Atrial fibrillation (AF) is the most common cardiac arrhythmia. It was estimated to affect up to 6.1 million Americans in 2010, and since AF is more common with increasing age, it is predicted to affect 12.1 million in the United States by 2030.1 AF increases the risk of stroke 5-fold across all age groups, and AF-related stroke incidence ranges from <1% to >20% per year in the absence of anticoagulation.2 AF is implicated in ≈15% of all strokes in the United States.3

Stroke prevention is central to the management of patients with AF. For many years, the use of oral anticoagulant therapy with warfarin, described as a vitamin K antagonist (VKA), has been the standard therapy for the prevention of thromboembolism in patients with AF.4,5 Warfarin is an inexpensive and effective therapeutic; however, its use is complicated by a narrow therapeutic window, which makes it difficult to maintain patients within a defined anticoagulation range. Additionally, warfarin is associated with numerous drug and dietary interactions, and its susceptibility to genetic variations makes dosage requirements vary widely among individuals. Regular blood monitoring and dose adjustment are necessary to maintain the international normalized ratio within the target therapeutic range.

The introduction of direct oral anticoagulants (DOACs) has expanded the therapeutic options for primary and secondary stroke prevention in patients with nonvalvular AF (NVAF). Unlike warfarin, DOACs act through the direct inhibition of coagulation factors thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban). DOACs do not require routine monitoring or dose adjustment and they have short half-lives, no food interactions, and relatively few drug interactions, which makes them more convenient alternatives to warfarin to reduce the risk of stroke and systemic embolism (SSE). However, in contrast to warfarin, no specific reversal agents are available for the management of bleeding events during anticoagulation therapy with factor Xa inhibitors. Idarucizumab has recently been approved by the US Food and Drug Administration for the reversal of dabigatran.6 Idarucizumab is a humanized monoclonal antibody fragment indicated in dabigatran-treated patients when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery or urgent procedures and in life-threatening or uncontrolled bleeding.6 Idarucizumab received accelerated approval based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers. Other reversal agents, including a recombinant protein for the reversal of factor Xa inhibitors and a small synthetic molecule for the reversal of all DOACs, are in development.7,8 To date, dabigatran, rivaroxaban, apixaban, and edoxaban have each been approved in the United States to reduce the risk of SSE in patients with NVAF as well as for the treatment of deep vein thrombosis and pulmonary embolism.

Large randomized controlled trials have assessed the efficacy and safety of the 4 approved DOACs for the prevention of SSE in patients with NVAF.9–12 The design of these trials was based on historic randomized controlled trials of adjusted-dose warfarin therapy for stroke prevention in patients with AF, which generally excluded patients with severe or moderate mitral stenosis and prosthetic heart valves. DOACs were associated with a similar or lower risk of SSE compared with warfarin. Additionally, rates of major and intracranial bleeding with any DOAC were similar to or lower than the rates with warfarin. As these studies established the efficacy and safety of DOACs to reduce the risk of SSE in patients with NVAF,9–12 they generally excluded patients with mitral stenosis or artificial heart valves or valve repair. However, they commonly included patients with other types of valvular heart disease (VHD), including mitral regurgitation,
aortic regurgitation, aortic stenosis, and mitral valve prolapse.

NVAF appears to have been interpreted differently in the designs of the DOAC pivotal trials. Because definitions of NVAF vary, there is uncertainty as to whether patients with certain valve diseases may be considered to have NVAF, and whether DOACs are appropriate for these patients. In a recent survey of physicians who treat patients with AF, only about one-half to two-thirds of respondents agreed that the existing definitions of NVAF were sufficiently clear. A clear definition of NVAF is missing from the current literature.

VHD is commonly associated with AF; a recent registry of patients with AF across 9 European countries showed that valvular abnormalities coexisted in 63.5% of AF patients. The presence of concomitant VHD significantly increases the risk of stroke in AF. The potential role of DOACs in patients with specific types of VHD has not been directly assessed. Current guidelines provide specific recommendations for the use of DOACs to reduce stroke risk in patients with NVAF; however, reduction in SSE risk in patients with AF in the setting of specific valvular heart lesions is less well defined. Current research is focused on identifying other potential roles of DOACs in specific clinical conditions, including AF associated with VHD or with a prosthetic heart valve. Thus, it is possible that the range of indications for DOAC use will expand in the future.

