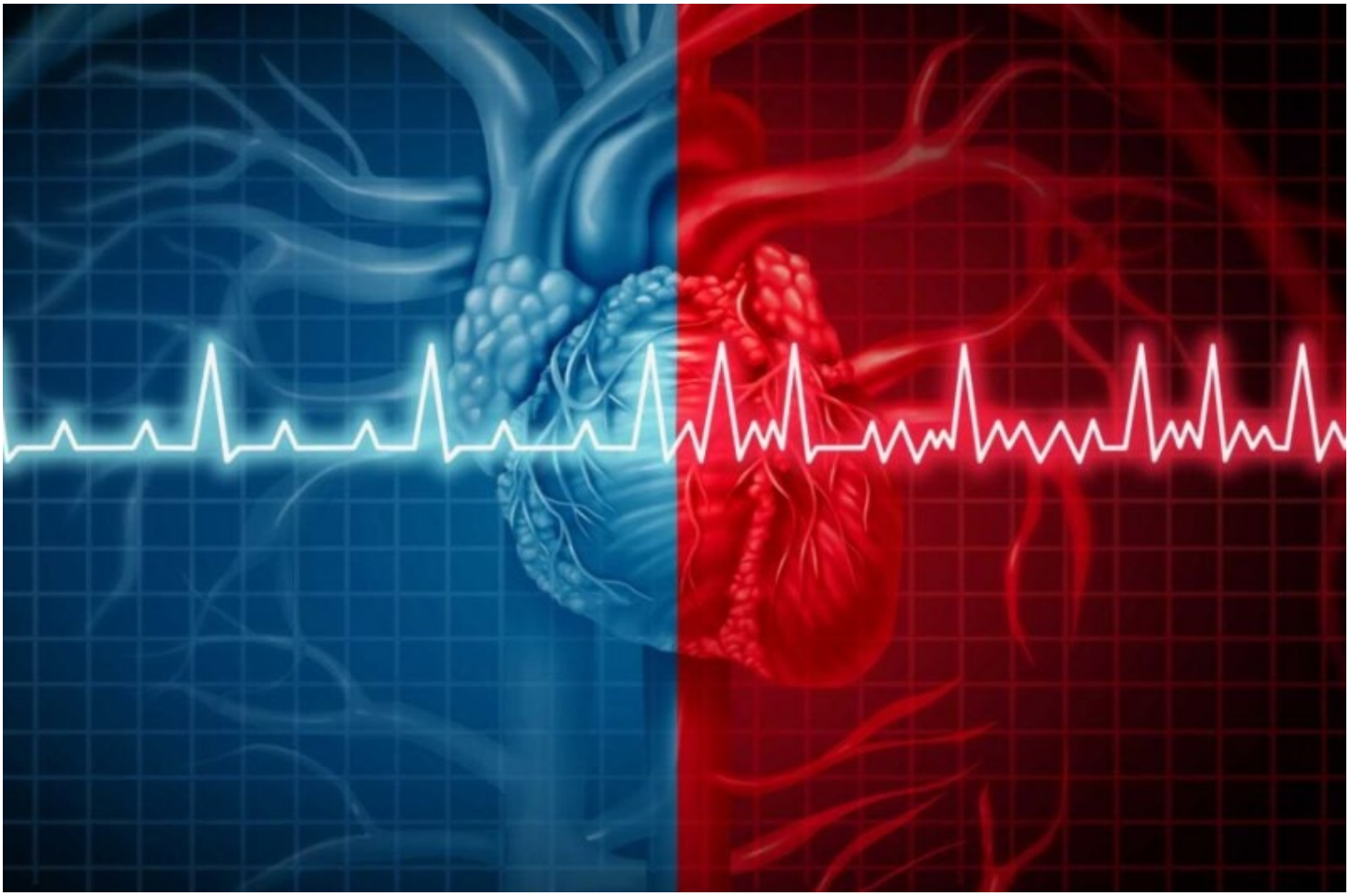
DO or DOn't? The Use of Direct Oral Anticoagulants in Patients with Atrial Fibrillation and Bioprosthetic Valves



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Controversies in Clinical Therapeutics

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Objectives for pharmacists

1. Discuss the current guideline recommendations of anticoagulation in patients with atrial fibrillation following valve replacement.
2. Analyze primary literature support the use of direct oral anticoagulation in patients with atrial fibrillation and bioprosthetic valves.
3. Evaluate the risk versus benefit of using direct oral anticoagulants compared to vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves.

Objectives for technicians

1. List anticoagulants used in patients with atrial fibrillation following valve replacement.
2. Identify direct oral anticoagulant or warfarin dosing utilized for stroke prevention in patients with atrial fibrillation.
3. Compare risk versus benefit of using direct oral anticoagulants compared to vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves.

Figure 1 – Anticoagulant Overview[1]

