# Direct Oral Anticoagulants and Valvular Heart Disease

**Background:** Direct oral anticoagulants (DOACs) apixaban, rivaroxaban, edoxaban, dabigatran are FDA approved to prevent recurrent VTE as well as stroke prevention in patients with nonvalvular atrial fibrillation (AF)[1-4] Landmark trials for approval of DOACs included up to 20% of patients who had some type of valvular defects[5]

## Guideline Definitions of Valvular Heart Disease

| Guideline | Definition of "Valvular Heart Disease" |
|---|---|
| CHEST[6] | Term no longer used. |
| ACC/AHA[7] | Valvular AF generally refers to AF in the setting of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or in the presence of an artificial (mechanical) heart valve. |
| EHRA[8] | EHRA Type 1 VHD: includes moderate–severe mitral stenosis of rheumatic origin and mechanical prosthetic valve replacement<br>EHRA Type 2 VHD: includes all other native valvular stenoses and insufficiencies as well as mitral valve repair, bioprosthetic valve replacements and transaortic valve intervention (TAVI) |

## Use of DOACs for Valvular Replacement

| Type of Valvular Replacement | Guideline Recommendation | | | Other Literature |
|---|---|---|---|---|
| | CHEST[6] | ACC/AHA[7] | EHRA[8] | |
| Mechanical prosthetic valve | AVOID USE | AVOID USE | AVOID USE | |
| Bioprosthetic valve | - | - | - | -DAWA study: discontinued due to lack of enrollment. Attempted to compare dabigatran to warfarin in bioprosthetic mitral and/or aortic valve replacement[12] |
| TAVR/TAVI | - | "The utility of DOACs in this population is unknown at this time" | Unknown: No prospective data available | -GALILEO trial-compared rivaroxaban to antiplatelet agents was stopped early due to higher rates of death or first VTE event and bleeding in the group that received rivaroxaban.[13]<br>- Per ACC/AHA guidelines, studies have shown that valve thrombosis occurs in patients who received antiplatelet therapy alone but not in patients who were treated with VKA. Anticoagulation with VKA for at least 3 months after TAVR in patients with low risk of bleeding is reasonable to consider.[7] |

## "Valvular Heart Disease" INCLUSION Criteria

| INCLUSION Criteria | Pivotal Trial | | | |
|---|---|---|---|---|
| | RE-LY[9-11] | ROCKET AF[9-11] | ARISTOTLE[9-11] | ENGAGE AF-TIMI[9-11] |
| Mitral Regurgitation | X | X | X | |
| Aortic Regurgitation | X | X | | |
| Tricuspid Regurgitation | X | | | |
| Aortic stenosis | X | X | | |
| Mild mitral stenosis | X | | X | |
| Annuloplasty with/without prosthetic ring | | X | | |
| Valvuloplasty | | X | | |
| Tricuspid stenosis | | | X | |
| Valve repair | | | X | X |
| Bioprosthetic valve | | | X | X |

## "Valvular Heart Disease" EXCLUSION Criteria

| EXCLUSION Criteria | Pivotal Trial | | | |
|---|---|---|---|---|
| | RE-LY[9-11] | ROCKET AF[9-11] | ARISTOTLE[9-11] | ENGAGE AF-TIMI[9-11] |
| Bioprosthetic Valve replacement | X | X | | |
| Hemodynamically relevant valve disease | X | | | |
| Active endocarditis | X | X | X | X |
| Mechanical valve replacement | X | X | X | X |
| Moderate-severe mitral stenosis | X | X | X | X |
| Unresected atrial myxoma | X | | | X |

## Use of DOACs for Atrial Fibrillation in the Setting of Valvular Heart Disease

| Type of Valvular Heart Disease | Guideline Recommendations | | | Other Literature |
|---|---|---|---|---|
| | CHEST[6] | ACC/AHA[7] | EHRA[8] | |
| Bioprosthetic Valve Replacement | - | - | Avoid use during first 3 months<br>Do not use for rheumatic mitral stenosis | -Sub-analyses of ARISTOTLE and ENGAGE AF-TIMI in patients who had bioprosthetic valves showed no difference in stroke or major bleeding.[14-15] |
| TAVR/TAVI | - | "The utility of DOACs in this population is unknown at this time" | Unknown: No prospective data yet | - In patients with AF undergoing TAVR, those treated with apixaban vs warfarin showed lower rates of life-threatening bleeding and a reduction in the composite early safety endpoint (all-cause mortality, stroke, life-threatening bleeding, AKI, coronary obstruction, major vascular complications and valve dysfunction requiring intervention).[16]<br>-In a retrospective analysis, patients with AF undergoing TAVR, continued anticoagulation with VKA or DOAC resulted in fewer deaths at 1 year than interrupting VKA therapy. DOACs actually had the fewest deaths of all groups.[17] |
| Active Endocarditis | - | - | - | |
| Moderate to severe mitral stenosis (including rheumatic stenosis) | AVOID USE | AVOID USE | AVOID USE | -DOAC (rivaroxaban, apixaban, dabigatran and edoxaban) compared to warfarin in patients with mitral stenosis (unspecified degree of mitral stenosis) demonstrated fewer incidences of TE in DOAC group and no difference in ICH.[18] |
| Mild Mitral stenosis | - | DOAC reasonable* | Eligible to consider DOAC | *Except for mitral stenosis from rheumatic origin->VKA only |
| Mitral regurgitation | - | DOAC reasonable | Eligible to consider DOAC | |
| Aortic stenosis or regurgitation | - | DOAC reasonable | Eligible to consider DOAC | |
| Tricuspid stenosis or regurgitation | - | DOAC reasonable | Eligible to consider DOAC | |
| Mitral Valve repair | - | - | Acceptable to use >3 months post-operatively | -ACC/AHA guidelines outline that patients with significant mitral stenosis requiring intervention were excluded.[7]<br>- Hypothesis generating: Case series of 27 patients with atrial fib and a biological prosthesis, repaired mitral valve, or tubular aortic graft were treated with rivaroxaban found no recurrent thrombosis and minor bleeding.[19] |

