

An Update on DIRECTing the Use of Direct Acting Oral Anticoagulants in Special Populations

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Disclosures

I do not have any relevant financial relationships with any commercial interests to disclose

Objectives

Pharmacists

- Identify labeled indications for DOACs
- Recognize guideline recommendations for DOAC use
- Discuss DOAC primary literature in special populations




Technicians

- List common DOACs used in atrial fibrillation
- Identify labeled indications for DOACs
- Recognize possible off-label uses for DOACs

The abbreviation “NOAC”: in or out?

OUT!

DOAC vs NOAC

DOAC	Direct acting oral anticoagulant	
NOAC	New/novel oral anticoagulant Non-vitamin K oral anticoagulant No anticoagulation	
TSOAC	Target-specific oral anticoagulant	

Direct Acting Oral Anticoagulants (DOACs)

Apixaban
(Eliquis)

Rivaroxaban
(Xarelto)

~~Dabigatran
(Pradaxa)~~

~~Edoxaban
(Savaya)~~

Current FDA Indications

Apixaban	Rivaroxaban
<ul style="list-style-type: none">• Nonvalvular AF• DVT/PE treatment & reduction in risk of recurrence• DVT prophylaxis after hip or knee replacement surgery	<ul style="list-style-type: none">• Nonvalvular AF• DVT/PE treatment & reduction in risk of recurrence• DVT prophylaxis after hip or knee replacement surgery• CAD risk reduction• PAD risk reduction

AF: atrial fibrillation

DVT: deep vein thrombosis

PE: pulmonary embolism

CAD: coronary artery disease

PAD: peripheral artery disease

DOAC Dosing in AF

Apixaban

- 5 mg po BID
- 2.5 mg po BID if 2 of the following:
 - Age \geq 80 years
 - Weight \leq 60 kg
 - SCr \geq 1.5 mg/dl

Rivaroxaban*

- Package insert
 - CrCl $>$ 50 ml/min: 20 mg po daily
 - CrCl \leq 50 ml/min: 15 mg po daily
- Lexicomp
 - CrCl $>$ 50 ml/min: 20 mg po daily
 - CrCl 15-50 ml/min: 15 mg po daily
 - CrCl $<$ 15 ml/min: avoid use

*Rivaroxaban for AF should be given with evening meal

CHA₂DS₂-VASc Scoring

CHA ₂ DS ₂ -VASc Risk Factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease	1
Age 65-74 years	1
Sex category (female)	1

Maximum score: 9

TIA: transient ischemic attack
TE: thromboembolism

CHA₂DS₂-VASc Scoring

CHA ₂ DS ₂ -VASc Score	Adjusted Stroke Rate (% per year)
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

HAS-BLED Scoring

HAS-BLED Risk Factor	Score
Hypertension	1
Abnormal renal or liver function	1 or 2
Stroke	1
Bleeding history	1
Labile INR	1
Elderly (age > 65)	1
Drugs or alcohol	1 or 2

Overview

Atrial fibrillation (AF)

- Obesity
- End stage renal disease (ESRD)
- Valvular heart disease (VHD)

Not AF

- Mechanical valves
- Left ventricular assist devices (LVAD)

Overview

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DOACs for AF & Obesity - Guidelines



- AF guidelines (2014, 2018, 2019)
 - No specific recommendations
- International Society on Thrombosis and Haemostasis (2021)
 - Addresses venous thromboembolism only
 - Recommend against peak and trough monitoring

DOACs for AF & Obesity – Recent Literature

ORIGINAL RESEARCH ARTICLE

PHARMACOTHERAPY 

Apixaban and rivaroxaban use for atrial fibrillation in patients with obesity and BMI ≥ 50 kg/m²

Cavan P. O’Kane¹  | Juan Carlo O. Avalon² | Jordan L. Lacoste¹  | Wei Fang³ |
Christopher M. Bianco⁴  | Laura Davisson^{2,5}  | Kara L. Piechowski¹