This review summarizes the evolving definition of NVAF as described by current guidelines and the inclusion and exclusion criteria for the DOAC pivotal trials in terms of native valve lesions. The thromboembolic risk and recommended treatment options in AF in the presence of different types of valvular heart lesions are discussed, followed by an assessment of the accumulated evidence for the efficacy and safety of DOACs in patients with AF and concomitant valvular heart lesions.

Evolving Definitions of NVAF

Definitions of NVAF have changed with successive editions of authoritative guidelines. According to the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2001 guidelines, NVAF was defined as rhythm disturbance occurring in the absence of rheumatic mitral valve disease or a prosthetic heart valve. In the 2006 update to these guidelines, the definition was revised to include AF in the absence of mitral valve repair. The ACC/AHA/Heart Rhythm Society (HRS) 2014 guidelines define NVAF as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair. The 2012 focused update of the ESC guidelines for the management of AF states that AF is conventionally described as “valvular” or “nonvalvular.” The ESC defines valvular AF as AF associated with rheumatic VHD (predominantly mitral stenosis) or prosthetic heart valves. The 2012 American College of Chest Physicians (ACCP) guidelines use the term “non-rheumatic AF” synonymously with NVAF.

In a recent consensus, the European Heart Rhythm Association, the European Association of Percutaneous Cardiovascular Interventions, Acute Cardiovascular Care Association (ACCA), HRS, and Asia Pacific Heart Rhythm Society defined NVAF as AF in the absence of prosthetic mechanical heart valves or hemodynamically significant valve disease, referring to a valve lesion severe enough to warrant surgical or percutaneous intervention or that would have an impact on survival or well-being.

Inclusion and Exclusion Criteria for DOAC Pivotal Trials

Large pivotal clinical trials have established the efficacy and safety of DOACs to reduce the risk of SSE in patients with NVAF. The DOAC pivotal trials excluded patients with significant mitral stenosis and prosthetic heart valves but not necessarily those with other types of VHD, such as mitral regurgitation or aortic disease. In all pivotal studies, NVAF was documented by electrocardiography. Elevated risk of stroke was indicated by age ≥75 years; history of SSE or transient ischemic attack (TIA); or CHADS2 score (which estimates risk based on the presence of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or TIA) ≥2. Inclusion and exclusion criteria varied with regard to VHD. Patients with AF in the setting of certain valvular diseases were excluded from the following trials (Table 1).

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ClinicalTrials.gov NCT00412984) trial excluded patients with moderate or severe mitral stenosis and conditions other than AF that required anticoagulation (ie, mechanical prosthetic heart valve). However, patients with VHD including those with aortic regurgitation, mild mitral stenosis, mitral regurgitation, tricuspid stenosis, tricuspid regurgitation, valve repair, and bioprosthetic valves were eligible for enrollment in the trial. In the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes; ClinicalTrials.gov NCT00496769) trial, which evaluated the efficacy and safety of apixaban versus aspirin in NVAF patients who were unsuitable for VKA therapy, the exclusion criteria were VHD requiring surgery and any other conditions requiring anticoagulation. The AVERROES trial was prematurely terminated after the first planned interim analysis revealed a treatment benefit in favor of apixaban for the prevention of SSE that exceeded 4 SDs (1.6% per year versus 3.7% per year, hazard ratio [HR] 0.45, 95% CI 0.32–0.62, DOI: 10.1161/JAHA.115.002776
Table 1. Exclusion Criteria Related to VHD to Identify Patients With NVAF in DOAC Versus Warfarin Pivotal Trials

| Exclusion Criteria | ROCKET-AF | RE-LY | ARISTOTLE | ENGAGE-AF | AVERROES |
|--------------------|-----------|-------|-----------|-----------|----------|
| Moderate or severe mitral stenosis | X         |       | X         |           |          |
| Prosthetic heart valve |             |       | X         |           |          |
| Mechanical heart valve | X         |       |           |           | X        |
| Hemodynamically significant valve disease | X         |       |           |           | X        |
| VHD requiring surgery |             |       |           |           | X        |
| Other conditions requiring anticoagulation | X         |       |           |           | X        |
| Unresected atrial myxoma |             |       |           |           | X        |

VHD indicates valvular heart disease; NVAF, nonvalvular atrial fibrillation; DOAC, direct oral anticoagulant; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long Term Anticoagulation Therapy; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE-AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Strokes.

