ACCP Cardiology PRN Journal Club

Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation and Valvular Heart Disease

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Disclosures

Neither Drs. Carson or Parra have any relevant disclosures concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Background

- Atrial fibrillation (AF) and valvular heart disease (VHD) often coexist
  - Up to 60% of patients with AF also have VHD
  - Increased risk of stroke and systemic embolic events (SSEE) independently and additively
- SSEE risk varies by type of valve disease
  - Stenotic > Regurgitant
  - Mitral > Aortic > Tricuspid ≈ Pulmonic
  - Mechanical valve > bioprosthetic valve

Lip GY, Europace 2014;16:308-319
Di Biase L, et al. J Am Heart Assoc. 2016;5(2):e002776

What is Non-Valvular AF?

- Non-valvular atrial fibrillation (NVAF) has a continuously evolving definition

"Rhythm disturbance occurring in the absence of rheumatic mitral valve disease or a prosthetic heart valve"
- ACC/AHA/ESC 2001 VHD Guidelines

"AF associated with rheumatic VHD (predominantly mitral stenosis) or prosthetic heart valves"
-2012 Focused Update to ECS VHD Guidelines

"Rhythm disturbance occurring in the absence of rheumatic mitral valve disease or a prosthetic heart valve and AF in the absence of mitral valve repair"
-ACC/AHA/ESC 2006 Focused Update to VHD Guidelines

"Non-rheumatic AF is used synonymously with NVAF"
-2012 American College of Chest Physicians Antithrombotic Therapy for AF Guidelines

"AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair"
- ACC/AHA/HRS 2014 VHD Guidelines

"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"
- EHRA, EAPCI, ACCA, HRS, and APHRS Consensus Statement

Di Biase L, et al. J Am Heart Assoc. 2016;5(2): e002776

What is Non-Valvular AF?

- After phase II trial examining dabigatran in patients with mechanical valves showed both excessive stroke and excessive bleeding, patients with various types of VAF excluded from phase III novel oral anticoagulant (NOAC) trials

Trial	Exclusion Criteria Related to VHD
RE-LY *(dabigatran)*	History of heart valve disease (prosthetic valve or hemodynamically relevant valve disease)
ROCKET-AF *(rivaroxaban)*	Hemodynamically significant mitral valve stenosis or prosthetic heart valve
ARISTOTLE *(apixaban)*	Valvular disease requiring surgery, prosthetic mechanical heart valve, moderate or severe mitral stenosis
ENGAGE AF-TIMI 48 *(edoxaban)*	Moderate or severe mitral stenosis, unresected atrial myxoma, or mechanical heart valve

Eikelboom JW, et al. N Engl J Med 2013;369:1206-14

Impact of Valvular AF on Anticoagulation

COR, LOE	Recommendation
I, A	Anticoagulation with a VKA and INR monitoring is recommended in patients with a mechanical prosthetic valve
I, B	Anticoagulation with a VKA to achieve an INR of 2.5 is recommended in patients with a mechanical aortic valve replacement (AVR)
	Anticoagulation with a VKA to achieve an INR of 3.0 is recommended in patients with a mechanical AVR and additional risk factors for VTE (AF, previous VTE, LV dysfunction, hypercoaguable state, or ball-in-cage valve)
	Anticoagulation with a VKA to achieve an INR of 3.0 is recommended in patients with a mechanical mitral valve replacement (MVR)
IIa, C	Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for the first 3 months after bioprosthetic MVR or repair
IIb, B	Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for the first 3 months after bioprosthetic AVR or repair
III, B	Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses

- VKAs are the only anticoagulant recommended for VAF

Nishimura RA, et al. J Thorac Cardiovasc Surg 2014;148(1):e1-e132

Prosthetic Heart Valves and FDA Product Labeling

- ***Dabigatran:*** Contraindication: Mechanical prosthetic heart valve. Warnings and Precautions: Bioprosthetic heart valves: PRADAXA use not recommended. The use of PRADAXA for the prophylaxis of thromboembolic events in patients with atrial fibrillation in the setting of other forms of valvular heart disease, including the presence of a bioprosthetic heart valve, has not been studied and is not recommended.
- ***Apixaban:*** Warnings and Precautions: Patients with Prosthetic Heart Valves The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.
- ***Rivaroxaban:*** Warnings and Precautions: Patients with Prosthetic Heart Valves The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.
- ***Edoxaban:*** Warning and Precautions: The safety and efficacy of SAVAYSA has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis. The use of SAVAYSA is not recommended in these patients.

Respective FDA approved product labeling as of 3/2017

Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Disease

Renda G, et al. J Am Coll Cardiol 2017;69(11):1363-1371

Trial Design

Objective

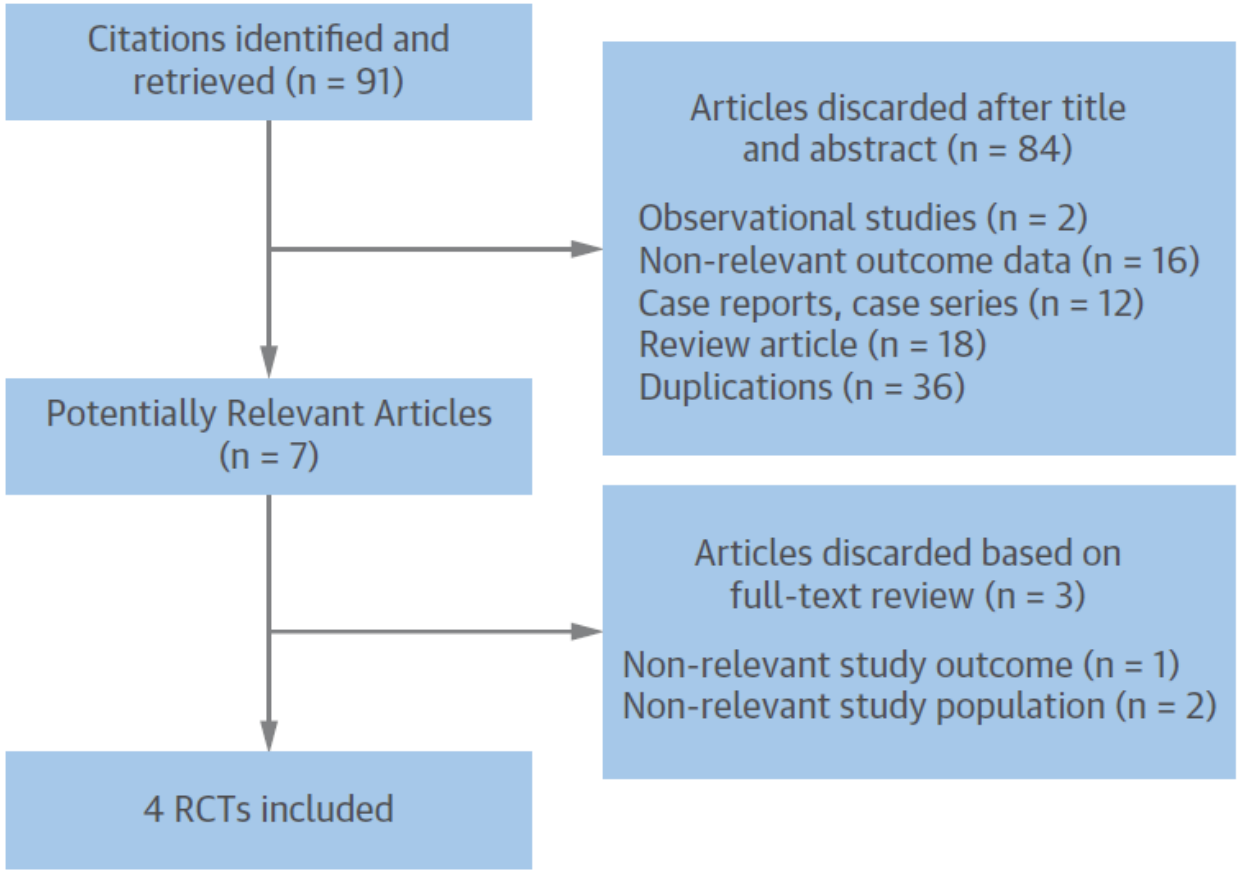
- Evaluate the relative safety and efficacy of NOACs in patients with VHD