**In the pipeline:**
**TAVR**: ATLANTIS trial (apixaban vs warfarin) [June 2020]; ENVISAGE-TAVI (edoxaban vs warfarin) [est. completion Nov. 2020]; ADAPT-TAVR (edoxaban vs DAPT) [est. completion Dec. 2020]
**Bioprosthetic valves**: RIVER (rivaroxaban vs warfarin) [est. completion Dec. 2019]; dabigatran in patients with AF and mitral biological prostheses
**Mechanical valve**: RIWAMP (rivaroxaban vs warfarin) [est. completion May 2020]; RMV (rivaroxaban vs warfarin)
**Rheumatic heart disease:** INVICTUS-ASA (rivaroxaban vs ASA)

## Conclusions:

Current literature suggests DOACs may be used for A.Fib in patients with a history of bioprosthetic valves, TAVR & other valvular abnormalities. DOACs should not be used to specifically anticoagulate patients for valve replacement (bioprosthetic, mechanical, TAVR/TAVI). It appears the use of DOACs should be avoided in patients with mechanical & bioprosthetic valves if indication for replacement was rheumatic mitral stenosis, moderate-severe mitral stenosis and/or active endocarditis.


References:
1. Connolly ST, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. *NEJM*. 2009; 361:1139-1151.
2. Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *NEJM*. 2011;365:883-891.
3. Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. *NEJM*. 2011; 365:981-992.
4. Giugliano RP, Ruff CT, Braunwald E et al. Edoxaban versus warfarin in patients with atrial fibrillation. *NEJM*. 2013; 369:2093-2104.
5. January CT, Wann LS, Calkins H et al. 2019 AHA/ACC/HRS Focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *JACC*. 2019; 140:125-151.
6. Whitlock RP, Sun JC, Fremes Se et al. Antithrombotic and thrombolytic therapy for valvular disease. *CHEST*. 2012;141(2):576s-600s
7. Nishimura RA, Otoo CM, Bonow RO et al. 2017 AHA/ACC Focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. *JACC*. 2017; 135:1159-1195.
8. Steffel J, Verhamme P, Potpara TS et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *European Heart Journal*. 2018;39:1330-1393.
9. Anderson SL, Marrs JC. Direct oral anticoagulant use in valvular heart disease. *Clinical Medicine Insights: Therapeutics*. 2017;10:1-6.
10. Biase LD. Use of direct oral anticoagulants in patients with atrial fibrillation and valvular heart lesions. *J Am Heart Assoc*. 2016;5(2):1-9.
11. Pan KL, Singer DE, Ovbiagele B et al. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017; 6(7):1-12.
12. Duraes AR, de Souza Roriz P, de Almeida Nunes B et al. Dabigatran versus warfarin after bioprosthesis valve replacement for the management of atrial fibrillation postoperatively: DAWA Pilot Study. *Drugs R D*. 2016;16(2):149-154.
13. Windecker S, Tijssen J, Giustino G et al. Trial design: rivaroxaban for the prevention of major cardiovascular events after transcatheter aortic valve replacement: rationale and design of the GALILEO study. *Am Heart J*. 2017;184:81-87.
14. Pokorney SD, Rao MP, Wojdyla DM, et al. Apixaban use in patients with atrial fibrillation with bioprosthetic valves: insights from ARISTOTLE. *Circulation*. 2015;132: A17277.
15. Carnicelli AP, De Caterina R, Halperin JL, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. *Circulation*. 2017;135:1273–1275.
16. Seeger J, Gonska B, Rodewald et al. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement . *JACC*. 2016; 10(1):66-74.
17. Mangner N, Crusius L, Haussig S et al. Continued vs interrupted oral anticoagulation during transfemoral transcatheter aortic valve implantation and impact of postoperative anticoagulant management on outcome in patients with atrial fibrillation. *Am J Cardiol*. 2019;123(7):1134-41.
18. Kim JY, Kim SH, Myong JP et al. Outcomes of direct oral anticoagulants in patients with mitral stenosis. *JACC*. 2019;73(10): 1123-31.
19. Acanfora D, Acanfora C, Scicchitano P, et al. Safety and feasibility of treatment with rivaroxaban for non-canonical indications: a case series analysis. Clin Drug Investing. 2016;36:857–862.



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