fondazione arianna ANTICOAGULAZIONE

PROMUOVE IL

2° CONVEGNO DI ANTICOAGULAZIONE.it

Quando I NOA non sono indicati

Valvulopatie con o senza FA

Bologna, 2 Febbraio 2017

Maddalena Lettino
Humanitas Research Hospital, Rozzano Mialno, Italy

Disclosure

Speaker fee: Aspen, Astra Zeneca, BMS, Boehringer, Eli Lilly, Daichii Sankio, Bayer, Pfizer, Sanofi

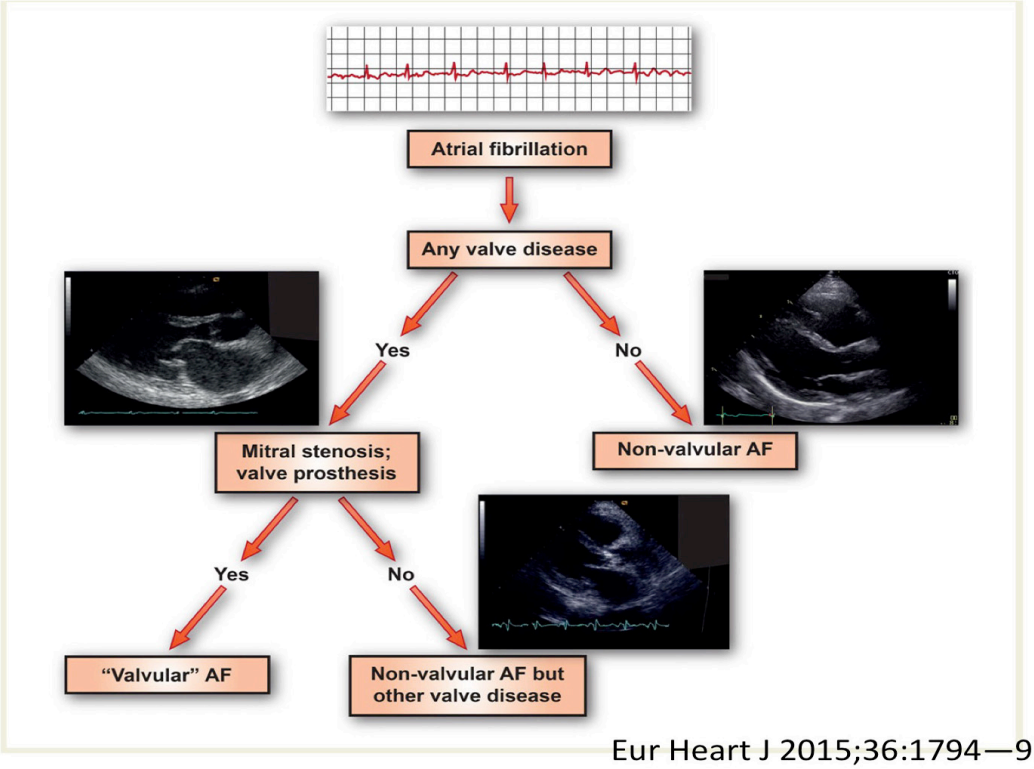
Advisory board member: AZ, Eli Lilly, Daiichi Sankyo, BMS, Pfizer, Sanofi, Bayer

- ✓ *AF with valvular heart disease (VHD)*
- ✓ *DOACs and VHD*
- ✓ *Mitral stenosis and thromboembolic risk*

Valvular heart diseases and AF

- *In valvular heart diseases structural changes from the pressure and volume overload alter the electrophisiological properties of the left atrium → AF*
- *The rheumatic process itself may lead to atrial fibrosis → AF*
- *VHD are frequently associated to other risk factors for AF (older age, hypertension, HF, diabetes, CAD)*

Subtypes of AF based on ESC guidelines 2006-2012



Eur Heart J 2015;36:1794—97

Exclusion criteria related to valve disease in phase II and phase III trials with the new anticoagulants in AF

Study drug	Study acronym/name	Year of publication	Atrial fibrillation exclusion criteria related to valve disease
Apixaban	AVERROES [5,7]	2011	Valvular disease requiring surgery, prosthetic mechanical heart valve
Apixaban	ARISTOTLE [11,14]	2011	Clinically significant (moderate or severe) mitral stenosis, prosthetic mechanical heart valve
Apixaban	ARISTOTLE-J [15]	2011	Valvular heart disease
Betrixaban	EXPLORE-Xa [4]	2013	Prosthetic mechanical heart valve
Dabigatran	PETRO [9]	2007	Mitral stenosis, prosthetic valves
Dabigatran	RE-LY [6,8]	2009	History of heart valve disorder (including haemodynamically relevant valve disease and prosthetic valve)
Edoxaban	Edoxaban phase II study [19]	2012	Comorbid rheumatic valvular disease, history of valvular surgery, infective endocarditis
Edoxaban	ENGAGE-AF-TIMI 48 [10,18]	2013	Moderate or severe mitral stenosis, unresected atrial myxoma, mechanical heart valve
Rivaroxaban	ROCKET-AF [17]	2011	Haemodynamically significant mitral valve stenosis, prosthetic heart valve
Rivaroxaban	J-ROCKET-AF [13]	2012	Haemodynamically significant mitral valve stenosis, prosthetic heart valve
Ximelagatran	SPORTIF III [12,16]	2003	Mitral stenosis, previous valvular heart surgery, active infective endocarditis
Ximelagatran	SPORTIF V [3,12]	2005	Mitral stenosis, previous valvular heart surgery, active infective endocarditis