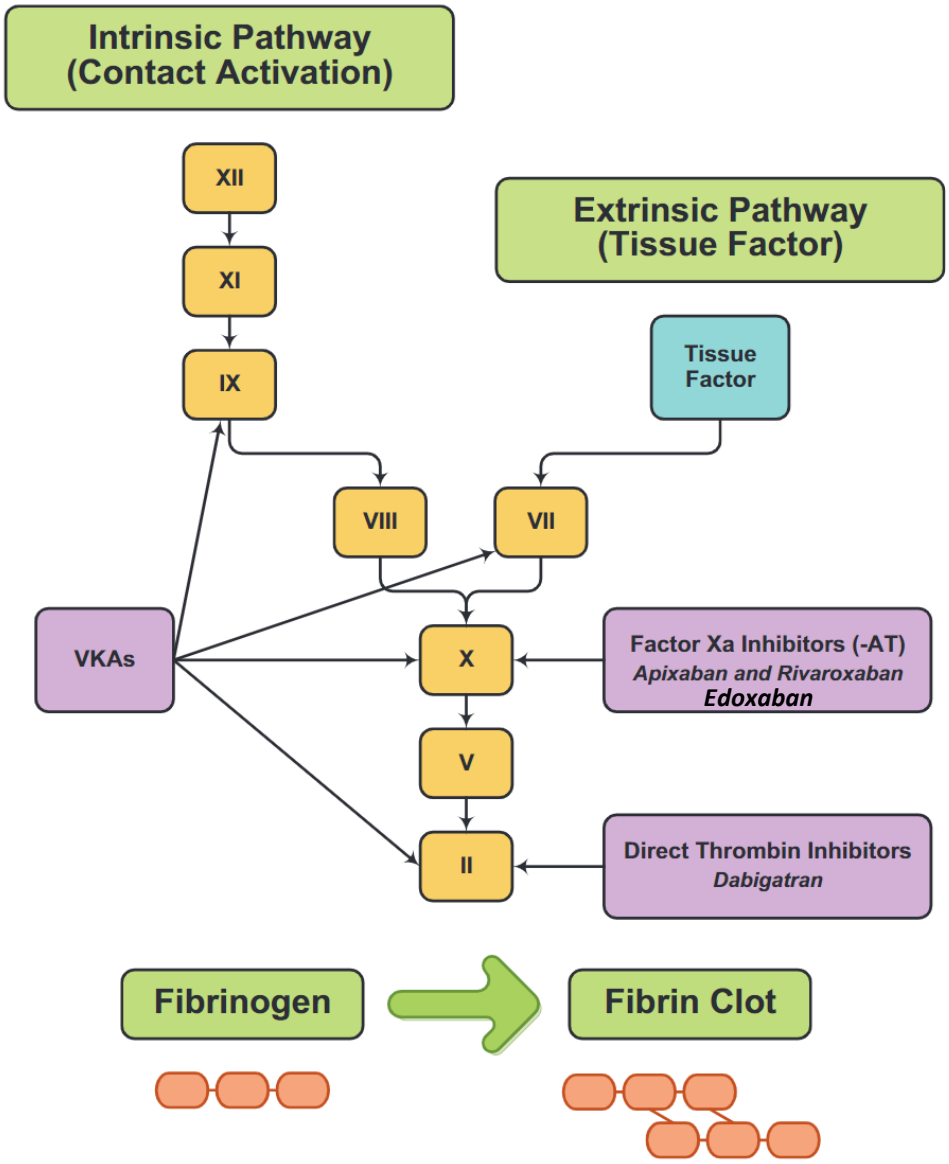


Table 1 – Overview of Oral Anticoagulants[2-6]

Drug	MOA	Dosing for AF	Renal Dosing for AF	Monitoring	Cost
Warfarin (Coumadin)	Vitamin K antagonist	Dosed to an INR of 2.0-3.0	Dosed to INR 2.0-3.0	INR twice weekly until in goal, then every 3-6 months thereafter	$0.61-1.02 per each
Edoxaban (Savaysa)	Factor Xa inhibitor	60mg PO daily	CrCl 15-50mL/min: 30mg once daily	Hemoglobin, hematocrit, platelets, renal function	$15.56 per each
Rivaroxaban (Xarelto)	Factor Xa inhibitor	20mg PO daily with the evening meal	CrCl 15-50mL/min: 15mg PO daily with the evening meal		$19.75 per each
Apixaban (Eliquis)	Factor Xa inhibitor	5mg PO BID	Weight <60kg, SCr >1.5, age >80: 2.5mg PO BID		$9.98 per each
Dabigatran (Pradaxa)	Direct thrombin inhibitor	150mg PO BID	CrCl 15-30mL/min: 75mg PO BID		$9.54 per each

Table 2 – Continued Overview of Oral Anticoagulants[7]

Drug	Advantages	Disadvantages
Warfarin	Can be used in end stage renal disease Cost	High risk of intracranial bleeding Drug and food interactions Complicated dosing
Direct Oral Anticoagulants (DOAC)	Less frequent lab monitoring Some trials demonstrate less bleeding compared to warfarin Simplified dosing	Cost Fewer studies in specific populations

Atrial Fibrillation[8]

- What is atrial fibrillation (AF)?
    - AF is a common type of cardiac arrythmia
    - It is due to abnormalities in the electrical signals in the atria of the heart, causing them to fibrillate

Table 3 – Types of AF

Types of AF	
Paroxysmal	- Episodes terminate spontaneously, but may reappear unpredictably
Persistent	- When an episode is continuous, and does not terminate spontaneously - Episodes lasting more than 7 days, and if it is associated with a rapid and uncontrolled ventricular response
Long standing persistent	- AF that is present for greater than 12 months - Can be due to failure to initiate pharmacologic intervention or failure of cardioversion
Permanent	- Normal sinus rhythm cannot be restored

- The Need for Anticoagulation in AF
    - Irregular atrial rhythm can cause blood to pool and clot
    - This clot can dislodge and cause a cardioembolic stroke
- Stroke Risk[9]
    - Risk stratification using the CHA_2DS_2 VASc Score
        - This estimates the risk of stroke
    - Men with a score ≥2 or women with a score ≥3 are indicated for anticoagulation

Table 4 – Review of CHA_2DS_2 VASc[10]

CHA_2DS_2 VASc	Points
C – Congenital Heart Failure	1
H – Hypertension	1
A – Age >75	2
D – Diabetes Mellitus	1
S – History of Stroke or TIA	2
V – Vascular Disease (PAD, MI)	1
A – Age 65-74	1
Sc – Sex Category (female)	1

- Bleeding Risk
  - The HAS-BLED Score is utilized to compare the risk versus benefit of stroke and bleeding risk in a patient with AF
  - A score ≥3 indicates a higher risk of bleeding
  - This does not mean one should discontinue anticoagulation, but should have careful follow up due to risk of bleeding

Table 5 – Review of HAS-BLED Score[10]

HAS-BLED		Points
H	Hypertension (Systolic >160mmHg)	1
A	Abnormal Liver or Renal Function (Dialysis, transplant, SCr >2.26mg/dL) (Cirrhosis or bilirubin >2x upper limit normal, AST/ALT >3x upper limit normal)	1
S	Stroke History	1
B	Prior Major Bleeding	1
L	Labile INR (Time in therapeutic range <60%)	1
E	Elderly (Age >65)	1
D	Drugs (aspirin, P2Y12, NSAIDs) or Alcohol (>8 drinks/week)	1

Current Guideline Recommendations[9]

- DOAC vs. VKA for Stroke Prevention in AF
  - DOACs in comparison are preferred over VKAs (warfarin)
    - The DOAC AF trials demonstrated either non-inferiority or superiority to warfarin in prevention of thromboembolism
    - These trials demonstrated either similar rates or reduced intracranial bleeding compared to warfarin

