Paziente con fibrillazione atriale e scompenso cardiaco

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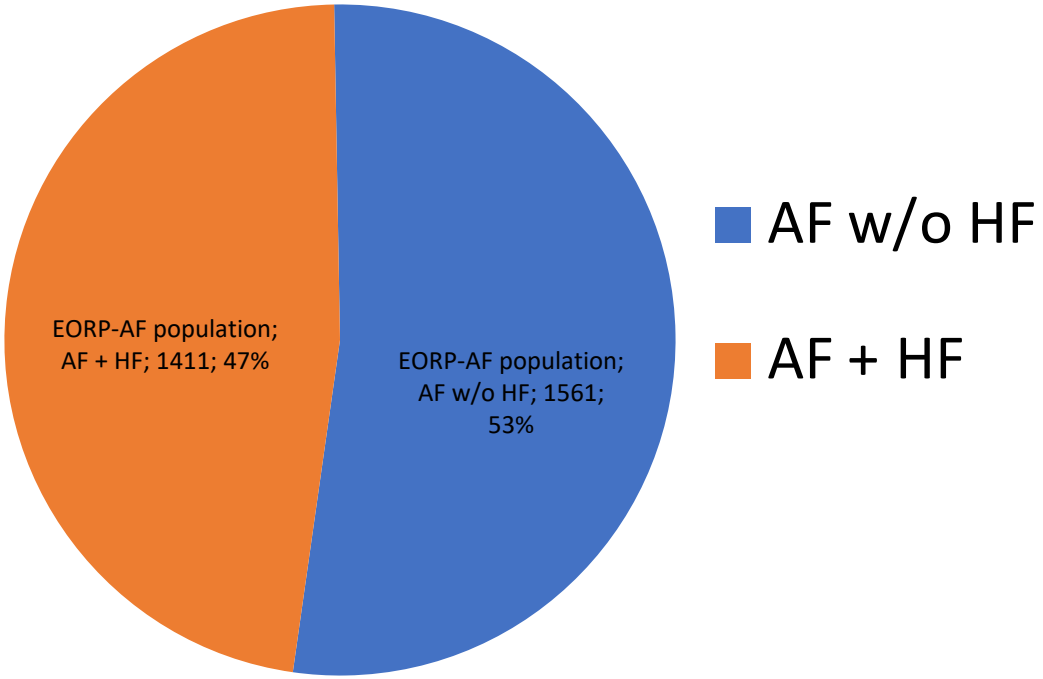
Heart failure in patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Pilot survey on Atrial Fibrillation

Gregory Y.H. Lip[1]*, Cécile Laroche[2], Mircea I. Popescu[3], Lars H. Rasmussen[4], Laura Vitali-Serdoz[5], Gheorghe-Andrei Dan[6], Zbigniew Kalarus[7], Harry J.G.M. Crijns[8], Mario M. Oliveira[9], Luigi Tavazzi[10], Aldo P. Maggioni[2], and Giuseppe Boriani[11]



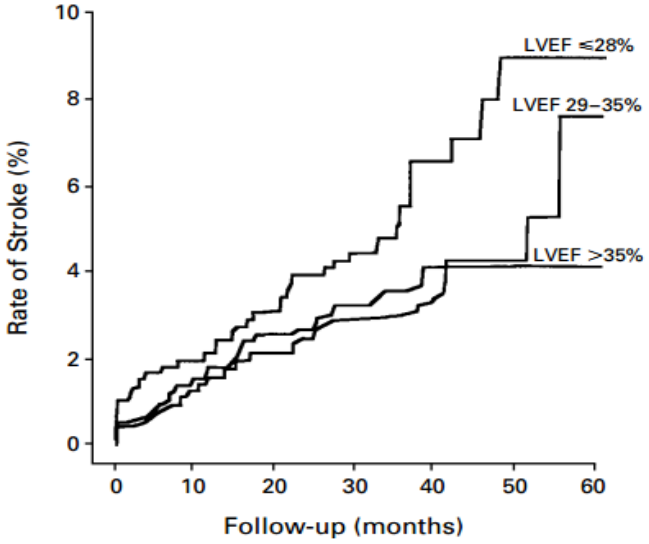
- In HF patients AF prevalence ranges from 12 to 50%
- Prevalence of AF increases with HF worsening

VENTRICULAR DYSFUNCTION AND THE RISK OF STROKE AFTER MYOCARDIAL INFARCTION

EVAN LOH, M.D., MARTIN ST. JOHN SUTTON, M.D., CHUAN-CHUAN C. WUN, PH.D., JEAN L. ROULEAU, M.D., GREG C. FLAKER, M.D., STEPHEN S. GOTTLIEB, M.D., GERVASIO A. LAMAS, M.D., LEMUEL A. MOYÉ, PH.D., SAMUEL Z. GOLDHABER, M.D., AND MARC A. PFEFFER, M.D., PH.D.