Arch Cardiovasc Dis 2015; 108: 530

VHD Populations in trials with DOACs

Trial	RE-LY, Dabigatran	ROCKET AF, Rivaroxaban	ARISTOTLE, Apixaban
Excluded population	Prosthetic heart valves; hemodynamically significant mitral stenosis; valve disease likely to require intervention before study end	Artificial valve prosthesis; hemodynamically significant mitral stenosis	Clinically significant (moderate or severe) mitral stenosis; mechanical valve prosthesis
VHD patient population included	N = 3950 (21.8%), mitral regurgitation (78.5%), tricuspid regurgitation (29.8%), aortic regurgitation (20.7%), aortic stenosis (11.9%), mild mitral stenosis (4.9%)	N = 2003 (14.0%), mitral regurgitation (89.6%), aortic regurgitation (24.8%), aortic stenosis (11%), other (0.6%)	N = 4808 (26.4%), mitral regurgitation (73.3%), tricuspid regurgitation (44.2%), aortic regurgitation (18.4%), aortic stenosis (8%), previous valve surgery (5.2%), mild mitral stenosis (2.7%)[1]

Clinical Cardiology 2016; DOI 10.1002/clc.22659

VHD Populations in trials with DOACs

Trial		
Excluded	ENGAGE-AF-TIMI 48[7,8]	Excluded patients with moderate or severe mitral stenosis, unresected atrial myxoma, and mechanical heart valve
VHD pat popula		Included all other valvular heart disease conditions and/or bioprosthetic heart valves and valve repair

Clinical Cardiology 2016; DOI 10.1002/clc.22659

Comparison of Dabigatran and Warfarin in Patients With Atrial Fibrillation and Valvular Heart DiseaseClinical Perspective

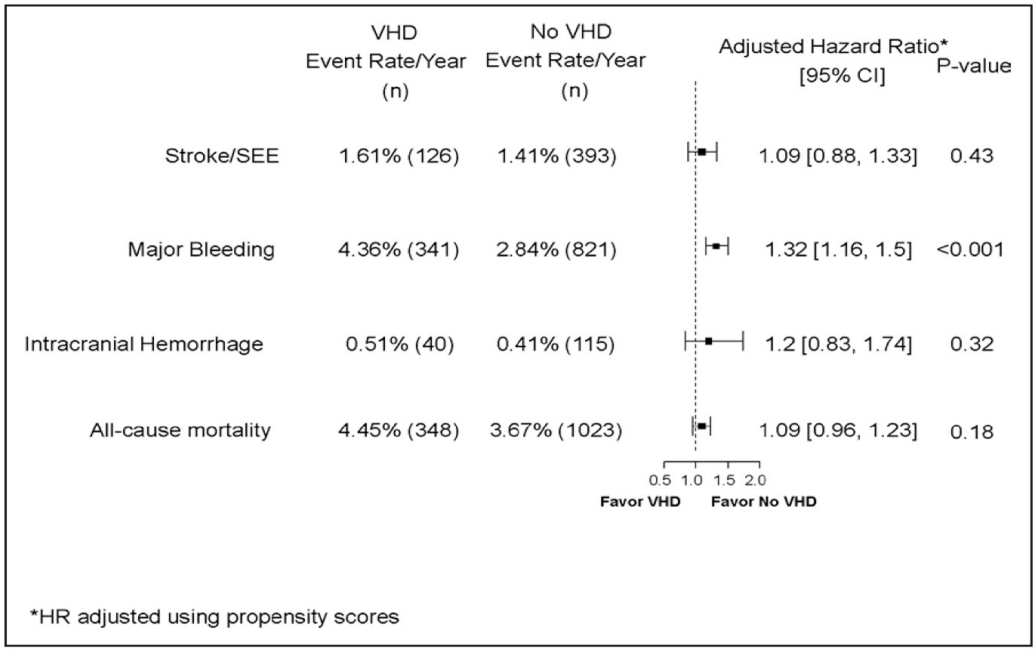
by Michael D. Ezekowitz, Rangadham Nagarakanti, Herbert Noack, Martina Brueckmann, Claire Litherland, Mark Jacobs, Andreas Clemens, Paul A. Reilly, Stuart J. Connolly, Salim Yusuf, and Lars Wallentin

- 3950 pts with VHD (21.8%): 3101 mitral regurgitation, 1179 tricuspid regurgitation, 817 aortic regurgitation, 417 aortic stenosis, 193 mild mitral stenosis.
- VHD pts had more HF, renal impairment, CAD and permanent AF
- Efficacy/safety consistent with the entire study results

Circulation 2016; 34(8):589-598

American Heart Association.