DOACs for AF & Obesity

Design	Single health-system, retrospective cohort of patients started on apixaban or rivaroxaban <ul style="list-style-type: none">Cohorts: BMI ≥ 50 kg/m² (n=299), BMI < 30 kg/m² (n=296)
Study Population	<i>Inclusion:</i> NVAf, BMI ≥ 50 kg/m ² (median BMI ~ 55 kg/m ²)
	<i>Exclusion:</i> Pregnancy, hypercoagulable disorder
Primary Outcome	Incidence of ischemic stroke with or without hemorrhagic conversion
Results	Occurrence of primary outcome in 1.3 per 100 patient-years in BMI ≥ 50 kg/m ² group and 2.0 per 100 patient-years in the BMI < 30 kg/m ² group (RR 0.65, 95% CI 0.38-1.82, p=0.544)
Conclusion	No statistically significant differences in the incidence of ischemic stroke or significant bleeding events between the two groups

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DOACs in patients with AF &
ESRD: in or out?



DEPENDS!

DOACs for AF & ESRD - Guidelines

2014 AHA/ACC/HRS Guideline

With CHA₂DS₂-VASc score ≥ 2 and end-stage CKD (CrCl < 15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation

IIa

Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits

III: No Benefit

DOACs for AF & ESRD - Guidelines

2014 AHA/ACC/HRS Guideline

TABLE 8 Dose Selection of Oral Anticoagulant Options for Patients With Nonvalvular AF and CKD (Based on Prescribing Information for the United States)*				
Renal Function	Warfarin (238)	Dabigatran† (177)	Rivaroxaban† (178)	Apixaban† (179)
Normal/mild impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	20 mg QD with the evening meal (CrCl >50 mL/min)	5.0 or 2.5 mg BID‡
Moderate impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	15 mg QD with the evening meal (CrCl 30–50 mL/min)	5.0 or 2.5 mg BID‡
Severe impairment	Dose adjusted for INR 2.0–3.0§	75 mg BID (CrCl 15–30 mL/min)	15 mg QD with the evening meal (CrCl 15–30 mL/min)	No recommendation. See Section 4.2.2.2¶
End-stage CKD not on dialysis	Dose adjusted for INR 2.0–3.0§	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation. See Section 4.2.2.2¶
End-stage CKD on dialysis	Dose adjusted for INR 2.0–3.0§	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation. See Section 4.2.2.2¶#

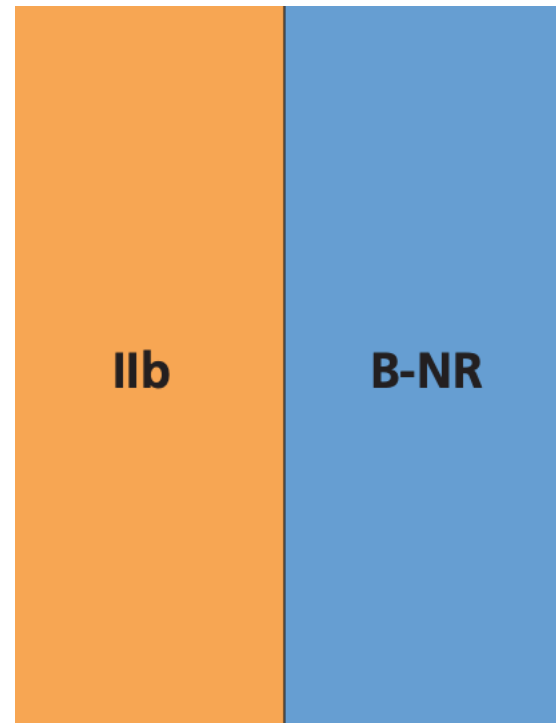
DOACs for AF & ESRD - Guidelines

2018 Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline

Renal function	Anticoagulant recommendations
Severe, non-dialysis CKD (stage IV, CrCl 15-30 ml/min)	<ul style="list-style-type: none">• VKAs• Rivaroxaban 15 mg po daily• Apixaban 2.5 mg po bid
End stage renal disease (CrCl <15 ml/min or dialysis dependent)	<ul style="list-style-type: none">• VKAs• Individualize decision making