Table 6 – Review of DOAC vs. Warfarin Trials[11-14]

Trial	Drug	Inferiority	Bleeding	Mortality
RE-LY	Dabigatran vs. warfarin	Superior for prevention of stroke	Similar bleeding	No difference
ROCKET-AF	Rivaroxaban vs. warfarin	Noninferior for prevention of stroke	Similar bleeding	No difference
ARISTOTLE	Apixaban vs. warfarin	Superior for prevention of stroke	Less major and minor bleeding	Less death from any cause
ENGAGE AF-TIMI 48	Edoxaban vs. warfarin	Noninferior for prevention of stroke	Lower bleeding	Decreased rates of CV death

- Non-valvular vs. Valvular AF
    - Non-valvular AF[15]
        - Supraventricular tachyarrhythmia with uncoordinated electrical activation and ineffective atrial contraction
        - The definition is one of exclusion, as non-valvular AF does not imply the absence of valvular AF
    - Valvular AF[9]
        - Refers to AF in the setting of moderate to severe mitral stenosis or in the presence of an artificial (mechanical) heart valve

Valvular Heart Disease

- What is valvular heart disease (VHD)?[16]
    - Damage to or a congenital defect in one or more heart valves
- Two types of problems
    - Stenosis
        - Valves fail to open properly
        - Can impede blood flow
    - Regurgitation
        - Valves do not close properly, allowing them to leak
        - This can permit backflow of blood
- Causes
    - Congenital, inflammation, or complication of infection
- Treatment
    - Valve replacement or valve repair
- Patients with no baseline indication for anticoagulation[17]
    - VKA should be considered in patients with a mitral or tricuspid bioprosthetic valve
    - Aspirin or VKA should be considered after surgical implant of aortic bioprosthesis
- VHD and AF[15]
    - VHD and AF are independent of each other
    - More than 1/3 of AF patients have some form of VHD
    - Having concurrent VHD and AF can increase the risk of thromboembolism and stroke

Table 7 – Review of Replacement Heart Valves[18] – 2017 AHA/ACC VHD Guidelines

Bioprosthetic versus Mechanical Heart Valve	
Bioprosthetic	**Mechanical**
Lower rates of bleeding	Higher rates of bleeding
Higher rates of reoperation	Lower rates of reoperation
Lower bleeding complications	Higher bleeding complications
Beneficial in patients aged >70 years	Beneficial in patients aged <60 years
Do not require lifelong anticoagulation	**Require** lifelong anticoagulation

Figure 2 – Types of Replacement Heart Valves[19]

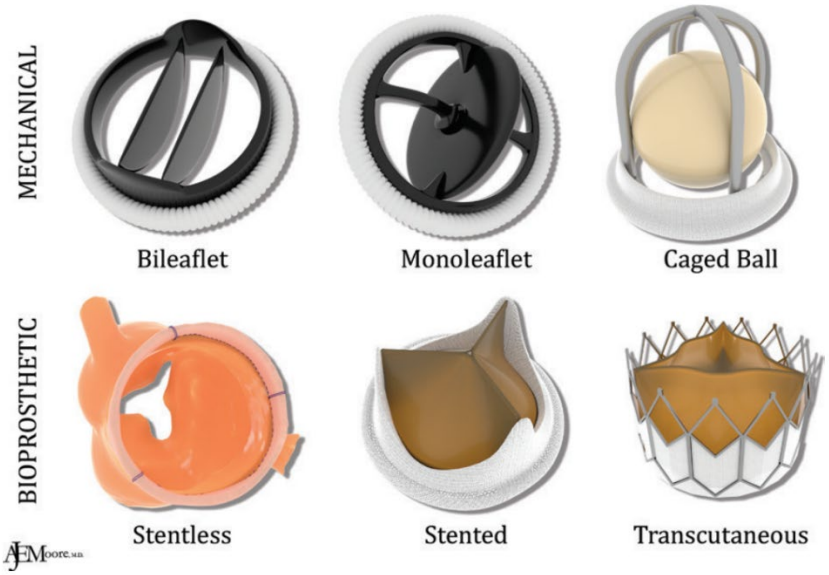
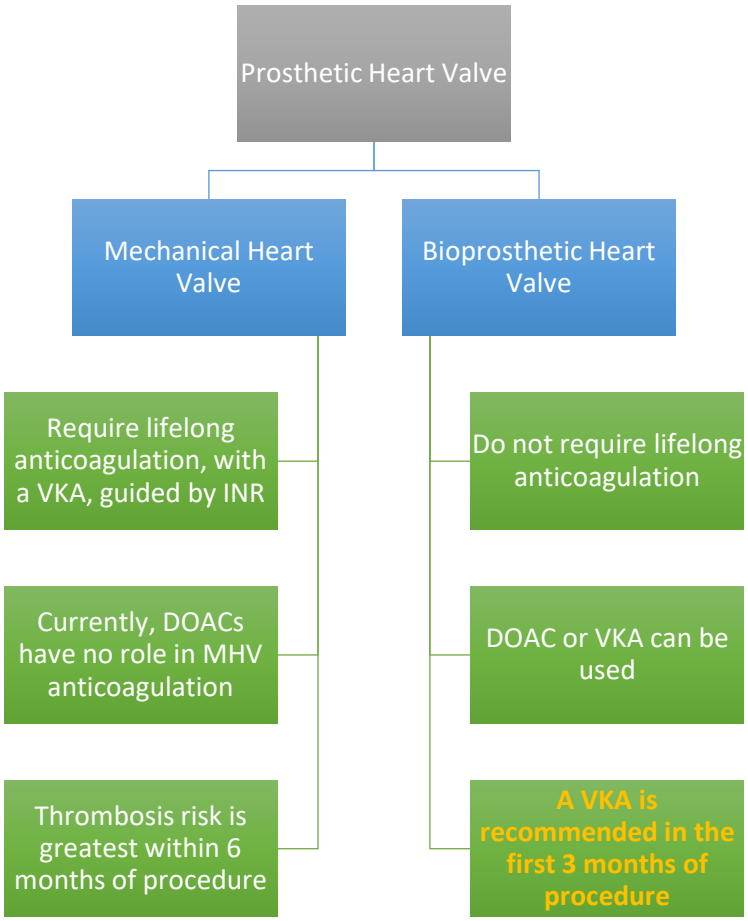