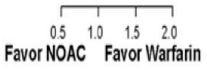
Dabigatran and VHD: efficacy and safety in the RE-LY trial



Circulation 2016; 134(8):589-598

Dabigatran and VHD: efficacy and safety in the RE-LY trial

RE-LY	NOAC Event Rate/Year (n)	Warfarin Event Rate/Year (n)	Hazard Ratio 95% CI	Interaction P-value
Dabigatran 150 mg, VHD	1.12 (30)	1.9 (49)	0.59 [0.37, 0.93]	0.63
Dabigatran 150 mg, No VHD	1.11 (104)	1.66 (153)	0.67 [0.52, 0.86]	
Dabigatran 110 mg, VHD	1.84 (47)	1.9 (49)	0.97 [0.65, 1.45]	0.65
Dabigatran 110 mg, No VHD	1.45 (136)	1.66 (153)	0.88 [0.70, 1.10]	



Stroke and Systemic Embolism

- Thus, the clinician can use the approved doses of dabigatran with confidence in patients with valve disease, excluding only those with prosthetic valve disease or patients with hemodynamic significant mitral stenosis.

Circulation 2016; 134(8):589-598

Dabigatran and valvular bioprosthesis: the DAWA pilot study

Key Points
There are no published study in humans evaluating the efficacy and safety of dabigatran or any other NOACs in patients with mitral and/or aortic bioprosthesis valve.
DAWA is a phase 2, prospective, open-label, randomized, pilot study. The main variable to be observed in this study is intracardiac thrombus. There are no formal primary or secondary clinical efficacy or safety outcomes because it is a pilot study.
The DAWA study encourages a larger multicentric prospective study to assess the use of new oral anticoagulants in patients with bioprosthesis valve.

Drugs R D 2016; 16; 149-154

27 pts randomized to warfarin or dabigatran 110 mg; primary EP: a new intracardiac thrombus at 90 dd on TEE

Inclusion criteria: prior bioprosthesis implantation and post-op AF (with no thrombus at baseline)

Dabigatran and valvular bioprosthesis: the DAWA pilot study

Event	Dabigatran (no. of patients)	Warfarin (no. of patients)
Intracardiac thrombus	0	1 (8.3)
Stroke or systemic embolism	0	1 (8.3)
Reversible ischemic neurological deficit	1 (6.7)	0
Bleeding[a]	1 (6.7)	2 (16.7)
Hospitalization	1 (6.7)	1 (8.3)
Death	0	1 (8.3)

Drugs R D 2016; 16; 149-154

European Heart Journal (2014) **35**, 3377–3385
doi:10.1093/eurheartj/ehu305

CLINICAL RESEARCH
Atrial fibrillation

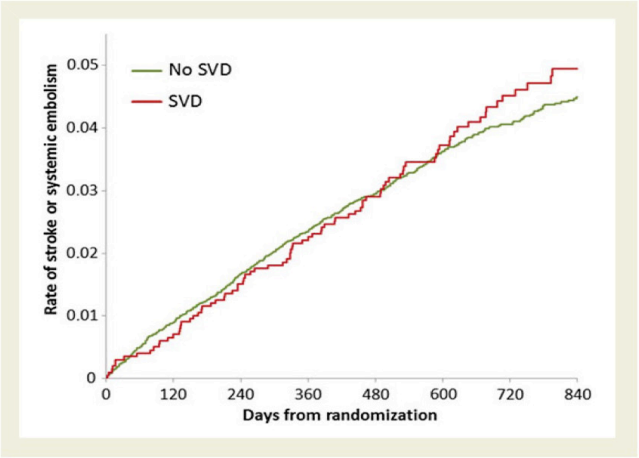
Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial

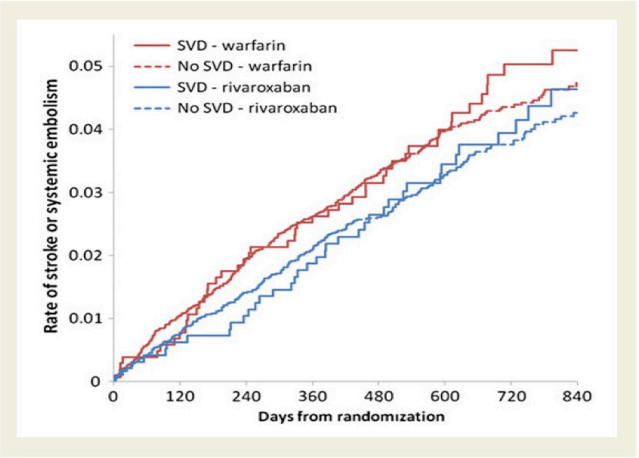
Günter Breithardt[1]*, Helmut Baumgartner[2], Scott D. Berkowitz[3], Anne S. Hellkamp[4],