DOACs for AF & ESRD - Guidelines

2019 AHA/ACC/HRS Focused Update

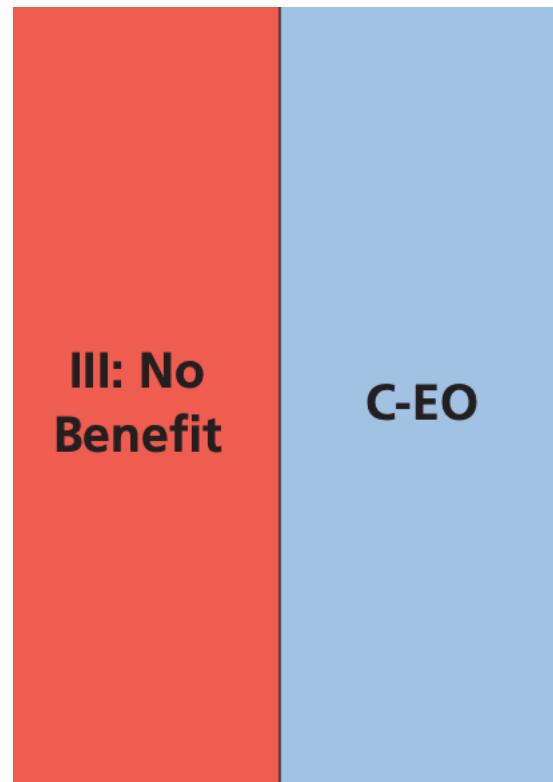


13. For patients with AF who have a CHA₂DS₂-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation^{S4.1.1-26,S4.1.1-29,S4.1.1-30}

MODIFIED: New evidence has been added. LOE was updated from B to B-NR. (Section 4.1. in the 2014 AF Guideline)

DOACs for AF & ESRD - Guidelines

2019 AHA/ACC/HRS Focused Update



16. In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk. ^{S4.1.1-8–S4.1.1-11,S4.1.1-36–S4.1.1-38}

MODIFIED: New data have been included. Edoxaban received FDA approval and has been added to the recommendation. LOE was updated from C to C-EO. (Section 4.1. in the 2014 AF Guideline)

DOACs for AF & ESRD – Literature

Cardiovascular Revascularization Medicine 30 (2021) 26–32



Contents lists available at [ScienceDirect](#)

Cardiovascular Revascularization Medicine



Safety and Efficacy of Apixaban, Rivaroxaban, and Warfarin in End-Stage Renal Disease With Atrial Fibrillation: A Systematic Review and Meta-Analysis



Hafez M. Abdullah ^a, Waqas Ullah ^{b,*}, Munnam Sohail Jafar ^b, Martin van Zyl ^c, Rehan Saeed ^b, Mahboob Alam ^d, M. Chadi Alraies ^e, David L. Fischman ^f

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DOACs for AF & ESRD – Literature

Design	Systematic review & meta-analysis of DOAC vs warfarin
Study Population	<ul style="list-style-type: none"> • Apixaban: 6 studies with 12,905 patients (2745 on apixaban; 10,160 on warfarin) • Rivaroxaban: 3 studies with 17,901 patients (2196 on rivaroxaban; 15,705 on warfarin)
Results	<p>Apixaban</p> <ul style="list-style-type: none"> • Lower risk of major bleeding with apixaban (HR 0.61, 95% CI 0.44-0.85; p=0.003); I²=10% • No significant difference in stroke (HR 1.09, 95% CI 0.85-1.39, p=0.5); I²=0%
	<p>Rivaroxaban</p> <ul style="list-style-type: none"> • No statistically significant difference in major bleeding (HR 0.95, 95% CI 0.5-1.81; p=0.88); I²=81% • No statistically significant difference in stroke (HR 1.39, 95% CI 0.59-3.29; p=0.45); I²=59%
Conclusion	Apixaban may have a lower risk of major bleeding and similar risk for stroke compared to warfarin. Rivaroxaban did not show a safety benefit over warfarin.