P<0.001, z=4.76). In ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ClinicalTrials.gov NCT00403767),22 patients with AF and concomitant mitral stenosis or prosthetic heart valves were excluded, whereas those with annuloplasty with or without prosthetic ring, commissurotomy, and/or valvuloplasty were permitted. Patients with hemodynamically significant VHD who did not meet the above exclusion criteria were included. Patients with NVAF who were at moderate-to-high risk of stroke (history of SSE or TIA, or ≥2 additional risk factors) were included.4 In RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy; ClinicalTrials.gov NCT00262600),23 patients with a history of heart valve disorder (ie, prosthetic valve or hemodynamically relevant VHD) were excluded. Patients with VHD were admitted to the RE-LY trial if the VHD was unlikely to require an intervention before study completion. In the ENGAGE-AF TIMI-48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; ClinicalTrials.gov NCT00781391)12 trial, patients with moderate-to-severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve were excluded. Patients with bioprothetic heart valves and/or valve repair were included.

The inclusion and exclusion criteria for the pivotal trials on which the indications for the DOACs are based are inconsistent. The rationale for excluding patients with mitral stenosis was the associated high risk of stroke and the likely need for surgery or intervention during the trials. Patients with prosthetic heart valves were excluded on the basis of their existing need for long-term anticoagulation.

Subanalyses of the DOAC Trials

After publication of the main results of the DOAC pivotal trials, post hoc subanalyses were conducted to evaluate the efficacy and safety of DOACs versus warfarin in patients with VHD who had been enrolled in these trials.

In ARISTOTLE,20 of 18 197 patients enrolled, 4808 (26.4%) had a history of VHD at baseline. Of these, 3526 (19.4%) patients had mitral regurgitation, 131 (0.7%) had mitral stenosis, 887 (4.9%) had aortic regurgitation, and 384 (2.1%) had aortic stenosis; 2124 (11.7%) of patients in the study had tricuspid regurgitation, and 251 had prior valve surgery, although it was not specified how many of these surgeries were bioprosthetic implants or valve repair (Table 2). Compared with patients without VHD, those with VHD were generally older, had higher mean CHADS2 scores, were more likely to have had a prior myocardial infarction (MI) and prior bleeding, and were less likely to have hypertension and diabetes. The rates of SSE and bleeding were higher in patients with VHD than in those without. Apixaban treatment resulted in a similarly lower risk of SSE (interaction P=0.38) with a similar improvement in major bleeding (interaction P=0.23) and all-cause mortality (interaction P=0.10) compared with warfarin in AF patients with and without VHD (Table 3).

In an analysis of the ROCKET-AF trial,22 among the 14 171 patients enrolled, 2003 (14.1%) had significant valvular disease (SVD) and 106 (5.3%) had prior cardiac valvular procedures, which included valvuloplasty (n=64, 60.4%) or other procedures (n=42, 39.6%) (Table 2). Patients with SVD were older and had more comorbidities than did patients without SVD. The rate of SSE with rivaroxaban versus warfarin was consistent among patients with SVD and without SVD (interaction P=0.76; Table 3). However, rates of major bleeding with rivaroxaban versus warfarin were higher in patients with SVD versus those without interaction P=0.01), even when controlling for risk factors and potential confounders (Table 3). All-cause mortality rates were comparable between patients with and without SVD (interaction P=0.60; Table 3).
Results from a preliminary post hoc analysis report at the 2014 ACC Annual Scientific Session showed that of the 18,113 patients enrolled in the RE-LY trial, 2,3950 (21.8%) had VHD as defined by the investigators. A total of 3,101 (17.1%) had mitral regurgitation, whereas 817 (4.5%) had aortic regurgitation, 471 (2.6%) had aortic stenosis, 1,179 (6.5%) had tricuspid regurgitation, and 193 (1.1%) had mild mitral stenosis (Table 2). Patients with VHD were older and more likely to have congestive heart failure, coronary artery disease, moderate renal impairment (creatinine clearance 30 to <50 mL/min), and higher CHADS2 scores compared with patients without VHD. Patients with and without VHD had a comparable risk of SSE (HR 1.09, 95% CI 0.85–1.33, P=0.43). Risk of SSE was comparable in patients with and without VHD, but risk of death and of major bleeding was higher in patients with VHD (P≤0.002). The relative benefits of dabigatran versus warfarin for SSE for both doses of dabigatran were comparable for patients with and without VHD (Table 3).