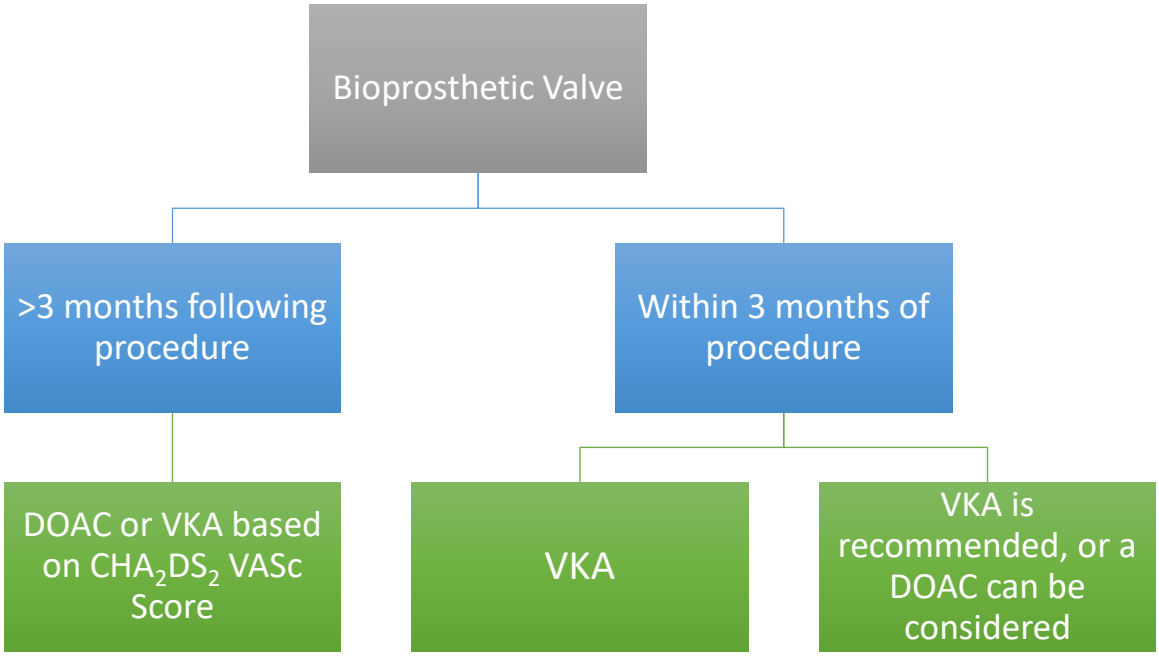
Figure 3 – Role of Anticoagulation in Valvular Heart Disease[17]



Mechanical Heart Valve (MHV) Anticoagulation Strategy[17]

- Only a VKA can be used in patients with MHV
- The RE-ALIGN trial was a phase II study comparing dabigatran to warfarin in patients following mechanical heart valve replacement
- The trial was stopped early due to increased risk of stroke and bleeding in the dabigatran group

Figure 4 – Bioprosthetic Valve (BPV) Anticoagulation Strategy for Patients with AF[17, 20]



Clinical Controversy

- In patients with AF, after the initial 3 months following BPV implantation, DOACs should be considered over VKAs
- The use of DOACs in BPV implantation in the first 3 months following valve replacement is currently uncertain

Figure 5 – Review of Clinical Controversy

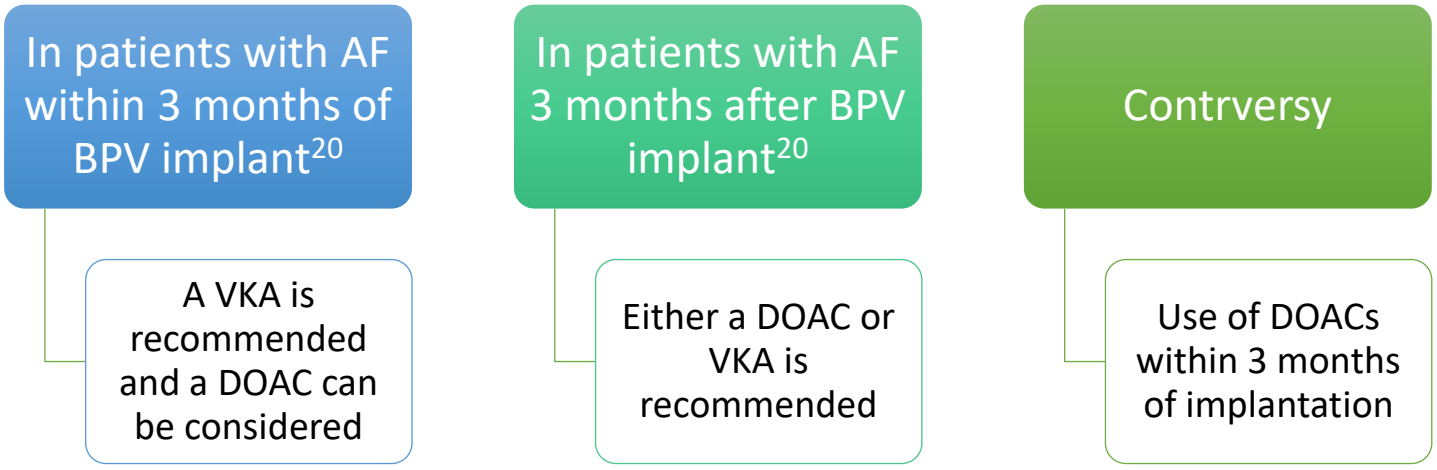


Table 8 – Review of ARISTOTLE Subgroup Analysis[21, 22]

Guimarães PO, Pokorney SD, Lopes RD, et al. Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: Insights from the ARISTOTLE trial. *Clin Cardiol*. 2019;42(5):568-571. doi:10.1002/clc.23178