Characteristic	N (%)
Valve location/abnormality[a]	
Aortic stenosis	215 (11.0%)
Aortic regurgitation	486 (24.8%)
Mitral regurgitation	1756 (89.6%)
Other (without any of preceding)	11 (0.6%)
Etiology[a]	
Rheumatic	62 (3.2%)
Congenital	15 (0.8%)
Calcific/degenerative	791 (40.4%)
Post-infarction and/or ischaemic	253 (12.9%)
Other	307 (15.7%)
Unknown	312 (15.9%)
No data	268 (13.7%)
Prior cardiac valvular procedures	106 (5.3%)
Valvuloplasty	64 (60.4%)
Other cardiac valvular procedure	42 (39.6%)

- 2003 pts with VHD (14.1%),
- VHD pts older, > HF, less previous stroke/TIA, similar $CHADS_2$ & HAS-BLED
- ↑ major bleeding with rivaroxaban in VHD

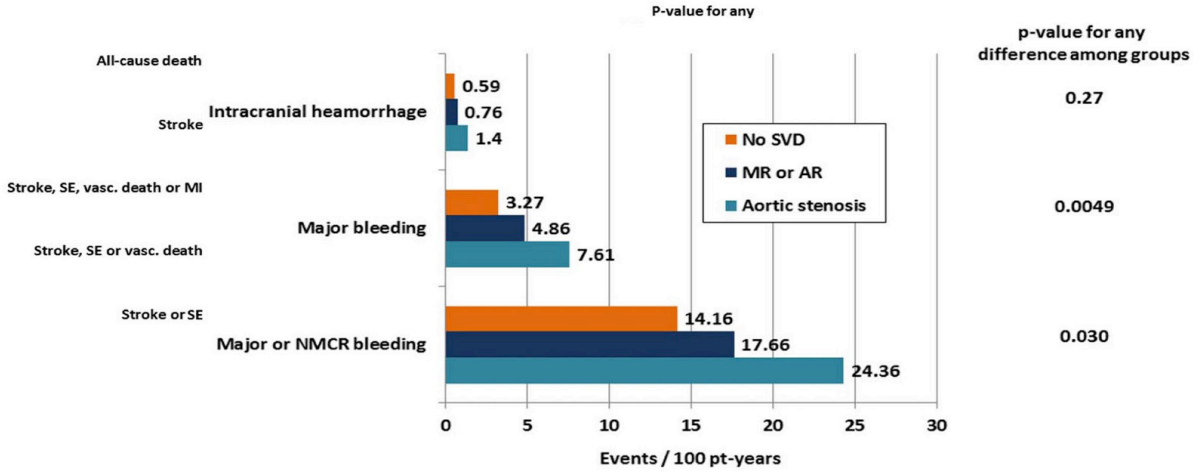
Stroke and SE with rivaroxaban in VHD vs NVHD in the ROCKET-AF trial





Eur Heart J 2014;35:3377—85

Ischemic and bleeding events in the ROCKET-AF trial by type of valve disease



Heart 2016;102:1036—43

Ischemic and bleeding events in the ROCKET-AF trial by type of valve disease

P-value for any

p-value for any

Stroke, SI

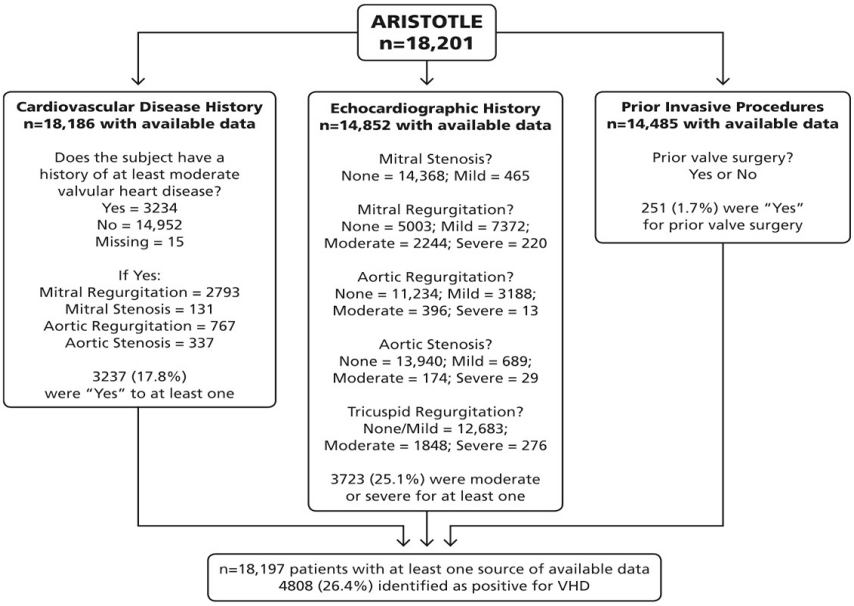
Strok

How might this impact on clinical practice?
We found that patients with atrial fibrillation and AS who are being treated with oral anticoagulation have efficacy and safety outcomes that are distinctly different from patients with other types or without any significant valve disease; this finding should encourage clinicians to carefully consider the risks of thromboembolic complications versus bleeding especially in patients with AS.