Design

- Systematic review and meta-analysis of available comparative trials of NOACs versus VKAs
- Included patients on appropriate FDA labeled doses of NOACs
  - A secondary analysis included all doses of NOACs studied in included trials

Renda G, et al. J Am Coll Cardiol 2017;69(11):1363-1371

Trial Design



RE-LY *(dabigatran)*	ROCKET-AF *(rivaroxaban)*	ARISTOTLE *(apixaban)*	ENGAGE AF-TIMI 48 *(edoxaban)*

Renda G, et al. J Am Coll Cardiol 2017;69(11):1363-1371

Statistical Analysis

- Outcome data extracted as hazard ratios (HRs) and 95% confidence intervals (CIs)
  - Unadjusted HRs reported, as each of the 4 trials utilized different adjustment models
- To evaluate for heterogeneity:
  - Cochran's Q test to assess dispersion of summary effects around combined effect, $p<0.10$ indicative
  - Percentage of variability testing, I^2 >50% indicative
  - Jackknife sensitivity analyses performed for each endpoint (combining labeled and lower doses of drugs)

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Study Endpoints

Primary Endpoint

- Stroke or SSEE
- Major bleeding

Secondary Endpoints

- Intracranial hemorrhage (ICH)
- All-cause death

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Baseline Characteristics

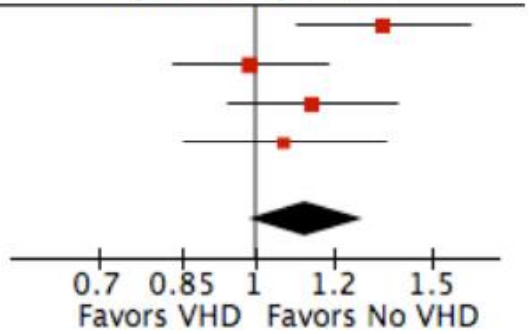
	RE-LY *(dabigatran)* n=18,113		ROCKET-AF *(rivaroxaban)* n=14,264		ARISTOTLE *(apixaban)* n=18,201		ENGAGE AF-TIMI 48 *(edoxaban)* n=21,105	
Patients with VHD	3,950 (22%)		2,003 (14%)		4,808 (26%)		2,824 (13%)	
Mean $CHADS_2$	2.1		3.5		2.1		2.8	
Study Design	Open-label RCT		Double-blinded RCT		Double-blinded RCT		Double-blinded RCT	
Median Time in Therapeutic Range	67%		58%		66%		68%	
VHD Status	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Median Age	74	72	75	72	71	69	73	72
Heart Failure, %	40	30	70	61	49	31	74	55
Previous SSEE, %	22	22	48	56	19	20	24	29
Sustained AF, %	NA	NA	83	81	88	84	80	74
CAD, %	33	26	24	16	17	13	40	32
Mean HAS-BLED	NA	NA	2.8	2.8	NA	NA	2.6	2.5

Renda G, et al. J Am Coll Cardiol 2017;69(11):1363-1371

A. Stroke/SEE

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
ARISTOTLE	0.2927	0.1007	25.1%	1.34 [1.10, 1.63]
ENGAGE AF-TIMI 48	-0.0101	0.0899	28.4%	0.99 [0.83, 1.18]
RE-LY	0.131	0.0984	25.7%	1.14 [0.94, 1.38]
ROCKET AF	0.0677	0.1174	20.8%	1.07 [0.85, 1.35]
Total (95% CI)			**100.0%**	**1.13 [0.99, 1.28]**