Background		
Objective	To look at the efficacy and safety apixaban compared to warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or repair	
Methods		
Study Design	- Randomized, double-blind, double dummy, multinational trial - Median duration of follow up was 1.8 years	
Patient Selection	**Inclusion Criteria** - Atrial fibrillation or flutter or 2 episodes of atrial fibrillation or flutter confirmed by electrocardiography at least 2 weeks apart in the 12 months - $CHADS_2$ score ≥ 1 - History of BPV replacement or native valve repair	**Exclusion Criteria** - Atrial fibrillation due to reversible cause - Condition other than atrial fibrillation that requires anticoagulation - Moderate to severe mitral stenosis or mechanical heart valve - Need for aspirin >165mg, or aspirin and clopidogrel - Severe renal insufficiency (serum creatinine >2.5mg/dL or creatinine clearance <25mL/min)
Intervention	- Apixaban 5mg by mouth twice daily (or 2.5mg by mouth twice daily if indicated for reduced dose) - Warfarin dosed to an INR of 2.0-3.0	
Outcomes	- **Primary Outcome** - Stroke or systemic embolism - **Secondary Outcomes** - Death from any cause - **Safety Outcomes** - Major bleeding (ISTH) - Composite of major bleeding and clinically non-major bleeding	
Statistical Analysis	- Intention-to-treat analysis - 18,000 patients to achieve a power of 90%	

Results

Baseline characteristics

Characteristic	Apixaban (n=87)	Warfarin (n=69)
Age (median, IQR)	72 (63-79)	74 (65-78)
Female (n, %)	34 (39.1)	27 (39.1)
Prior stroke, TIA, or SE (n, %)	24 (27.6)	12 (17.4)
INR time in therapeutic range (median %)	-	66
History of bioprosthetic valve replacement (n, %)	104 (66.7)	
HAS-BLED (n, %)		
0-1	24 (27.6)	18 (26.1)
2	32 (36.8)	28 (40.6)
>3	31 (35.6)	23.3 (33.3)
$CHADS_2$ (n, %)		
≤1	31 (35.6)	18 (26.1)
2	26 (29.9)	28 (40.6)
≥3	30 (34.5)	23 (33.3)

Efficacy

Endpoint	Apixaban (n=87)	Warfarin (n=69)	HR (95% CI)	p-value
Stroke or systemic embolism (rate, n)	2.77 (4)	1.64 (2)	1.714 (0.313-9.372)	0.53
Death from any cause (rate, n)	4.61 (7)	4.79 (6)	1.017 (0.341-3.037)	0.98

Safety	<table><tr><th>Endpoint</th><th>Apixaban (n=87)</th><th>Warfarin (n=69)</th><th>p-value</th></tr><tr><td>**Major bleeding (rate, n)**</td><td>5.87 (7)</td><td>6.44 (7)</td><td>0.82</td></tr><tr><td>**Major or clinically relevant non-major bleeding (rate, n)**</td><td>7.68 (9)</td><td>9.50 (10)</td><td>0.59</td></tr></table>
Author's Conclusions	
Author's Conclusions	- Patients with bioprosthetic valves can receive apixaban for stroke prevention as a safe and effective option compared to warfarin
My Discussion and Conclusion	
Critique	- **Limitations**: Small subgroup analysis, low amount of events, unknown duration following bioprosthetic valve procedure, unknown INR time in therapeutic range, not all patients had a bioprosthetic valve replacement - **Strengths:** Double blind, multinational, high number of patients with concurrent comorbidities such as hypertension, coronary artery disease, and prior history of stroke or TIA, all included patients had AF
My Bottom Line	- In patients with AF who have received a BPV, efficacy and safety outcomes did not significantly differ between warfarin and apixaban, indicating apixaban may be a safe and effective option in patients following BPV implantation. At the time, this was the only data to support the use of apixaban in patients with bioprosthetic valves.

Table 9 – Review of ENGAGE TIMI-48 Subgroup Analysis[23]

Owens RE, Kabra R, Oliphant CS. Edoxaban Use in Nonvalvular Atrial Fibrillation With Valvular Heart Disease-Insights from ENGAGE AF-TIMI 48. *Clin Cardiol*. 2017;40(8):612-613. doi:10.1002/clc.22690		
Background		
Objective	To determine the safety and efficacy of edoxaban as compared to warfarin in patients with atrial fibrillation. This subgroup analysis took the opportunity to analyze the subgroup of patients with atrial fibrillation and a bioprosthetic valve.	
Methods		
Study Design	- Randomized, double blind, double dummy trial - Median duration of follow up was 2.8 years	
Patient Selection	**Inclusion Criteria** - Atrial fibrillation documented by means of electrical tracing within 12 months preceding randomization - $CHADS_2$ Score ≥ 2 - Anticoagulation planned for the duration of the trial - Patients with bioprosthetic valves (aortic or mitral)	**Exclusion Criteria** - Atrial fibrillation due to a reversible disorder - Estimated creatinine clearance < 30mL/min - High risk of bleeding - Use of dual antiplatelet therapy - Moderate-severe mitral stenosis and mechanical heart valves - Other indications for anticoagulation therapy - Acute coronary syndromes, coronary revascularization, or stroke within 30 days of randomization
Intervention	- Edoxaban 60mg PO daily (dose halved for CrCl 30-50mL/min, weight less than 60kg, or concomitant use of verapamil or quinidine) - Edoxaban 30mg PO daily (dose halved for CrCl 30-50mL/min, weight less than 60kg, or concomitant use of verapamil or quinidine) - Warfarin dosed to an INR of 2.0-3.0	
Outcomes	- **Primary Outcome** - Stroke or systemic embolic event (SEE) - Net outcome (Stroke/SEE, major bleeding, death) - **Secondary Outcomes** - Composite of ischemic stroke/SEE, major adverse cardiac events (MACE): myocardial infarctions, stroke, or cardiovascular death - Composite of stroke/SEE, all-cause mortality, and life threatening or fatal bleeding (alternate net outcome) - **Safety Outcomes** - Major bleeding (ISTH)	

Statistical Analysis

- Intention-to-treat
- With approximately 672 primary end point events, the study would have more than 87% power

Results

Baseline characteristics

Characteristic	Overall (n=191)
Age (median, IQR)	75 (69-79)
Female (%)	36.6
$CHADS_2$ (mean, SD)	3.0 (1.0)
HAS-BLED (mean, SD)	2.7 (1.1)
INR time in therapeutic range	68.9%
Previous stroke or TIA	20.9%
History of bioprosthetic valve replacement (n, %)	Mitral: 131 (68.6) Aortic: 60 (31.4)