Table 2. History of VHD in Patients Randomized in ARISTOTLE, ROCKET-AF, and RE-LY

|                | ARISTOTLE Total (N=18,197) | RE-LY Total (N=18,113) | ROCKET-AF Total (N=14,171) |
|----------------|---------------------------|------------------------|---------------------------|
| At least moderate VHD, n (%) | 4,808 (26.4) | 3,950 (21.8) | 2,003 (14.1) |
| Mitral regurgitation | 3,526 (19.4) | 3,101 (17.1) | 1,756 (12.3) |
| Mitral stenosis | 131 (0.7) | 193 (1.1) | ... |
| Aortic regurgitation | 887 (4.9) | 817 (4.5) | 486 (3.4) |
| Aortic stenosis | 384 (2.1) | 471 (2.6) | 215 (1.5) |
| Tricuspid regurgitation | 2,124 (11.7) | 1,179 (6.5) | ... |
| Valve surgery | ... | 251 (1.4) | ... |
| Prior cardiac valvular procedure | ... | ... | 106 (5.3) |
| Other | ... | ... | 11 (0.6) |

VHD indicates valvular heart disease; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long Term Anticoagulation Therapy.

Table 3. Efficacy and Safety of DOACs Versus Warfarin in Patients With or Without VHD in the ARISTOTLE, ROCKET-AF, and RE-LY Studies

|                | ARISTOTLE Total (N=18,197) | RE-LY Total (N=18,113) | ROCKET-AF Total (N=14,171) |
|----------------|---------------------------|------------------------|---------------------------|
|                 | 110 mg Dabigatran | 150 mg Dabigatran | 110 mg Dabigatran | 150 mg Dabigatran | 110 mg Dabigatran | 150 mg Dabigatran |
| SSE            |                        |                        |                        |
| HR (95% CI)    | 0.70 (0.51–0.97) | 0.84 (0.67–1.04) | 0.97 (0.65–1.45) | 0.88 (0.70–1.10) | 0.67 (0.52–0.86) | 0.59 (0.37–0.93) | 0.83 (0.55–1.27) | 0.89 (0.75–1.07) |
| P interaction  | 0.38 | NS | NS | NS | NS | NS | 0.76 |
| Major bleeding |                        |                        |                        |
| HR (95% CI)    | 0.79 (0.61–1.04) | 0.65 (0.55–0.77) | 0.72 (0.54–0.96) | 0.85 (0.71–1.02) | 0.89 (0.68–1.16) | 0.99 (0.83–1.17) | 1.56 (1.14–2.14) | 0.98 (0.84–1.15) |
| P interaction  | 0.23 | NS | NS | NS | NS | NS | 0.01 |
| All-cause mortality |                        |                        |                        |
| HR (95% CI)    | 1.01 (0.84–1.22) | 0.84 (0.73–0.96) | NA | NA | NA | NA | 0.98 (0.75–1.29) | 0.91 (0.80–1.03) |
| P interaction  | 0.10 | NS | NS | NS | NS | NS | 0.60 |

DOAC indicates direct oral anticoagulant; VHD, valvular heart disease; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long Term Anticoagulation Therapy; HR, hazard ratio; NA, not available; NS, not significant; SSE, stroke and systemic embolism.
patients with and without VHD (P-values were nonsignificant; Table 3).

Generally, in the ARISTOTLE, ROCKET-AF, and RE-LY trials, patients with VHD were older and had more comorbidities, including congestive heart failure, prior MI, and renal disease, compared with patients without VHD. In ROCKET-AF and RE-LY, stroke rates were similar in patients with and without VHD after adjusting for baseline criteria; however, in ARISTOTLE, the rate of SSE was higher in patients with VHD. Major bleeding rates were higher in patients with VHD versus in patients without VHD in all 3 trials. Overall, in the 3 subanalyses of patients with AF and VHD, the risk of SSE was comparable in patients with and without VHD, which demonstrates that the benefits of apixaban, dabigatran, and rivaroxaban over warfarin for stroke prevention were consistent in these patients. To date, no data on the efficacy and safety of edoxaban versus warfarin in patients with VHD are available from the ENGAGE-AF TIMI-48 trial.