Overview

Atrial fibrillation (AF)

- Obesity
- End stage renal disease (ESRD)
- Valvular heart disease (VHD)

Not AF

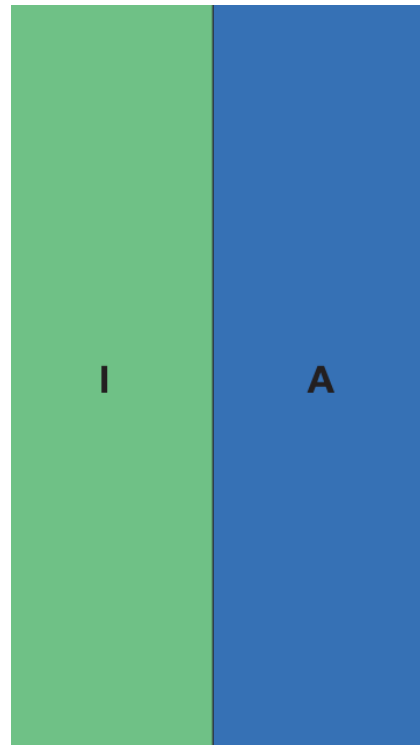
- Mechanical valves
- Left ventricular assist devices (LVAD)

DOACs for AF & VHD - Guidelines

- 2014 AHA/ACC/HRS Guideline
 - Nonvalvular AF = absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair
- 2018 Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline
 - Calls use of nonvalvular AF “unfortunate & misleading”
- 2019 AHA/ACC/HRS Focused Update
 - Removed nonvalvular AF verbiage

DOACs for AF & VHD - Guidelines

2019 AHA/ACC/HRS Focused Update



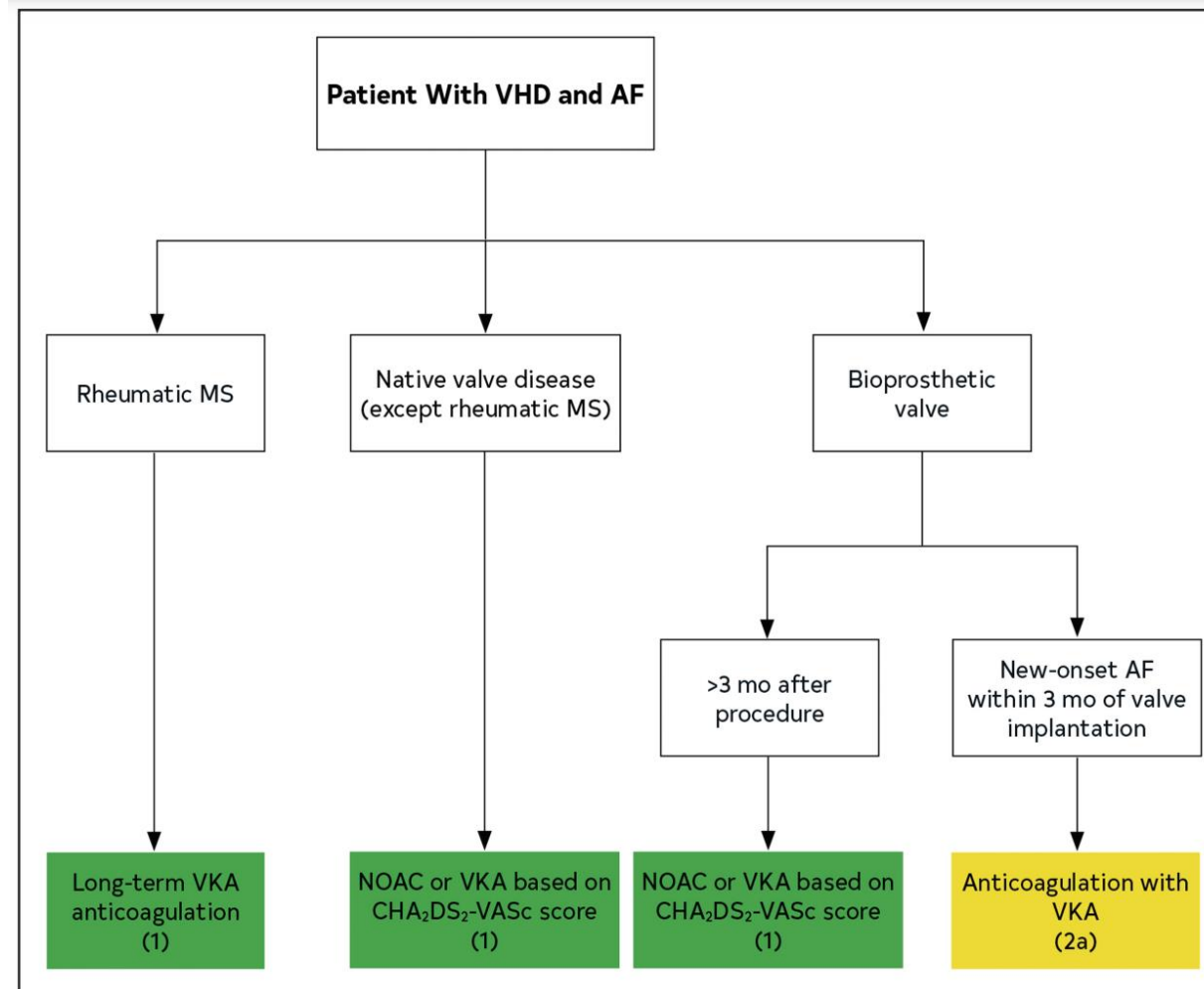
2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).^{S4.1.1-8–S4.1.1-11}