Efficacy

Endpoint	High dose edoxaban (HDE) (n=63)	Low dose edoxaban (LDE) (n=58)	Warfarin (n=70)	HR (95% CI)	p-value	NNT
Stroke or systemic embolic event (HDE vs warfarin)	-	-	-	0.37 (0.10-1.42)	0.15	-
Net outcome (Stroke/SEE, major bleeding, death) (HDE vs warfarin)	7.53%/year	-	15.77%/year	0.46 (0.23-0.91)	0.03	13

Safety

Endpoint	High dose edoxaban (HDE) (n=63)	Low dose edoxaban (LDE) (n=58)	Warfarin (n=70)	HR (95% CI)	p-value	NNH
Major Bleeding (HDE vs warfarin)	-	-	-	0.50 (0.15-1.67)	0.26	-

Author's Conclusions

Author's Conclusions

- Patients with bioprosthetic valves treated with higher dose edoxaban had similar rates of stroke/SEE and major bleeding compared with warfarin
- Compared with warfarin, patients with bioprosthetic valves treated with high dose edoxaban had lower rates of myocardial infarction, stroke, and cardiovascular death and primary net outcome
- In patients with AF who have received a BPV who were treated with edoxaban in doses recommended for AF, there were similar rates of the primary and safety endpoint

My Discussion and Conclusion

Critique

- **Limitations**: Not all endpoints' rates were disclosed, small subgroup analysis, limited number of patients, little reporting on baseline characteristics and comorbidities, unknown duration following bioprosthetic valve procedure
- **Strengths:** Protocol specifically allowed patients with bioprosthetic valve replacement or repair, all patients had AF and a bioprosthetic heart valve implantation

My Bottom Line

- In patients with AF who have received a BPV, efficacy and safety outcomes were similar with some significant differences favoring edoxaban, indicating that edoxaban can be considered a safe and effective option in patients following BPV implantation. This data continued to increase knowledge in this specific patient population

Table 10 – Review of DAWA Pilot Trial[24]

Durães 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. doi:10.1007/s40268-016-0124-1

Background

Objective

To determine the safety and efficacy of dabigatran use in patients with atrial fibrillation at least 3 months after bioprosthetic valve implantation

Methods

Study Design

- Phase 2, prospective, open-label, randomized pilot study

Patient Selection

Inclusion Criteria
- 18-64 years old
- Mitral and/or aortic bioprosthetic valve replacement at least 3 months prior to entering this study
- Documented atrial fibrillation postoperatively
- Non-contrast brain computed tomography (CT) without hemorrhage or findings of acute cerebral infarction on the last 2 days of screening were necessary

Exclusion Criteria
- Previous hemorrhagic stroke
- Ischemic stroke in the last 6 months
- Severe renal impairment (CrCl <30mL/min)
- Active liver disease (any etiology)
- Concomitant use of any antiplatelet (aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, etc.)
- Increased risk of bleeding
- Uncontrolled hypertension

Intervention

- Dabigatran 110mg by mouth twice daily
- Warfarin dosed to an INR of 2.0-3.0

Outcomes

- **Primary Outcome**
- Detection of intracardiac thrombus in TEE at the end of follow-up (90 days)
- **Secondary/Safety Outcomes**
- Dense spontaneous echo contrast (SEC)
- Stroke (ischemic or hemorrhagic) or systemic embolism
- Reversible ischemic neurological deficit
- Bleeding event (major or minor) (ISTH)
- Hospitalization
- Death

Statistical Analysis

- Primary analysis was intention-to-treat
- Safety analysis was performed on all patients treated

Results

Baseline characteristics

Characteristic	Dabigatran (n=15)	Warfarin (n=12)
Age, years (mean, SD)	48.8 (10.4)	45.7 (6)
Female (n, %)	10 (66.6)	7 (58.3)
Hypertension (n, %)	7 (46.7)	6 (50)
Previous stroke (n, %)	4 (26.7)	4 (33.3)
HAS-BLED (median, IQR)	0 (0-1)	0 (0-1)
INR time in therapeutic range (mean, SD)	-	66.5 (7)

Efficacy/Safety

Endpoint	Dabigatran (n=15)	Warfarin (n=12)	RR (95% CI)	p-value
Intracardiac Thrombus (n, %)	0	1 (8.3)	1.1 (0.9-1.3)	0.42
Dense SEC (n, %)	7 (46.7)	3 (25%)	HR 0.38 (0.1-2.0)	0.23
Stroke or systemic embolism (n, %)	0	1 (8.3)	1.1 (0.9-1.9)	0.44
Reversible ischemic neurological deficit (n, %)	1 (6.7)	0	0.9 (0.8-1.0)	0.55
Bleeding (n, %)	1 (6.7)	2 (16.7)	2.8 (0.2-35)	0.41
Hospitalization (n, %)	1 (6.7)	1 (8.3)	1.3 (0.7-22)	0.70
Death (n, %)	0	1 (8.3)	1.1 (0.9-1.3)	0.44

Author's Conclusions

Author's Conclusions

- The trial was stopped early due to significant decrease of eligible candidates for enrollment. There was also a high rate of intracardiac thrombus detected in the selection phase.
- Despite the small sample size, this was the first randomized control trial that has held a direct comparison between a direct oral anticoagulant and warfarin in patients with a bioprosthetic valve and atrial fibrillation until now
- Both primary and secondary endpoints had few events in either group

My Discussion and Conclusion	
Critique	- **Limitations**: Only looked at DOAC use greater than 3 months following bioprosthetic valve replacement, small population, trial stopped early - **Strengths:** One of the first randomized trials to study use of a DOAC vs warfarin specifically in patients with a history of bioprosthetic valve replacement, specific inclusion of patients with AF and bioprosthetic valve
My Bottom Line	- In patients with AF who have received a BPV, efficacy and safety outcomes did not differ significantly between warfarin and dabigatran, indicating that dabigatran may be considered a safe and effective option in patients following BPV implantation. This trial continued to expand clinical knowledge on the use of DOACs in this specific population

Table 11 – Review of RIVER Trial[25]