Patients with mechanical prosthetic heart valves were excluded from the pivotal trials of the DOACs. Results of subsequent studies led to revision of the dabigatran (Pradaxa®; Boehringer Ingelheim Pharmaceuticals, Inc) product label to recommend against the use of dabigatran in patients with NVAF in the setting of other forms of VHD. In the RE-ALIGN (Dabigatran Etxilate in Patients With Mechanical Heart Valves; ClinicalTrial.gov NCT01452347) trial, the use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications compared with warfarin.24 These findings suggest that DOACs may be used in selected patients with AF who do not have mechanical heart valve prostheses. Until more data become available, only apixaban and rivaroxaban can be considered at this time for use in patients with NVAF with other valve lesions, regardless of whether such lesions are clinically significant. However, the use of DOACs in this patient population should be approached with caution and the clinical judgment of the treating physician should guide treatment decisions on a case-by-case basis.

**Risk of Stroke in AF With VHD**

VHD, regardless of the disease type and severity, is associated with an increased risk of stroke,25 and the risk of thromboembolic events is further amplified in the presence of AF.26

**Mitral Stenosis**

Rheumatic fever is the most common cause of mitral stenosis; however, the disease has been uncommon in the United States since the 1970s. Although the vast majority of mitral stenosis in the world results from rheumatic heart disease, nonrheumatic mitral stenosis is increasingly frequent in the elderly population.24 Patients with rheumatic mitral valve disease have the highest risk of systemic thromboembolism among those with any common form of acquired VHD.27 The efficacy of DOACs in reducing the risk of thromboembolism has not been directly evaluated in patients with mitral stenosis. Anticoagulation with VKA has long been recommended for patients with mitral stenosis and AF or prior embolism; such patients were generally excluded from anticoagulation trials assessing the utility of thromboembolic prevention.28 According to the current ACC/AHA and ACCP guidelines for VHD, anticoagulation with a VKA or heparin is recommended in patients with AF and mitral stenosis. Anticoagulation should be continued indefinitely in patients with mitral stenosis and concurrent AF, a prior embolic event, or a left atrial thrombus.27,28

**Mitral Regurgitation**

Limited and conflicting data are available regarding the effect of mitral regurgitation on stroke risk. A number of studies have arrived at conflicting conclusions regarding the relative stroke risk in patients with mitral regurgitation compared with those without, and in patients with mild versus severe mitral regurgitation.29–32 There are currently no specific recommendations for thromboembolic prophylaxis in patients with AF and mitral regurgitation.

**Other VHD**

Mitral valve prolapse is a common valvular disease that occurs in 1.0% to 2.5% of the population.33 There is conflicting evidence of an association between mitral valve prolapse and stroke. Additionally, there are currently no published reports of a differential risk of thromboembolism in AF in the presence of aortic stenosis or aortic insufficiency.

**Mechanical Versus Bioprosthetic Heart Valves**

Patients with mechanical heart valves are at an increased risk of stroke compared with patients without, and they require continuous anticoagulation.34 The annual risk of thromboembolic events in patients with a mechanical heart valve is 1% to 2% versus 0.7% with a bioprosthetic valve, even with antithrombotic therapy.28 Mechanical valves in the mitral position are generally more thrombogenic than those in the aortic position.27

DOI: 10.1161/JAHA.115.002776
According to the ACC/AHA/HRS and 2010 ESC guidelines for the management of AF, conventional management is recommended in the setting of VHD. In patients with AF who have mechanical heart valves, VKA therapy is indicated for the prevention of SSE, and anticoagulation should be based on the type and position of the prosthesis, maintaining an international normalized ratio of at least 2.5 for valves in the mitral position and at least 2.0 for aortic valves.35 The ACC/AHA/HRS guidelines specify that dabigatran should not be used in patients with AF and a mechanical heart valve. In the 2014 ACC/AHA28 guidelines for the management of patients with VHD, DOAC use is not recommended in patients with mechanical valve prostheses.