NEW: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.

AF “except with moderate to severe mitral stenosis or a mechanical heart valve”

DOACs for AF & VHD - Guidelines

2020 ACC/AHA Valvular Heart Disease Guideline



VKA: Vitamin K antagonist

(Non)valvular AF terminology:
in or out?

OUT!

DOACs for AF & VHD – Literature

Received: 30 March 2021 | Revised: 12 July 2021 | Accepted: 31 July 2021

DOI: 10.1002/ccd.29911

ORIGINAL STUDIES

WILEY

Direct oral anticoagulants in patients with atrial fibrillation and bioprosthetic valve replacement: A meta-analysis

Spencer C. Lacy MD, MPH¹  | Garly R. Saint Croix MD² | Kadijah Porter MD³ |
Azeem Latib MD⁴ | Nirat Beohar MD² 

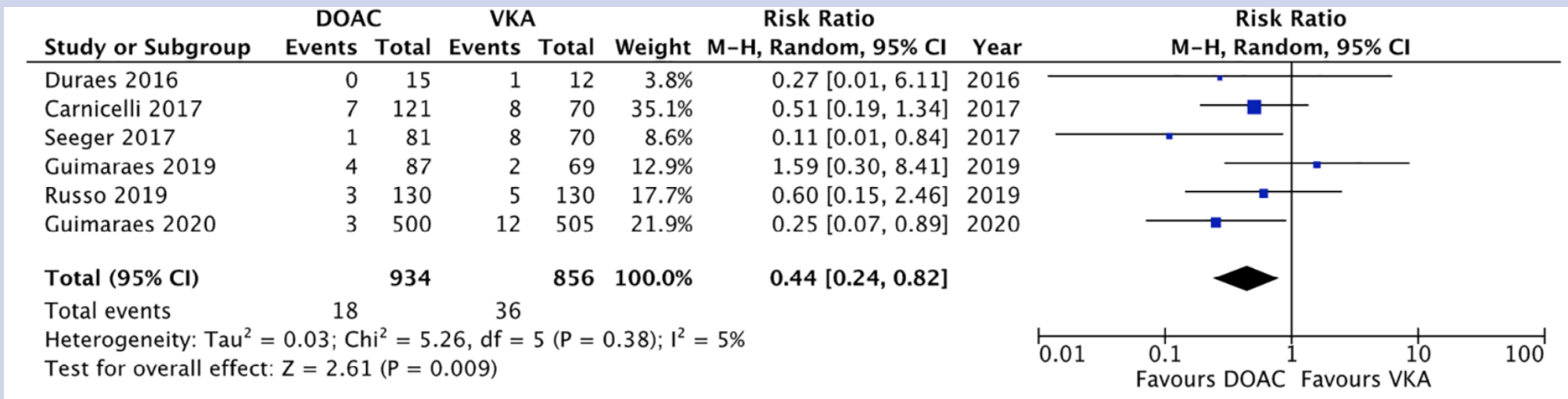
DOACs for AF & VHD – Literature

Design	Systematic review & meta-analysis of DOACs vs warfarin
Study selection	<ul style="list-style-type: none">• Articles including patients with AF and bioprosthetic valve replacement or repair (BVR) with primary or secondary outcomes being stroke, major bleeding, or death• Included 6 studies (n=1911)