Events / 100 pt-years

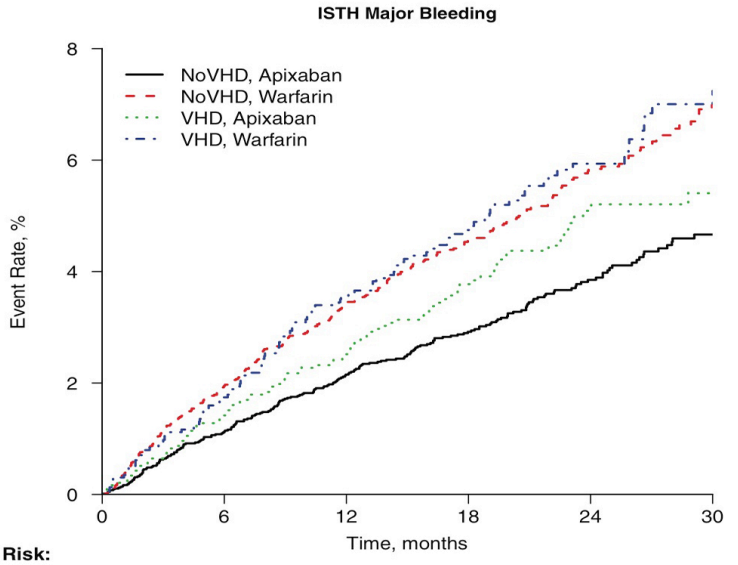
Heart 2016;102:1036—43

VHD and the ARISTOTLE trial



Circulation 2015;132: 624—632

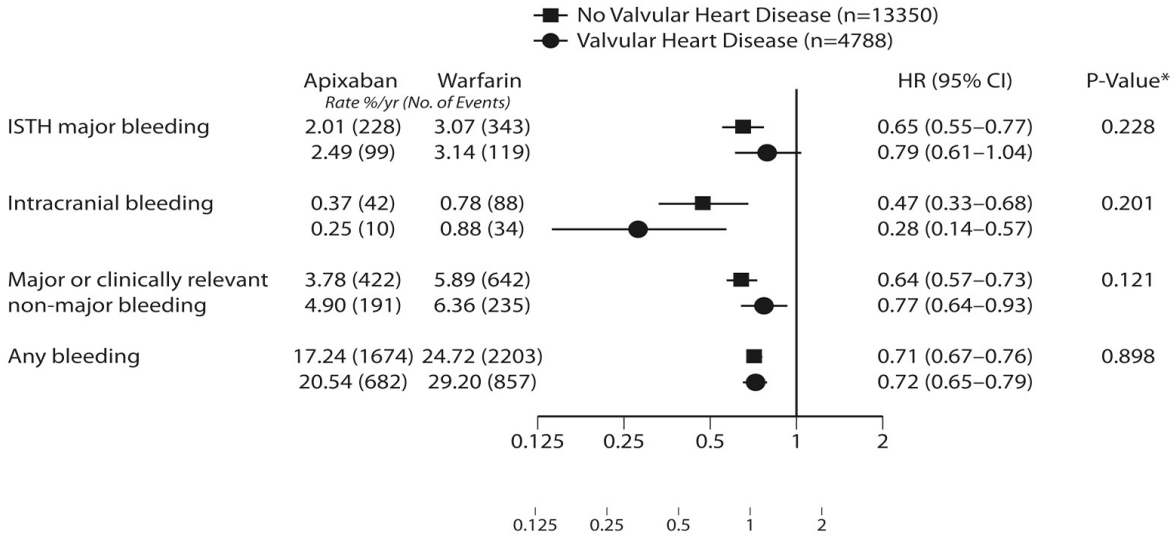
VHD and the ARISTOTLE trial



No. at Risk:						
NoVHD, Apixaban	6659	5989	5610	4130	2451	1219
NoVHD, Warfarin	6691	5911	5512	3997	2354	1200
VHD, Apixaban	2428	2131	1974	1391	816	409
VHD, Warfarin	2360	2015	1842	1333	793	392

Circulation 2015;132: 624—632

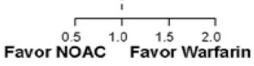
VHD and the ARISTOTLE trial



Circulation 2015;132: 624—632

Stroke and SE with DOACs in VHD vs NVHD

	NOAC Event Rate/Year (n)	Warfarin Event Rate/Year (n)	Hazard Ratio 95% CI	Interaction P-value
RE-LY				
Dabigatran 150 mg, VHD	1.12 (30)	1.9 (49)	0.59 [0.37, 0.93]	0.63
Dabigatran 150 mg, No VHD	1.11 (104)	1.66 (153)	0.67 [0.52, 0.86]	
Dabigatran 110 mg, VHD	1.84 (47)	1.9 (49)	0.97 [0.65, 1.45]	0.65
Dabigatran 110 mg, No VHD	1.45 (136)	1.66 (153)	0.88 [0.70, 1.10]	
ARISTOTLE				0.38
Apixaban 5mg, VHD	1.46 (64)	2.08 (89)	0.70 [0.51, 0.97]	
Apixaban 5mg, No VHD	1.2 (148)	1.43 (176)	0.84 [0.67, 1.04]	
ROCKET AF				0.70
Rivaroxaban 20 mg, VHD	2.01 (38)	2.43 (50)	0.83 [0.55, 1.27]	
Rivaroxaban 20 mg, No VHD	1.96 (231)	2.22 (256)	0.89 [0.75, 1.07]	