Bioprosthetic valves are considered to be less thrombogenic than mechanical heart valves. Additionally, bovine pericardial valves appear to be less susceptible than porcine valves to valve thrombosis.35 It has been historically accepted that long-term anticoagulation is unnecessary in patients with bioprosthetic valves and no additional risk factors,36 and the ACC/AHA guidelines recommend only aspirin for these patients. However, because of an increased risk of thromboembolism during the first 3 months after implantation of a bioprosthetic valve, anticoagulation with warfarin is often used, especially when the valve is in the mitral position.33 To date, there is little evidence of the use of DOACs in patients with bioprosthetic heart valves. However, a recent study in a series of 105 patients showed that catheter ablation of AF with uninterrupted DOAC use in patients with biological heart valves is feasible and safe.37

Case Studies
At present, few data are available on the efficacy and safety of DOACs in VHD. However, several case studies of complications with DOAC use in the setting of valvular abnormalities have been reported. To date, several cases of thrombosis complicating dabigatran use in the setting of mechanical valve prosthesis have been published. All of these cases report mechanical valve thromboembolism after a switch from warfarin to dabigatran in the setting of either mitral or aortic heart valves. Two fatal cases of mitral valve thrombosis were reported, with neither patient surviving repeat valve replacement surgery.38 There was one report of nonfatal bioprosthetic mitral valve thrombosis leading to massive stroke after a switch from warfarin to dabigatran. Currently, there is one documented case of thrombosis in a patient with AF and coexistent valvular disease (mitral stenosis) without valve replacement during dabigatran anticoagulation.46 To date, there are no published reports for any other DOAC relating to thromboembolism in patients with AF associated with VHD.

On the basis of these case reports, evidence is mounting that dabigatran is associated with mechanical valve thrombosis. Therefore, patients with mechanical heart valves, regardless of position (mitral or aortic), should not be treated with dabigatran as a replacement for warfarin. Additionally, these case reports highlight the risk of serious adverse events when switching treatment regimens from VKA to the direct thrombin inhibitor dabigatran in patients with AF and underlying valvular disease.

The role of DOACs in patients with mechanical or prosthetic heart valves requires further research. Currently, there are no published clinical trials and few case reports evaluating the use of the other DOACs (apixaban, rivaroxaban, and edoxaban) in patients with mechanical valves. It is expected that results from the ongoing CATHAR (Comparison of Antithrombotic Treatments After Aortic Valve Replacement. Rivaroxaban: A New Antithrombotic Treatment for Patients With Mechanical Prosthetic Aortic Heart Valve; ClinicalTrials.gov NCT02128841) trial, a phase 2 study to assess the effectiveness and safety of rivaroxaban for the prevention of major complications in patients undergoing mechanical aortic valve replacement, will elucidate the role of rivaroxaban in this population.47

Discussion
Patients with AF and concomitant VHD are often seen in clinical practice. Many of these patients are categorized as having NVAF based on current definitions. As a result of the landmark clinical trials RE-LY, ROCKET-AF, and ARISTOTLE, which compared warfarin to dabigatran, rivaroxaban, and apixaban, respectively, the pharmacologic options for managing stroke risk in patients with NVAF have expanded.

Review of the DOAC trial subanalyses indicates that the effects of DOACs versus warfarin on SSE did not differ between patients with and without VHD. A higher prevalence of major or nonmajor clinically relevant bleeding was observed among patients with VHD in all 3 substudies. However, the notable differences in inclusion and exclusion criteria for the 3 trials highlight the weakness of the term “NVAF” in the selection of patients for DOAC treatment. Outside of the pivotal clinical trials, NVAF has not been well defined. There is currently no consensus on the definition of NVAF, even when current practice guidelines are examined. The term NVAF may not be appropriate as an umbrella term for patients who might benefit from DOACs, as the use of an imprecise term may lead to inappropriate clinical management of these patients. Although insufficient data are available to optimally guide clinical practice in NVAF with VHD, results of further studies will better identify candidates for DOAC therapy.
Accumulated evidence from controlled study subanalyses, case reports, and current practice guidelines suggests that patients with AF and normal valves, or with defective valves that do not require surgical intervention, may be considered as having NVAF. With the exception of mechanical heart valves and severe mitral stenosis, there is a lack of evidence of increased stroke risk in the presence of other types of valvular abnormalities. In this author’s opinion, any form of VHD not severe enough to require surgical intervention, including rheumatic and nonrheumatic mitral stenosis, may be considered NVAF. Many patients with mild or moderate VHD who were excluded from the pivotal DOAC trials could have been included.