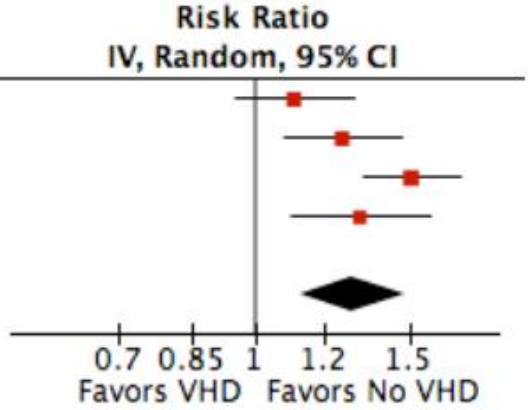
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.24$, df = 3 (P = 0.16); $I^2 = 43\%$
Test for overall effect: Z = 1.78 (P = 0.08)



B. Major Bleeding

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
ARISTOTLE	0.1044	0.0794	24.9%	1.11 [0.95, 1.30]
ENGAGE AF-TIMI 48	0.2311	0.0786	25.0%	1.26 [1.08, 1.47]
RE-LY	0.4121	0.0648	27.9%	1.51 [1.33, 1.71]
ROCKET AF	0.2776	0.093	22.2%	1.32 [1.10, 1.58]
Total (95% CI)			**100.0%**	**1.30 [1.13, 1.49]**

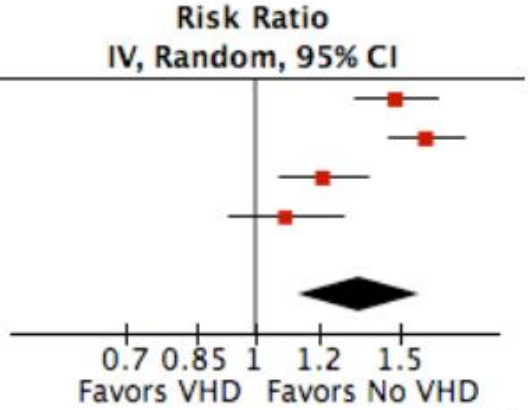
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.40$, df = 3 (P = 0.02); $I^2 = 68\%$
Test for overall effect: Z = 3.76 (P = 0.0002)



C. All-cause death

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
ARISTOTLE	0.392	0.0584	25.6%	1.48 [1.32, 1.66]
ENGAGE AF-TIMI 48	0.4762	0.0534	26.1%	1.61 [1.45, 1.79]
RE-LY	0.1906	0.0627	25.2%	1.21 [1.07, 1.37]
ROCKET AF	0.0862	0.081	23.1%	1.09 [0.93, 1.28]
Total (95% CI)			**100.0%**	**1.34 [1.13, 1.59]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 22.62$, df = 3 (P < 0.0001); $I^2 = 87\%$
Test for overall effect: Z = 3.40 (P = 0.0007)