DOACs for AF & VHD – Literature

Results

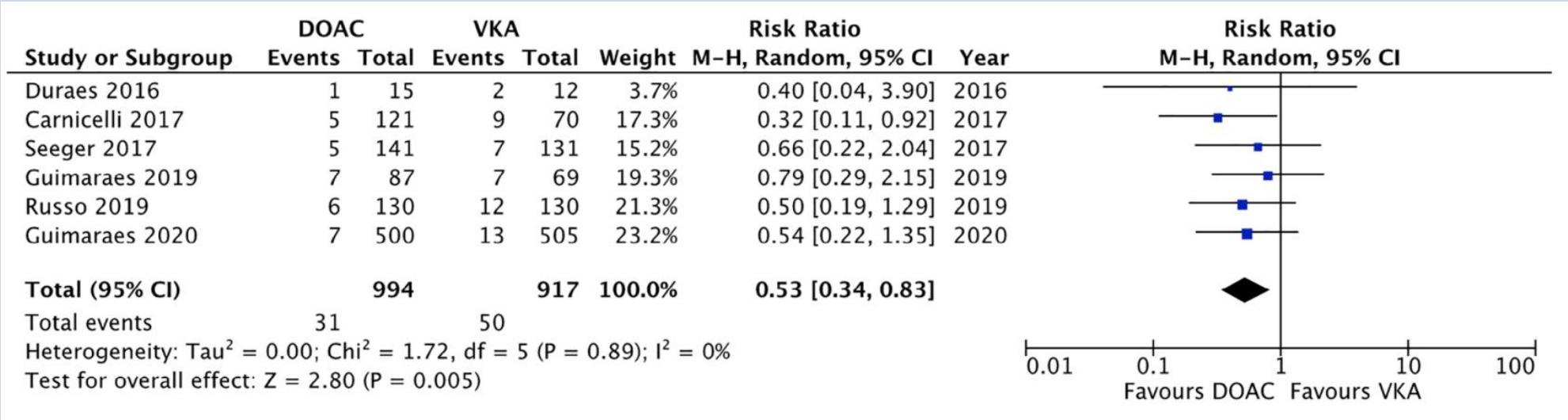
Stroke events



DOACs for AF & VHD – Literature

Results

Major bleeding events



DOACs for AF & VHD – Literature

Results	Mortality							
	Study or Subgroup	DOAC		VKA		Risk Ratio		Year
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		
	0	15	1	12	1.9%	0.27 [0.01, 6.11]	2016	
	19	81	6	50	26.3%	1.95 [0.84, 4.56]	2017	
	7	87	6	69	17.3%	0.93 [0.33, 2.63]	2019	
	1	130	2	120	3.3%	0.46 [0.04, 5.02]	2019	
	20	500	20	505	51.2%	1.01 [0.55, 1.85]	2020	
	Total (95% CI)		813		756 100.0%		1.12 [0.73, 1.74]	
	Total events		47		35			
	Heterogeneity: Tau ² = 0.00; Chi ² = 3.23, df = 4 (P = 0.52); I ² = 0%							
	Test for overall effect: Z = 0.53 (P = 0.60)							

Conclusion DOACs are superior to VKAs for stroke and major bleeding and similar in mortality for patients with BVR and AF

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- Obesity
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Not AF

- **Mechanical valves**
- Left ventricular assist devices (LVAD)

Do patients with a mechanical valve
or LVAD require anticoagulation
independently of AF?

YES!

DOACs for Mechanical Valves - Guidelines

2020 ACC/AHA Valvular Heart Disease Guideline



4. In patients with mechanical heart valves with or without AF who require long-term anticoagulation with VKA to prevent valve thrombosis, NOACs are not recommended.⁷


DOACs for Mechanical Valves - Literature

American Journal of Cardiovascular Drugs (2021) 21:363–371
<https://doi.org/10.1007/s40256-020-00449-3>

ORIGINAL RESEARCH ARTICLE



Rivaroxaban Versus Warfarin in Patients with Mechanical Heart Valves: Open-Label, Proof-of-Concept trial—The RIWA study

Andre Rodrigues Duraes^{1,2}  · Yasmin de Souza Lima Bitar² · Igor Santos Schonhofen³ · Kethyren Santos Oliveira Travassos⁴ · Larissa Vitória Pereira⁵ · Jose Admirço Lima Filho³ · Mansueto Gomes Neto¹ · Roque Aras Junior^{1,2} · Leonardo Roever⁶