Guimarães HP, Lopes RD, de Barros E Silva PGM, et al. Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve. *N Engl J Med*. 2020;383(22):2117-2126. doi:10.1056/NEJMoa2029603		
Background		
Objective	To assess the efficacy and safety of rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve	
Methods		
Study Design	- Randomized, non-inferiority, open-label trial with blinded adjudication of outcomes	
Patient Selection	**Inclusion Criteria** - Permanent, paroxysmal, or persistent atrial fibrillation or flutter - Bioprosthetic valve who were receiving (or planning to receive) oral anticoagulation for thromboembolism prophylaxis - Eligible at least 48 hours after undergoing mitral-valve surgery	**Exclusion Criteria** - Contraindication to either rivaroxaban or warfarin - Uncontrolled hypertension (Systolic >180mmHg, diastolic >100mmHg) - Active internal bleeding - Treatment with aspirin doses >100mg or double antiplatelet therapy within 5 days of randomization - Anemia (hemoglobin <7.5g/dL) - CrCl <30mL/min - Significant liver disease or alanine aminotransferase >3x upper limit of normal - Transient atrial fibrillation caused by surgery - Placement of mechanical valves
Intervention	- Rivaroxaban 20mg PO daily (CrCl 30-49mL/min received 15mg PO daily) - Warfarin dosed to an INR of 2.0-3.0	
Outcomes	- **Primary Outcome** - Composite of death, major cardiovascular events (TIA, valve thrombosis, systemic embolism not related to CNS, or hospitalization for heart failure), or major bleeding at 12 months - **Secondary Outcomes** - Composite of death from cardiovascular causes or thromboembolic events (stroke, TIA, deep vein thrombosis, pulmonary embolism, valve thrombosis, or systemic embolism not related to CNS) - **Safety Outcomes** - Bleeding events (major, clinically relevant non-major bleeding, minor, and total) per TIMI and BARC	
Statistical Analysis	- Intention-to-treat for all patients who had undergone randomization - Primary outcome was reported according to restricted mean survival time (RMST) - Enrollment of 1000 patients would provide 80% power to detect a non-inferiority margin of 8 days	
Results		

Baseline characteristics

Characteristic	Rivaroxaban (n=500)	Warfarin (n=505)
Age, years (mean, SD)	59.4 (2.4)	59.2 (11.8)
Female (n, %)	311 (62.2)	296 (58.6)
Previous stroke (n, %)	63 (12.6)	66 (13.1)
Creatinine clearance (median, IQR)	77.4 (58.8-95.7)	77.7 (59.1-96.8)
CHA_2DS_2-VASc Score (mean, SD)	2.7 (1.5)	2.5 (1.3)
HAS-BLED Score (mean, SD)	1.6 (0.6)	1.6 (0.9)
INR time in therapeutic range (median, IQR)	-	65 (51.3-70.5)

Interval between mitral valve implantation and randomization (n, %)		
<3mo	94 (18.8)	95 (18.8)
3mo – <1yr	91 (18.2)	78 (15.4)
1yr – <5yr	160 (32.0)	164 (32.5)
5yr – <10yr	148 (29.6)	160 (31.7)
Missing data	7 (1.4)	8 (1.6)

Efficacy

Endpoint	Rivaroxaban (n=500)	Warfarin (n=505)	RMST difference or HR (95% CI)	p-value	NNT
Primary composite outcome (time to event)	347.5 days	340.1 days	7.4 days (-1.4-16.3)	<0.001 (non-inferiority)	-
Death from cardiovascular causes or thromboembolic events (n, %)	17 (3.4)	26 (5.1)	0.65 (0.35-1.2)	-	-
Any stroke (n, %)	3 (0.6)	12 (2.4)	0.25 (0.07-0.88)	-	56
Valve thrombosis (n, %)	5 (1.0)	3 (0.6)	1.68 (0.40-7.01)	-	-
Hospitalization for heart failure (n, %)	22 (4.4)	19 (3.8)	1.15 (0.62-2.13)	-	-

Endpoints in patients randomized up to 3 months after surgery

Endpoint	Rivaroxaban (n=94)	Warfarin (n=95)	HR (95% CI)	NNT
Primary composite outcome (n, %)	6 (6.38)	18 (18.95)	0.31 (0.12-0.79)	8

Safety

Endpoint	Rivaroxaban (n=500)	Warfarin (n=505)	HR (95% CI)
Any bleeding (n, %)	65 (13.0)	78 (15.4)	0.83 (0.59-1.15)
Major bleeding (n, %)	7 (1.4)	13 (2.6)	0.54 (0.21-1.35)
Clinically relevant non-major bleeding (n, %)	24 (4.8)	23 (4.6)	1.05 (0.60-1.87)

-

Author's Conclusions

Author's Conclusions

- Patients with atrial fibrillation who had undergone bioprosthetic mitral valve surgery receiving rivaroxaban were free of a primary endpoint including death, major cardiovascular effects, or major bleeding for 7.4 days longer than those who received warfarin, and was found to be non-inferior

My Discussion and Conclusion

Critique

- **Limitations**: Open label, however attempted to mitigate this through the blinded end point adjudication of end points, low percentage of patients having received valve replacement within 3 months of randomization, necessitating the need for further studies in this population, single center population in Brazil
- **Strengths:** Blind assessment of outcomes, large population, specific inclusion of patients with AF and bioprosthetic valve

My Bottom Line

- In patients with AF who have received a BPV, efficacy outcomes were statistically significant demonstrating rivaroxaban was non-inferior to warfarin, while safety outcomes did not differ significantly when compared to warfarin, indicating that rivaroxaban may be considered a safe and effective option in patients following BPV implantation
- This trial continued to bring new findings to the use of a direct oral anticoagulant within 3 months of bioprosthetic valve replacement. Patients who have had a bioprosthetic mitral valve replaced carry a greater thromboembolism risk than those who have an aortic replacement

Table 12 – Review of ENAVLE Trial[26]

Shim CY, Seo J, Kim YJ, et al. Efficacy and safety of edoxaban in patients early after surgical bioprosthetic valve implantation or valve repair: A randomized clinical trial [published online ahead of print, 2021 Feb 9]. *J Thorac Cardiovasc Surg*. 2021;S0022-5223(21)00228-2.