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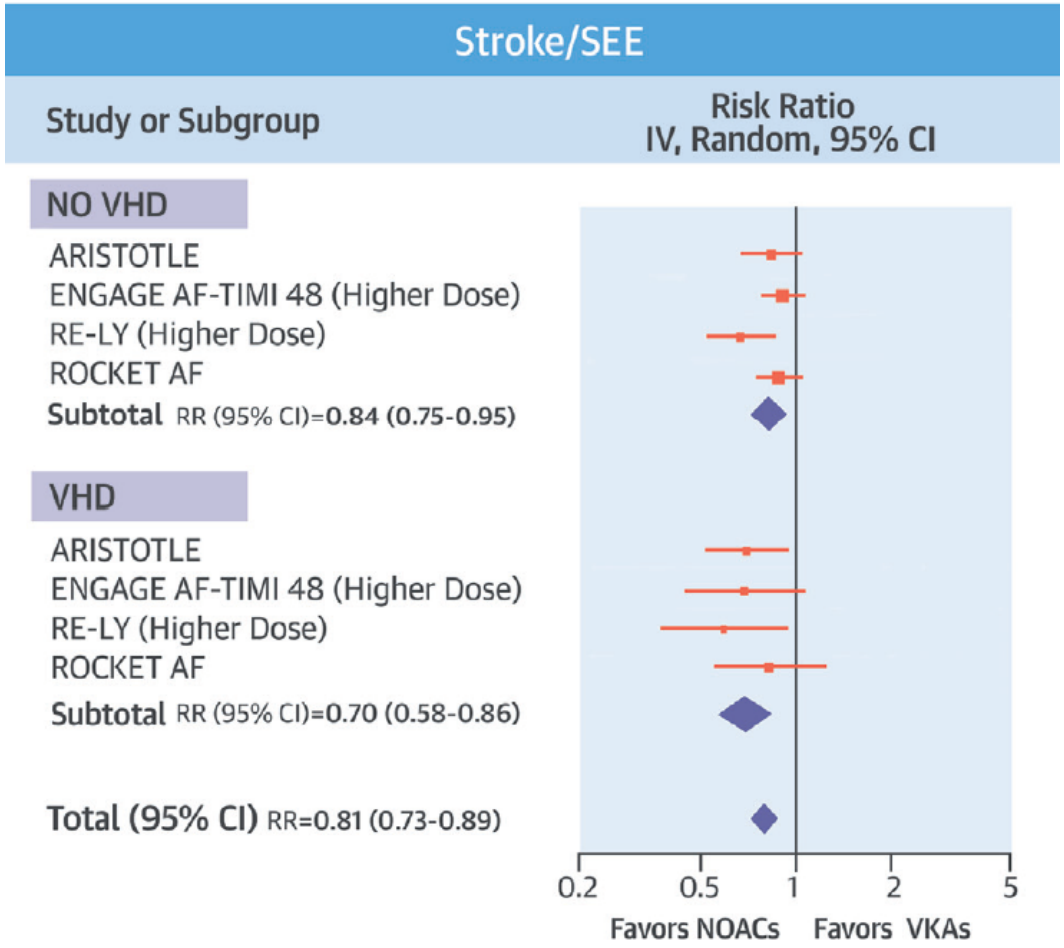
OS Figure 1

Results - SSEE

- Rates overall lower and consistent with or without VHD
- Trend toward better ischemic stroke prevention by NOACs in ARISTOTLE and ENGAGE AF-TIMI 48