Importantly, none of the pivotal DOAC trials were designed or powered to study the effectiveness of DOACs in patients with valve disease. Patients with VHD who were not excluded from the pivotal trials (eg, those with bioprosthetic heart valves, mitral regurgitation, and aortic stenosis), and those with valvular lesions that are not specifically contraindicated in the product information, may be considered for treatment with DOACs. However, it is important to note that this clinical perspective should be interpreted with caution, particularly by prescribing physicians in the United States. Given the definition of NVAF according to the 2014 AHA/ACC/HRS guidelines, prescribers and patients in the United States need to be aware that for patients with AF and bioprosthetic heart valves, treatment with DOACs is contrary to current FDA recommendations.

Results from the RE-ALIGN trial and specific case reports of the use of dabigatran for the prevention of embolic events in patients with AF and coexistent native VHD indicate that the direct thrombin inhibitor is not effective in preventing thrombosis and should be avoided in patients with mechanical valve replacements. Until data are available on the use of apixaban, rivaroxaban, and edoxaban in patients with mechanical heart valves, such patients should be anticoagulated with warfarin. The localization of thrombus formation appears to differ in patients with NVAF and those with valvular AF.48 In NVAF, thrombi predominantly develop in the left atrial appendage. This difference may influence efficacy and outcomes of anticoagulant therapy.49 Results from a recent study showed that specific left atrial appendage morphology correlates with the risk of stroke in patients with NVAF. This observation may have an impact on anticoagulation management in patients with NVAF, particularly those with a low-to-intermediate risk of stroke.50

Decisions regarding the use of VKAs versus DOACs can be challenging in patients with AF and concomitant VHD. Currently, there are few data on the efficacy and safety of DOACs in VHD, and there is little direct evidence to support treatment recommendations in clinical practice. Efforts should be made to improve understanding of the benefits and risks of DOAC treatment in patients with AF and concomitant VHD. Specific and widely acceptable definitions of valvular AF and NVAF are needed to guide clinical practice and the design of future trials. Further controlled studies and analyses of results from trial participants identified as having had VHD would be informative to help clearly identify appropriate candidates for treatment with DOACs. As patients with AF and VHD are known to be at a higher risk of thromboembolism than those without, the future challenge will be to translate the findings of the DOAC trials into clinical practice.

Acknowledgments

Professional medical writing and editorial assistance was provided by Kate Jesien, PhD, at Caudex Medical.

Sources of Funding

Funded by Bristol-Myers Squibb and Pfizer Inc.

Disclosures

Di Biase is a consultant for Biosense Webster, St Jude Medical, and Stereotaxis. He has received honoraria/travel reimbursement from Boston Scientific, Medtronic, Biotronik, Epiep, Pfizer, Bristol-Myers Squibb, and Janssen.

References

1. Colilla S, Crow A, Pekun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol. 2013;112:1142–1147.

2. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Atilhoft G, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011;342:d124.

3. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, Hylek EM, Schulman S, Go AS, Hughes M, Spencer FA, Manning WJ, Halperin JL, Lip GY; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e531S–e575S.

4. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heiduschel H, Aliferi O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohnloser SH, Kolb P, Le Heuzey JY, Ponikowski P, Rutten FH; European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369–2429.

5. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation—an update of the 2010 ESC guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. Europace. 2012;14:1385–1413.

6. Boehringer Ingelheim Pharmaceuticals, Inc. PRAXBIND (idarucizumab) prescribing information. Available at: http://us.boehringer-ingelheim.com/content/dam/internet/opu/us_EN/documents/Media_Press_Releases/2015/Praxbind.pdf. Accessed November 11, 2015.
DOACs and Valvular Heart Disease

Di Biase

DOI: 10.1161/JAHA.115.002776

10. Patel MR, Mahaffey KW, Garg J, Pan G, Erol C, Diaz R, Bahit MC, Cartunek J, De Caterina R, Goto S, Ryzul W, Zhu J, Granger CB, Alexander JH. Axiaban compared with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the ARISTOTLE trial. Circulation. 2015;132:624–632.

22. Breithardt G, Baumgart M, Schilb M, Wallentin L. Comparison of dabigatran with warfarin in patients with nonrheumatic atrial fibrillation but underlying heart disease: results of a physicians randomized comparison of dabigatran with warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY trial. Poster presented at: ACC 2014; March 29–31, 2014; Washington, DC. Abstract.

25. Brown RD, Wann JS, Sicks J, Roden DM, Wiberg DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. Stroke. 1996;27:373–380.