DOACs for Mechanical Valves – Literature

Design	Randomized, open label, single center, proof-of-concept trial <ul style="list-style-type: none">• Cohorts: rivaroxaban 15 mg po BID with food (n=23); warfarin with INR 2.5-3.5 for mitral position or aortic position + AF or INR 2-3 for aortic position (n=21)
Study Population	<i>Inclusion:</i> 3 months post-op from bileaflet mechanical mitral and/or aortic valve
	<i>Exclusion:</i> previous hemorrhagic stroke, ischemic stroke in past 3 months, CrCl < 30 ml/min, active liver disease, use of <i>any</i> antiplatelet (e.g., aspirin), increased risk of bleeding, gastrointestinal bleed within the past year
Primary Outcome	Composite of stroke, transient ischemic attack (TIA), silent brain infarction (SBI), systemic embolism (SE)

DOACs for Mechanical Valves – Literature

Results	Primary outcome occurred in 1 patient (4.3%) in the rivaroxaban group and 3 patients (14.3%) in the warfarin group (risk ratio 0.27; 95% confidence interval 0.02-2.85; p=0.25)
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Outcome	Rivaroxaban (n=23) No, (%)	Warfarin (n=21) No, (%)	Relative risk	P value
Ischemic stroke	0	2 (9.5)	0.9 (0.78-1.03)	0.13
Transient ischemic attack	1 (4.3)	0	1.04 (0.95-1.14)	0.33
Silent brain infarction	0	1 (4.8)	0.95 (0.86-1.04)	0.29
Systemic embolism	0	0	NA	NA

Conclusion: Rivaroxaban 15 mg po bid has similar thromboembolic and bleeding events compared to warfarin and warrants further investigation

DOACs for Mechanical Valves – Clinical Trials

- RENOVAATE: rivaroxaban vs VKA for mechanical aortic valve replacement
 - Prospective, randomized, active controlled trial estimated to be completed December 2024
- PROACT Xa: apixaban vs VKA for On-X mechanical aortic valve
 - Prospective, randomized, active controlled trial
 - Stopped in September; increased stroke in apixaban group

Overview

Atrial fibrillation (AF)

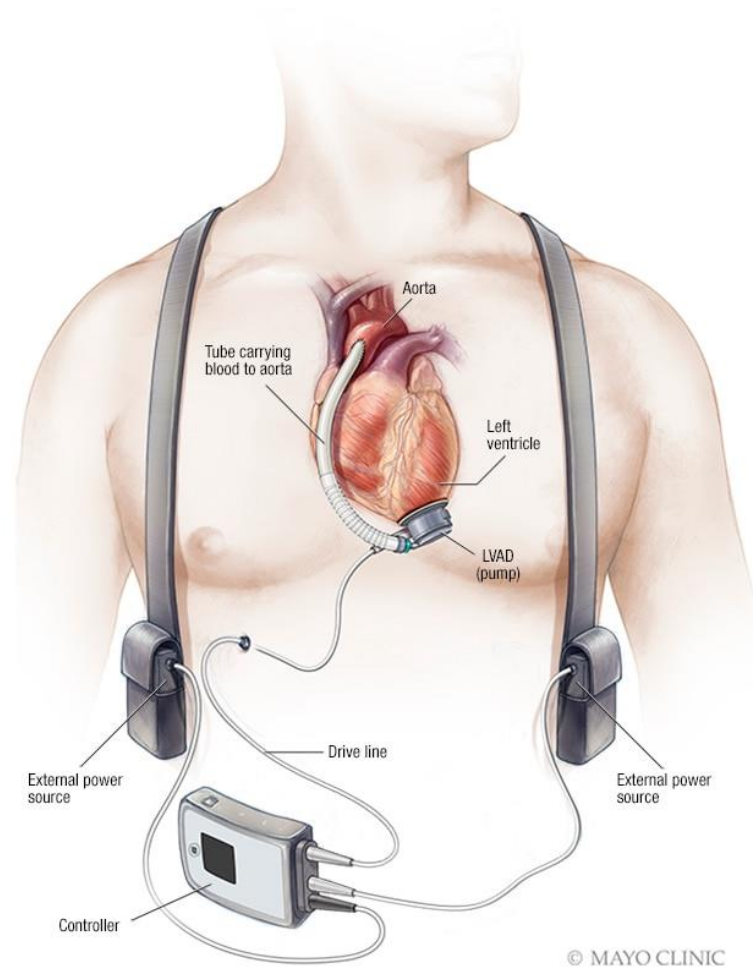
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Not AF