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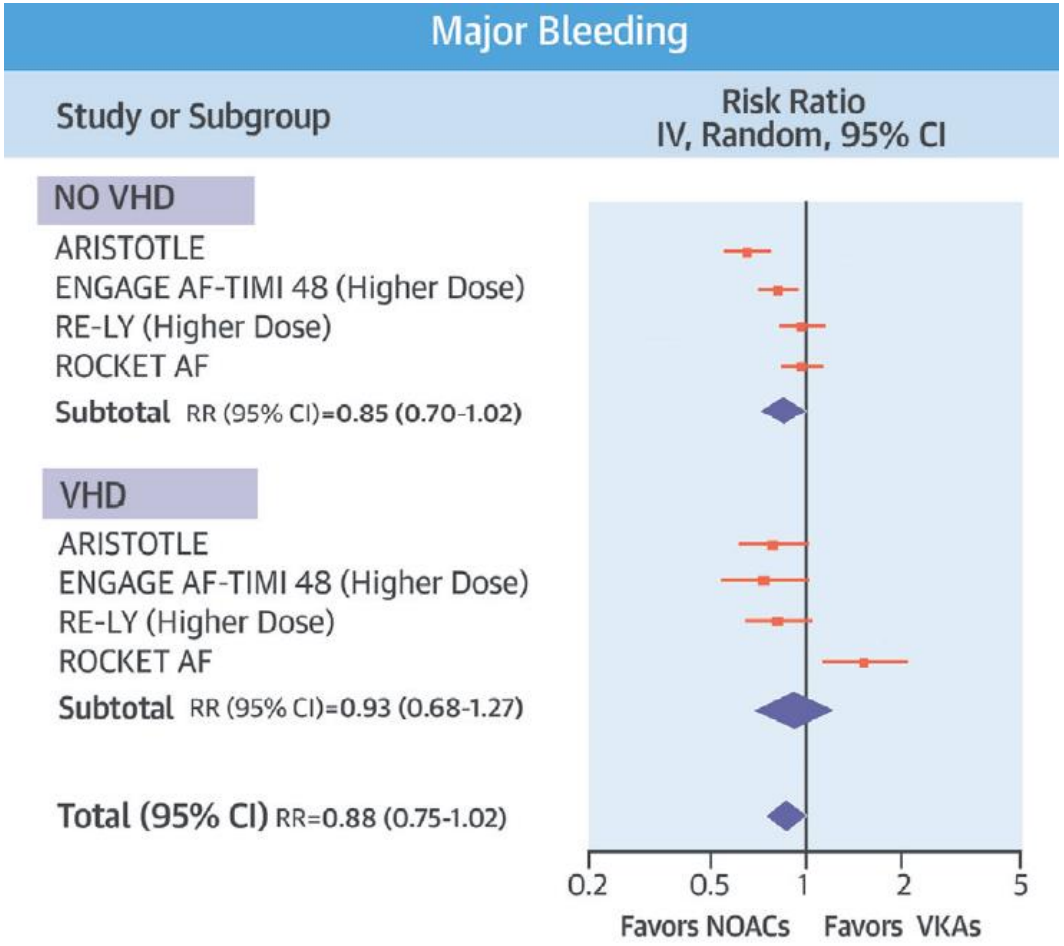
Results – Major Bleeding

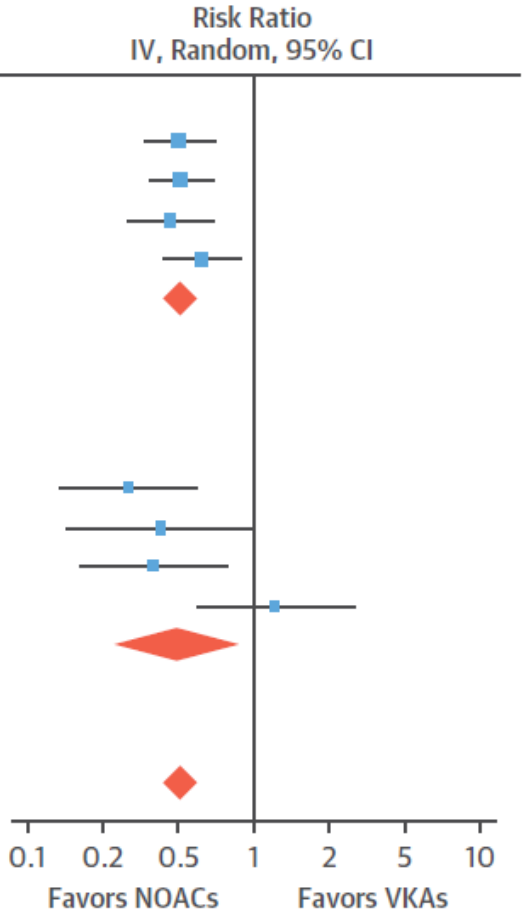
- Rates overall similar and consistent with or without VHD
- I^2=78%, Cochran's Q p<0.0001, indicating significant heterogeneity