Circulation 2016; 134(8):589-598

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Trial record **1 of 6** for: RIVER rivaroxaban
Previous Study | Return to List | Next Study ▸

RIvaroxaban for Valvular Heart diseasE and atRial Fibrillation Trial -RIVER Trial

This study is currently recruiting participants. (see Contacts and Locations)
Verified December 2016 by Hospital do Coracao

Sponsor:
Hospital do Coracao

Information provided by (Responsible Party):
Hospital do Coracao

ClinicalTrials.gov Identifier:
NCT02303795

First received: November 19, 2014
Last updated: December 15, 2016
Last verified: December 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Phase II, randomized, open-label, non-inferiority clinical trial to explore safety and efficacy **of rivaroxaban** compared with warfarin in patients with AF with Bioprosthetic Mitral Valves

European Heart Journal (2014) **35**, 3328–3335
doi:10.1093/eurheartj/ehu352

CURRENT OPINION

What is 'valvular' atrial fibrillation? A reappraisal

Raffaele De Caterina[1] and A. John Camm[2]*

[1]Institute of Cardiology and Center of Excellence on Aging, G. D'Annunzio University – Chieti, and G. Monasterio Foundation, Pisa, Italy; and [2]Division of Clinical Sciences, St George's University of London, London, UK

We propose the term 'mechanical and rheumatic mitral valvular AF' (acronym: MARM-AF) as an accurate description of a disease entity worthy of being kept separated from other forms of AF, but with possible internal differences between the two conditions here encompassed.

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

EHRA PRACTICAL GUIDE

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4],

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

Europace 2015;17(10):1467—507

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

EHRA PRACTICAL GUIDE

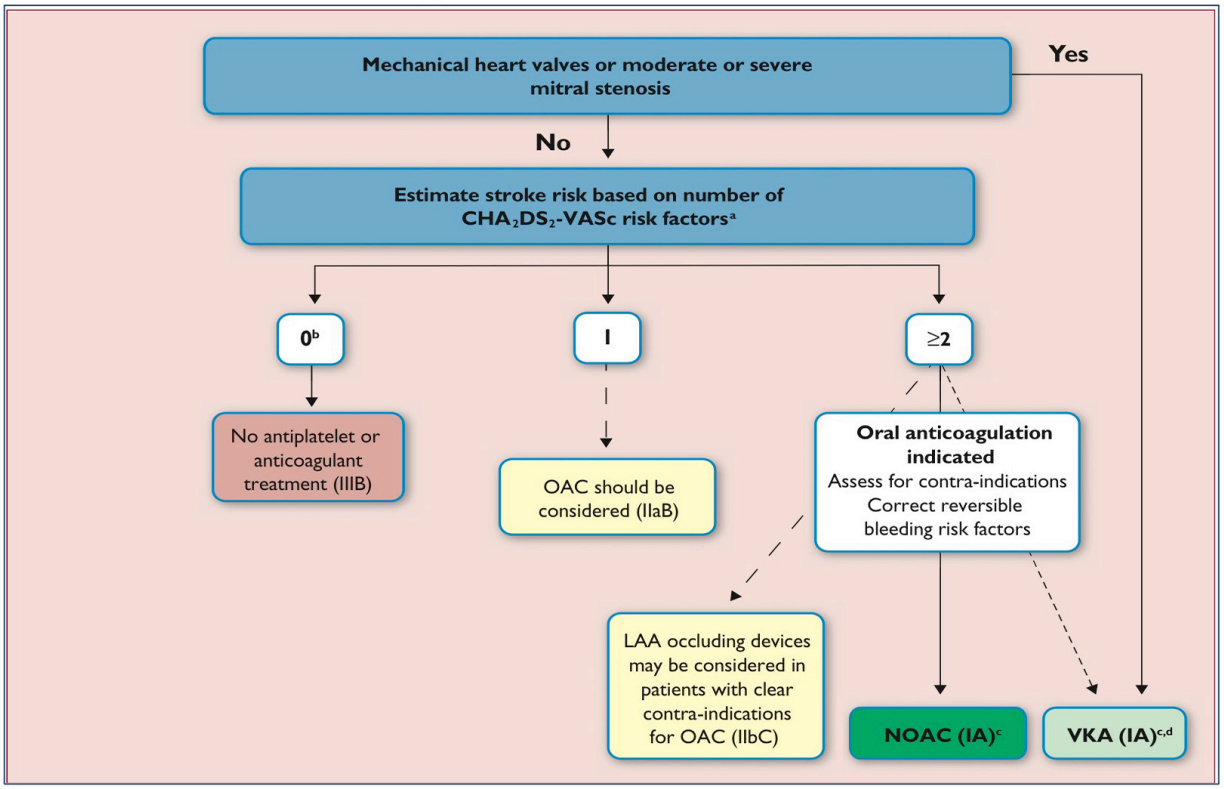
Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4],