27. Whitleck RP, Sun JC, Eames SE, Rubins FD, Teoh KH; American College of Chest Physicians. Antithrombotic and thrombolytic therapy for valvular heart disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e576S–e600S.

28. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, de Leon AC Jr, Faxon DP, Freed MD, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(2):e85–e157.

29. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, de Leon AC Jr, Faxon DP, Freed MD, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(2):e85–e157.

30. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, de Leon AC Jr, Faxon DP, Freed MD, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(2):e85–e157.

31. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, de Leon AC Jr, Faxon DP, Freed MD, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(2):e85–e157.

32. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, de Leon AC Jr, Faxon DP, Freed MD, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(2):e85–e157.

33. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, de Leon AC Jr, Faxon DP, Freed MD, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(2):e85–e157.

34. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, de Leon AC Jr, Faxon DP, Freed MD, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(2):e85–e157.

35. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, de Leon AC Jr, Faxon DP, Freed MD, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(2):e85–e157.
34. Salem DN, O’Gara PT, Madias C, Pauker SG; American College of Chest Physicians. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133 (6 suppl):593S–629S.
35. Grunkemeier GL, Li HH, Naftel DC, Starr A, Rahimtoola SH. Long-term performance of heart valve prostheses. Curr Probl Cardiol. 2000;25:73–154.
36. Butchart EG. Antithrombotic management in patients with prosthetic valves: a comparison of American and European guidelines. Heart. 2009;95:430–436.
37. Di Biase L, Trivedi C, Mohanty P, Mohanty S, Gianni C, Bai R, Santangeli P. Periprocedural and long term safety and feasibility of treatment with novel oral anticoagulants in patients with biological valve and atrial fibrillation. Presented at: American College of Cardiology 64th Annual Scientific Session [P-255]; March 14–16, 2015; San Diego, CA.
38. Atar S, Wishniak A, Shurman A, Shriwi S, Brezins M. Fatal association of mechanical valve thrombosis with dabigatran. Chest. 2013;144:327–328.
39. Akgullu C, Eryilmaz U, Kurtoglu T. [Severe thrombosis of bioprosthesis mitral valve after dabigatran]. Turk Kardiyol Dern Ars. 2013;41:529–533 [Turkish].
40. Coulter S, Campos K. Thrombosis on a mechanical valve anticoagulated with dabigatran. J Thromb Thrombolysis. 2014;37:84–86.
41. Kuwauchi S, Watanabe S, Abe K, Yamasaki M, Ito J, Kawazoe K. Thromboembolism in a patient with a mechanical mitral valve during anticoagulation with dabigatran etexilate. Ann Thorac Surg. 2013;96:1863–1864.
42. Price J, Hynes M, Labinaz M, Ruel M, Boodhwani M. Mechanical valve thrombosis with dabigatran. J Am Coll Cardiol. 2012;60:1710–1711.
43. Chu JW, Chen VH, Bunton R. Thrombosis of a mechanical heart valve despite dabigatran. Ann Intern Med. 2012;157:304.
44. Stewart RA, Astell H, Young L, White HD. Thrombosis on a mechanical aortic valve whilst anti-coagulated with dabigatran. Heart Lung Circ. 2012;21:53–55.
45. Chaudhry M. Drowning in blood: a rare but fatal complication of rivaroxaban. Crit Care Med. 2012;40:316.
46. Luis SA, Poon K, Luis C, Shukla A, Bett N, Hamilton-Craig C. Massive left atrial thrombus in a patient with rheumatic mitral stenosis and atrial fibrillation while anticoagulated with dabigatran. Circ Cardiovasc Imaging. 2013;6:491–492.
47. ClinicalTrials.gov. Comparison of antithrombotic treatments after aortic valve replacement. Rivaroxaban: a new antithrombotic treatment for patients with mechanical prosthetic aortic heart valve (CATHAR). Available at: http://clinicaltrials.gov/ct2/show/NCT02128841. Accessed February 10, 2015.
48. Blenkinsop JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996;61:755–759.
49. Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. J Am Coll Cardiol. 1994;24:755–762.
50. Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S, Horton R, Sanchez JE, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Gallahouse Gl, Burkhardt JD, Cesarani F, Scaglione M, Natale A, Gaia F. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study J Am Coll Cardiol. 2012;60:531–538.

Key Words: anticoagulants • atrial fibrillation • treatment • valvular heart disease