Renda G, et al. J Am Coll Cardiol 2017;69(11):1363-1371

Results – ICH

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
NO VHD				
ARISTOTLE	-0.755	0.1804	19.5%	0.47 [0.33, 0.67]
ENGAGE AF-TIMI 48 (higher dose)	-0.734	0.1612	21.8%	0.48 [0.35, 0.66]
RE-LY (higher dose)	-0.844	0.2189	15.6%	0.43 [0.28, 0.66]
ROCKET AF	-0.5276	0.1983	17.6%	0.59 [0.40, 0.87]
Subtotal (95% CI)			74.5%	0.49 [0.41, 0.59]
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.30$, df = 3 (P = 0.73); $I^2 = 0\%$				
Test for overall effect: Z = 7.67 (P < 0.00001)				
VHD				
ARISTOTLE VHD	-1.273	0.3537	7.8%	0.28 [0.14, 0.56]
ENGAGE AF-TIMI 48 VHD (higher dose)	-0.9416	0.4875	4.5%	0.39 [0.15, 1.01]
RE-LY VHD (higher dose)	-1.0217	0.3828	6.8%	0.36 [0.17, 0.76]
ROCKET AF VHD	0.239	0.3999	6.4%	1.27 [0.58, 2.78]
Subtotal (95% CI)			25.5%	0.47 [0.24, 0.93]
Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 8.94$, df = 3 (P = 0.03); $I^2 = 66\%$				
Test for overall effect: Z = 2.17 (P = 0.03)				
Total (95% CI)			100.0%	0.48 [0.39, 0.60]
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.33$, df = 7 (P = 0.17); $I^2 = 32\%$				
Test for overall effect: Z = 6.65 (P < 0.00001)				
Test for subgroup interactions: $Chi^2 = 0.01$, df = 1 (P = 0.91), $I^2 = 0\%$				



- NOACs reduced ICH compared to warfarin, consistently in patients with and without VHD

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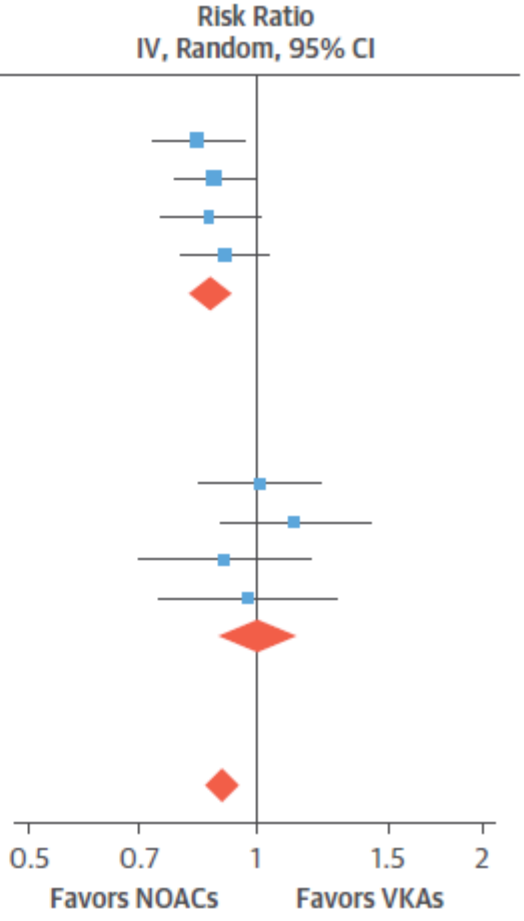
Results – All-Cause Death

