacement.

CONCLUSIONS

The need for a safe and effective alternative to VKAs remains unmet, yet research on this field has largely halted, following the negative findings of the RE-ALIGN trial. In our opinion, the unfavorable results of 1 single trial should not deter us from further testing of a valuable and convenient therapeutic approach. The current longer survival with MHV than with bioprostheses despite the hurdles of traditional VKA anticoagulation, together with the better safety profile of the NOACs in comparison with VKAs, should prompt further experimentation in this important area.

ARTICLE INFORMATION

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Disclosures

Dr Aimo reports no conflicts of interest. Dr Giugliano reports serving as a consultant and had received honoraria from Bristol-Myers Squibb, Janssen, Daiichi Sankyo, Merck, and Sanofi, and grant support through his institution from Daiichi Sankyo, Merck, Johnson & Johnson, Sanofi, and AstraZeneca. Dr De Caterina reports Steering Committee membership and National Coordination for Italy of several studies on NOACs in cardiovascular disease, including APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events–2), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment), ENGAGE AF-TIMI 38 (Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation), 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); and fees, honoraria, and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck, and Portola, as well.

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