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Anticoagulation for LVAD - Guidelines

- No specific guidelines
- Warfarin + aspirin recommended per package insert for HeartMate3



DOACs for LVAD – Literature

ASAIO Journal 2022

Adult Circulatory Support

Apixaban: Alternative Anticoagulation for HeartMate 3 Ventricular Assist Device

KATHERINE R. WHITEHOUSE, DIVYA AVULA, TANVIR KAHLON, DEVAN COSTELLE, CHRISTINA DUNBAR-MATOS,
SIDDHARTH PAHWA, JAIMIN R. TRIVEDI, AND MARK S. SLAUGHTER 

DOACs for LVAD – Literature

Design	Retrospective single center review of patients who received HeartMate 3 (HM3); converted to prospective cohort Cohorts: warfarin (n=20), apixaban (n=15)
Study Population	<i>Inclusion:</i> HM3 implanted from January 1, 2016 – January 31, 2021
	<i>Exclusion:</i> none specified
Outcomes	Death, stroke, bleeding, other thrombotic complication

DOACs for LVAD – Literature

Results		Warfarin (n=20)	Apixaban (n=15)	P value
	Death	5% (n=1)	12% (n=2)	0.57
	Stroke	5% (n=1)	0 (0)	1
	Bleeding	30% (n=5)	6% (n=1)	0.1
	Other thrombotic complication	10% (n=2)	6% (n=1)	1
No statistically significant difference in thrombotic complications, stroke, or death between the two groups at 1 year				
Conclusion	Apixaban may be a safe alternative to warfarin in LVAD HM3 patients and warrants further investigation			

DOACs for LVAD – Clinical Trials

- DOT HeartMate 3 Study
 - Prospective, single-center, randomized controlled trial of apixaban vs warfarin
- Dabigatran as an Alternative Anticoagulant in Patients With Left Ventricular Assist Device
 - Phase 2, single-center study of VKA or dabigatran for long-term anticoagulation after implantation of HeartWare
 - Terminated early due to safety concerns

Conclusions

- Current guidelines may not reflect the most up to date literature for DOACs in special populations
- Apixaban and rivaroxaban can be considered for obese patients with AF & patients with BVR & AF
- Apixaban can be considered for patients with ESRD and AF
- Literature supporting DOAC use for patients with mechanical valves and LVADs is emerging

RR is a 68-year-old male with a new diagnosis of AF. His PMH includes T2DM, HTN, HFpEF, CAD with PCI 4 years ago, and obesity (BMI 55 kg/m²). Which of the following would you recommend for anticoagulation for his AF?

- A. No anticoagulation
- B. Apixaban
- C. Rivaroxaban
- D. B or C

TD is a 70-year-old male with PMH of HTN, ESRD on HD, T2DM, and HFrEF. He is admitted with new diagnosis of AF. He says it is not feasible to have his INR checked as an outpatient. Which of the following anticoagulants would you recommend for TD?

- A. Apixaban
- B. Rivaroxaban
- C. Warfarin
- D. Dabigatran

CM is a 75-year-old female with a new diagnosis of AF. She has a PMH of HTN, HLD, mild AoS, and T2DM. Which of the following anticoagulants would be appropriate for her?

- A. Warfarin
- B. Apixaban
- C. Rivaroxaban
- D. All of the above

LP is a 70-year-old male who is on apixaban for AF. He is s/p mechanical mitral valve replacement. Which anticoagulant would be most appropriate for LP?

A. Warfarin

B. Apixaban

C. Rivaroxaban

D. None of the above

RT is a 68-year-old female undergoing LVAD HM3 implant. She is nearing discharge and is adamant that she does not want to take warfarin. Which anticoagulant *may* be an *off-label* option for her to use?

- A. Aspirin alone without an anticoagulant
- B. Apixaban
- C. Rivaroxaban
- D. Dabigatran