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
NO VHD				
ARISTOTLE	-0.1744	0.0716	16.8%	0.84 [0.73, 0.97]
ENGAGE AF-TIMI 48 (higher dose)	-0.1278	0.0615	22.7%	0.88 [0.78, 0.99]
RE-LY (higher dose)	-0.1393	0.0757	15.0%	0.87 [0.75, 1.01]
ROCKET AF	-0.0943	0.0657	19.9%	0.91 [0.80, 1.04]
Subtotal (95% CI)			**74.5%**	**0.88 [0.82, 0.94]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.69$, df = 3 (P = 0.87); $I^2 = 0\%$				
Test for overall effect: Z = 3.87 (P = 0.0001)				
VHD				
ARISTOTLE VHD	0.01	0.094	9.7%	1.01 [0.84, 1.21]
ENGAGE AF-TIMI 48 VHD (higher dose)	0.1222	0.1161	6.4%	1.13 [0.90, 1.42]
RE-LY VHD (higher dose)	-0.0943	0.1339	4.8%	0.91 [0.70, 1.18]
ROCKET AF VHD	-0.0202	0.1365	4.6%	0.98 [0.75, 1.28]
Subtotal (95% CI)			**25.5%**	**1.01 [0.90, 1.14]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.59$, df = 3 (P = 0.66); $I^2 = 0\%$				
Test for overall effect: Z = 0.22 (P = 0.82)				
Total (95% CI)			**100.0%**	**0.91 [0.86, 0.96]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.90$, df = 7 (P = 0.44); $I^2 = 0\%$				
Test for overall effect: Z = 3.23 (P = 0.001)				
Test for subgroup interactions: $Chi^2 = 4.62$, df = 1 (P = 0.03), $I^2 = 78.4\%$				



- NOACs did not reduce all-cause death compared to warfarin in patients with and without VHD

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Results – Subgroup Analysis

- Subgroup analysis included dabigatran 110 mg twice daily doses and edoxaban 30 mg daily doses
- Results overall similar
  - Decreased magnitude of risk reduction in SSEE
  - Less major bleeding
  - ICH risk reduction amplified
  - Lack of improvement in all-cause death remained unchanged

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Conclusions

- Definitions of NVAF vary widely, and caution should be taken to identify the individual type of VHD discussed
- Coexistance of VHD as seen in the pivotal NVAF trials did not affect overall safety and efficacy of NOAC therapy
- Warfarin remains the recommended therapy for patients with moderate/severe mitral stenosis and mechanical valves
- Additional studies are necessary to determine the safety and efficacy of NOACs in patients with bioprosthetic valves and valve repair surgeries

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Critique

Strengths

- Large, diverse RCT's utilized in meta-analysis
- Thorough classification of type and prevalence of valve disease
- Care taken to ensure that heterogeneity of data was evaluated and bias eliminated when possible

Limitations

- Aggregate data abstracted from original publications
- Differing study designs and inclusion/exclusion criteria amongst included trials
- Varied definitions of NVAF
- No core laboratory echocardiographic assessment of valve disease
- Heterogeneity observed in evaluation of bleeding

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Impact on Clinical Practice

- 2017 AHA/ACC Focused Update of Valvular Heart Disease Guideline

COR, LOE	Recommendation
I, B-NR	Among patients with AF and rheumatic mitral stenosis, anticoagulation with a VKA still is indicated
I, C-LD	Anticoagulation should be used among patients with AF and a CHA2DS2-VASc score ≥ 2 in the setting of native aortic valve disease, tricuspid valve disease or MR
IIa, C-LD	**The use of a DOAC is reasonable among patients with native aortic valve disease, tricuspid valve disease or MR; and AF with a CHA_2DS_2-VASc score ≥ 2**

Nishimura RA, et al. Circulation 2017 doi:10.1161/CIR.0000000000000503 (Epub ahead of print)

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- Monique Conway, PharmD, BCPS

Additional Citations

- RE-LY

Connolly SJ, et al. *N Engl J Med* 2009;361:1139-51

- ROCKET-AF

Patel MR, et al . *N Engl J Med* 2011;365:883-91

- ARISTOTLE

Granger CB, et al. *N Engl J Med* 2011;365:981-92

- ENGAGE AF-TIMI 48

Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104

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