Background

Objective

Compare safety and efficacy of edoxaban with warfarin in patients early after surgical bioprosthetic valve implantation or valve repair

Methods

Study Design

- Prospective, randomized, open-label trial

Patient Selection

Inclusion Criteria
- Ages 20-85 having undergone successful surgical bioprosthetic valve implantation in either the mitral valve or aortic position, or valve repair
- Within 3 months of BPV implantation
- Randomization was 5-9 days post-operation, but before discharge

Exclusion Criteria
- Contraindications to heparin, warfarin, or edoxaban
- Mechanical heart valve in any position
- Bioprosthetic transcatheter implantation or mitral edge-to-edge repair
- High risk for bleeding
- Creatinine clearance <30mL/min
- Infective endocarditis
- Any liver disease associated with coagulopathy

Intervention

- Edoxaban 60mg by mouth daily (30mg if CrCL 30-50mL/min or weight <60kg)
- Warfarin dosed to an INR of 2.0-3.0

Outcomes

- **Primary Outcome**
- Composite of death from any cause, clinical thrombotic events (stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism, deep vein thrombosis, or pulmonary embolism), or asymptomatic intracardiac thrombosis (subclinical leaflet thrombosis or thrombus within cardiac cavity) 12 weeks after randomization
- **Secondary Outcomes**
- Primary efficacy plus major bleeding
- Primary efficacy plus major bleeding plus clinically relevant non-major bleeding (CRNM)
- Primary efficacy plus major bleeding plus CRNM bleeding plus cardiovascular rehospitalization
- **Safety Outcomes**
- Major bleeding (ISTH)
- Composite of major and clinically relevant non-major bleeding (ISTH)

Statistical Analysis

- With 220 patients the study would achieve 90% power to show non-inferiority of warfarin to edoxaban at a 1 sided 2.5% significance level

Results

Baseline characteristics

Characteristic	Edoxaban (n=109)	Warfarin (n=109)
Age, years (mean, SD)	67 (12.3)	67.7 (10.0)
Female (n, %)	57 (52)	47 (43)
Atrial Fibrillation (n, %)	65 (60)	61 (56)
Hypertension (n, %)	65 (60)	63 (58)
Prior stroke (n, %)	10 (9)	6 (6)
CHA_2DS_2 VASc Score (mean, SD)	2.8 (1.6)	2.6 (1.5)
HAS-BLED Score (mean, SD)	1.7 (1.0)	1.5 (1.0)
INR time in therapeutic range (%)	-	53.4
Aortic valve replacement (n, %)	107 (49)	
Mitral valve replacement (n, %)	45 (21)	

Efficacy

Endpoint	Edoxaban (n=109)	Warfarin (n=109)	Risk Difference (95% CI)	p-value	NNT
Primary Outcome (n, %)	0 (0)	4 (3.67)	-0.0367 (-0.0720 to -0.0014)	<0.001	28
Death (n, %)	0 (0)	0 (0)	-	-	-
Clinical thrombotic event (n, %)	0 (0)	1 (0.92)	-	-	-
Asymptomatic intracardiac thrombus (n, %)	0 (0)	1 (0.92)	-	-	-

	Primary efficacy plus major bleeding (n, %)	3 (2.75)	5 (4.59)	-0.0183 (-0.0682 to 0.0315)	0.002	-
	Primary efficacy plus CRNM bleeding (n, %)	4 (3.67)	6 (5.50)	-0.0183 (-0.0738 to 0.0371)	0.002	-
	Primary efficacy plus major bleeding plus CRNM plus cardiovascular rehospitalization (n, %)	8 (7.34)	10 (9.17)	-0.0183 (-0.0914 to 0.0547)	0.007	-

Safety

Endpoint	Edoxaban (n=109)	Warfarin (n=109)	Risk Difference (95% CI)	p-value	NNH
Major bleeding (n, %)	3 (2.75)	1 (0.92)	0.0183 (-0.0172-0.0539)	0.013	54
Clinically relevant non-major bleeding (n, %)	1 (0.92)	1 (0.92)	0 (-0.0253-0.0253)	0.002	-
Major bleeding and clinically relevant non-major bleeding (n, %)	4 (3.67)	2 (1.83)	0.0183 (-0.0250-0.0617)	0.018	54

Author's Conclusions

Author's Conclusions

- Edoxaban was non-inferior to warfarin in preventing thromboembolism in the first 3 months following bioprosthetic valve replacement or repair

My Discussion and Conclusion

Critique

- **Limitations**: Small population, single center population in Korea, only about 60% of the population had AF, and both aortic and mitral valve replacements included
- **Strengths:** Included patients within the first 3 months following valve replacement, comparing a DOAC to the current standard of care, even though the study did not meet power, a statistical difference was still seen in the primary outcome

My Bottom Line

- This is one of the first randomized control trials looking at DOAC use in the first 3 months following bioprosthetic valve replacement.
- In patients with AF who have received a BPV, efficacy and safety outcomes were statistically significant demonstrating edoxaban was non-inferior to warfarin, indicating edoxaban could be a safe and effective option in patients following BPV implantation

Final Recommendations

Current Guideline Recommendations

- Per the 2020 AHA/ACC VHD Guidelines, only VKAs are recommended within 3 months of BPV implantation[20]
- Per the 2021 ESC VHD Guidelines, a VKA is recommended, and a DOAC may be considered[17]

Literature Considerations

- RIVER only had about 20% of patients within 3 months of BPV implant
- ENAVLE had a small population with roughly 60% of patients having AF
- Limited primary literature focusing specifically on DOAC use within 3 months of BPV implantation

My Recommendation

- **In patients with AF within 3 months of BPV implantation**
  - **Consider rivaroxaban 20mg by mouth once daily or edoxaban 60mg by mouth once daily based on evidence from the RIVER and ENAVLE trials.**
- **Other DOACs may be acceptable, but it is currently unknown if benefits are a class effect.**

Population Considerations

- Renal Considerations
  - Edoxaban cannot be used in CrCl >95mL/min, <15mL/min, hemodialysis, or peritoneal dialysis[3]
  - Rivaroxaban cannot be used in CrCl <15mL/min, hemodialysis, or peritoneal dialysis[4]
  - Of note: RIVER and ENAVLE had CrCl cutoffs of <30mL/min
- Bleeding risks[17]
  - Child-Turcotte-Pugh Class B or C
  - Concurrent use of antiplatelet agents
  - History of GI bleed and stroke
- Moderate to severe mitral stenosis, rheumatic mitral stenosis, or mechanical heart valves

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