		Eligible					Contra-indicated
Group	Year	Moderate to severe mitral stenosis	Mechanichal heart valve	Bioprosthetic heart valve	TAVI	Mitral valve repair	Native valvular disease
ESC	2012	X	X	X	X	√	√
HRS/ACC/AHA	2014	X	X	X	X	X	√
EHRA	2015	X	X	√	√	√	√
				Except for the first 3 m postoperatively	May require combination with antiplatelet therapy	Except for the first 3-6 m postoperatively	
Hypertrophic cardiomyopathy				✓ (but no prospective data)			

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

Europace 2015;17(10):1467—507

ESC guidelines AF 2016



Thrombus location in rheumatic vs non-rheumatic valvular heart disease

Rheumatic AF

Table 2. Review of Published Reports Detailing the Frequency and Site of Thrombus Location in Patients With Rheumatic Atrial Fibrillation

Setting	No. of Patients	Thrombus Location: LA Appendage	Thrombus Location: LA Cavity	Reference No.
Operation	581	26	17	38
Autopsy	136	12	11	39
Operation	818	20	23	27
TEE	50	12	4	28
Operation	21	6	0	29
Operation	293	11	10	30
TEE/Operation	110	13	8	31
TEE/Operation	19	5	0	32
TEE	20	1	1	33
Operation	581	25	16	34
Autopsy	26	13	5	4
TEE	260	17	16	36
Operation	80	33	13	37
Autopsy	509	60	68	35
Total	3,504	254	192	

Non-rheumatic AF

Table 1. Review of Published Reports Detailing the Frequency and Site of Thrombus Location in Patients With Nonrheumatic Atrial Fibrillation

Setting	No. of Patients	Thrombus Location: LA Appendage	Thrombus Location: LA Cavity	Reference No.
TEE[a]	317	66	1	40
TEE	233	34	1	25
Autopsy	506	35	12	39
TEE	52	2	2	28
TEE	48	12	1	41
TEE and Operation	171	8	3	24
SPAF III TEE Study	359	19	1	42
TEE	272	19	0	26
TEE	60	6	0	43
Total	1,288	201	21	

[a] 5% of this cohort had mitral stenosis or a prosthetic mitral valve.

Ann Thorac Surg 1996;61:755 – 759

Mitral stenosis and thromboembolic complications

The incidence of thromboembolic complications is higher in patients with rheumatic mitral stenosis (≈4% per year)and is a major cause of mortality and morbidity….

Comparison of patients with normal sinus rhythm ($n=139$) with or without clot[a]

Variable	With clot $n=16$	Without clot $n=123$	P value
Age (years)	27.0±10.6	27.6±8.4	NS
Duration of symptoms (months):	34.8±34.5	27.9±22.2	<0.05
LVEF %	69.5±7.7	72.1±8.7	NS
MVA (cm^2)	0.75±0.09	0.81±0.15	NS
MDG (mmHg)	17.4±5.1	15.6±5.0	NS
LAD (mm)	50.9±6.4	46.4±6.2	<0.05
LA area (cm^2)	34.1±10.2	28.6±6.2	0.01
SEC:			
Present	9(56.3%)	46(37.4%)	<0.05
Absent	7 (43.7%)	77(62.6%)	

[a] For abbreviations, refer to Table 1.

Mitral stenosis and thromboembolic complications

The incidence of thromboembolic complications is higher in patients with rheumatic mitral stenosis (≈4% per year)and is a major cause of mortality and morbidity....

Comparison of patients with normal sinus rhythm without clot[a]

Variable	With clot $n=16$	Without $n=123$	
Age (years)	27.0±10.6	27.6±8.4	
Duration of symptoms (months):	34.8±34.5	27.9±22	
LVEF %	69.5±7.7	72.1±8.7	NS
MVA (cm^2)	0.75±0.09	0.81±0.15	NS
MDG (mmHg)	17.4±5.1	15.6±5.0	NS
LAD (mm)	50.9±6.4	46.4±6.2	<0.05
LA area (cm^2)	34.1±10.2	28.6±6.2	0.01
SEC:			
Present	9(56.3%)	46(37.4%)	<0.05
Absent	7 (43.7%)	77(62.6%)	

[a] For abbreviations, refer to Table 1.

	Normal Subjects (n = 15)	Patients With Mitral Stenosis (n = 12)		
		PV	RA	LA
PF4 (ng/ml)	8.5 ± 1.8	10.8 ± 2.1	20.3 ± 6.1	22.3 ± 5.7
βTG (ng/ml)	34.3 ± 4.2	39.1 ± 5.3	48.4 ± 9.9	55.1 ± 12.2
FPA (ng/ml)	1.08 ± 0.19	6.73 ± 1.53*	6.31 ± 0.75	19.35 ± 4.64†‡
TAT (ng/ml)	1.75 ± 0.19	2.63 ± 0.44	3.98 ± 0.60	11.45 ± 2.29§‖
DD (ng/ml)	55.4 ± 5.9	67.9 ± 10.2	63.8 ± 7.6	63.3 ± 7.1
PIC (μg/ml)	0.55 ± 0.04	0.69 ± 0.08	0.68 ± 0.07	0.69 ± 0.07
vWF:Ag (%)	99 ± 7	168 ± 25¶	150 ± 23	151 ± 23

Int J Cardiol. 2000;73(3):273-279 – *JACC* 1995; 25:107-12

Mitral stenosis with or without AF

Mitral stenosis is frequently associated with AF: up to 80% of patients with mitral stenosis and systemic embolism have AF

ESC Guidelines 2012

Indication to anticoagulation in mitral stenosis in SR	Class of Recommendation	LOE
When there has been a prior embolism or a thrombus is present in the left atrium	I	C
Dense spontaneous echo-contrast on TOE or enlarged LA (V>60 ml/m2)	IIa	C

Eur Heart J 2012;33:2451—96

Mitral Valve Stenosis: ACCP 2012

2.0.1. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm, we suggest not using antiplatelet or VKA therapy (Grade 2C).

2.0.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 55 mm, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy or antiplatelet (Grade 2C).

CHEST 2012; 141: e576S-e600S

Mitral Valve Stenosis: ACCP 2012

2.0.1. In patients with rheumatic mitral valve disease an
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2.0.2. In
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VKA thera

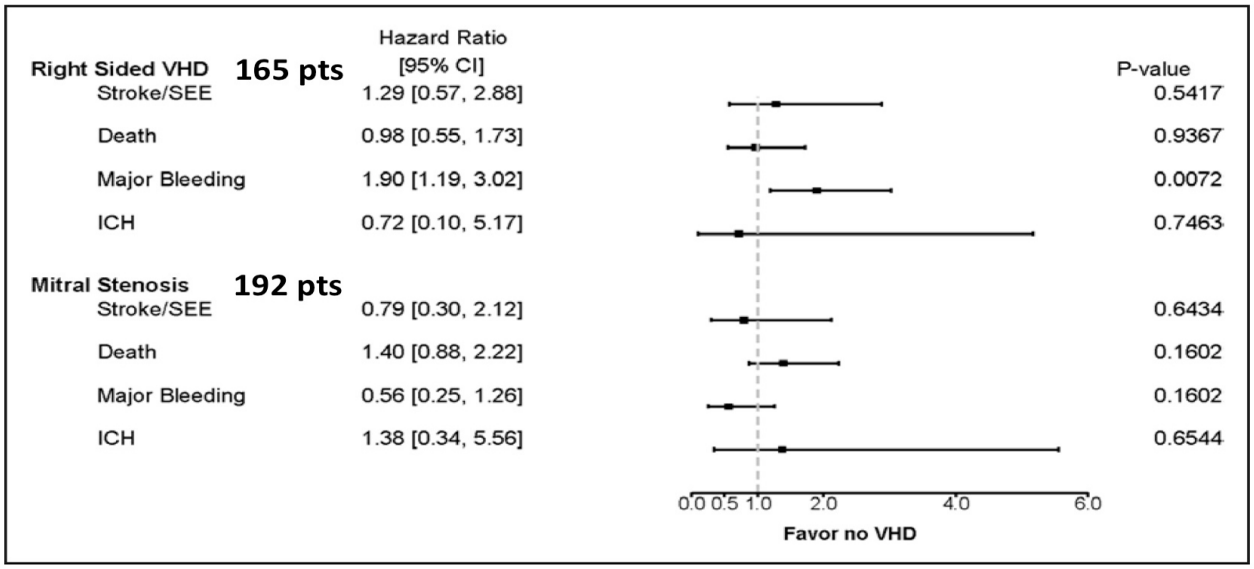
2.0.3. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of left atrial thrombus, we recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy (Grade 1A).

2.0.4. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of AF or previous systemic embolism, we recommend VKA therapy (target

(Grade 1°A)

CHEST 2012; 141: e576S-e600S

Dabigatran and VHD: efficacy and safety in the RE-LY trial



Circulation 2016; 134(8):589-598

Conclusions

- The term NVAF and the inclusion and exclusion criteria in NOACs pivotal trials have created some confusion in physicians' minds about patients who are eligible or not for this therapy
- NOACs can be safely used in patients with native valvular diseases, regardless of their severity, and probably in bioprosthetic heart valve recipients
- The only contraindications remain the presence of a mechanical heart valve and moderate-to-severe mitral stenosis
- Future studies are warranted to increase the level of evidence of the safety and efficacy of NOACs in specific populations