TABLE 2. RISK FACTORS FOR STROKE IN THE MULTIVARIATE ANALYSIS.*

RISK FACTOR	RELATIVE RISK (95% CI)	WALD CHI-SQUARE	P VALUE
LVEF (for each decrease of 5 percentage points)	1.18 (1.02–1.36)	4.71	0.03
Age (for each increase of 5 yr)	1.18 (1.05–1.33)	7.80	<0.001
Anticoagulant therapy during follow-up	0.19 (0.13–0.27)	81.95	<0.001
Aspirin use during follow-up	0.44 (0.29–0.65)	16.61	<0.001
Current smoking at randomization	1.40 (0.89–2.20)	2.12	NS
History of hypertension	1.12 (0.72–1.73)	0.25	NS
History of diabetes	1.34 (0.83–2.14)	1.44	NS
Previous myocardial infarction	0.97 (0.62–1.51)	0.02	NS
Recurrent myocardial infarction	0.87 (0.47–1.59)	0.22	NS
Assignment to captopril	1.28 (0.84–1.93)	1.27	NS
Atrial fibrillation or flutter before randomization	1.62 (0.93–2.78)	2.94	NS
Thrombolytic therapy	0.62 (0.37–1.02)	3.51	0.061



Loh et al, NEJM 1997

Heart failure and thromboembolic risk

Hypotheses:

- deceleration of peripheral and intracardiac blood flow due to peripheral congestion and impaired cardiac contractility
- endothelial dysfunction (impaired NO response)
- prolonged bed rest in severely ill cases
- the presence of coagulation defects as, for example, in the case of ventricular assist devices

VKA limitations

- Intra- and interpatient variability in dose response
- susceptibility to drug–drug and drug–food interactions
- narrow therapeutic index necessitate periodic monitoring of physiologic response to warfarin using the international normalized ratio (INR)

HF and VKA: the bleeding risk

Table 3 Predictors of stable INR control status (c-statistic = 0.69)

Predictor	Adjusted odds ratio	95% CI
Age		
> 70 years	1.93	1.56–2.38
≤70 years	–	–
Sex		
Female	–	–
Male	1.44	1.16–1.78
INR target		
2.0	2.80	1.83–4.28
2.5	–	–
≥3.0	0.28	0.17–0.47
Primary indication for anticoagulation therapy		
Atrial fibrillation	–	–
Venous thromboembolism	0.81	0.63–1.04
Heart valve disorder	1.13	0.65–1.98
Other	1.01	0.77–1.31
Risk factors		
Diabetes mellitus		
Yes	–	–
No	1.69	0.93–3.08
Hypertension		
Yes	–	–
No	0.98	0.77–1.24
Heart failure		
Yes	–	–
No	2.08	1.36–3.17

Table 2 Unadjusted outcomes during 365-day follow-up period

Characteristic	Stable group (n = 533)	Comparator group (n = 2555)	P-value
Received heparin* (%)	1.1	7.1	<0.001
Deceased (n, %)	2, 0.4	51, 2.0	0.005†
AC-related death (n, %)	0, 0.0	2, 0.1	0.518†
AC-related thrombosis (n, %)	1, 0.2	34, 1.3	0.022†
Arterial thromboembolism	0, 0	1, 0.04	
Deep vein thrombosis	0, 0	4, 0.2	
Pulmonary embolism	0, 0	6, 0.2	
Stroke	1, 0.2	14, 0.5	
Thrombophlebitis	0, 0	1, 0.04	
Other	0, 0	8, 0.3	
AC-related bleeding (n, %)	11, 2.1	104, 4.1	0.026
Epistaxis	2, 0.4	24, 0.9	
Gastrointestinal	5, 0.9	44, 1.7	
Hemarthrosis	0, 0	3, 0.1	
Hematoma	0, 0	6, 0.2	
Hematuria	1, 0.2	10, 0.4	
Intracranial	1, 0.2	8, 0.3	
Other	2, 0.4	9, 0.4	
AC-related bleeding or thrombosis (n, %)	12, 2.3	136, 5.3	0.003

Witt et al, J Thromb Haemost 2010

Predictors of TTR<55%

Impact of demographics and co-morbidities on likelihood of lower time in therapeutic range

Characteristic	OR (95% CI)	p
Age ≥75 (vs <75) (yrs)	0.94 (0.88–1.01)	NS
Men (vs women)	0.78 (0.73–0.83)	<0.001
United States region		
Northeast	1.00 (Referent)	—
West	1.39 (1.26–1.54)	<0.001
South	1.38 (1.26–1.52)	<0.001
Midwest	1.04 (0.95–1.14)	NS
Co-morbidities (vs not present)		
Heart failure	1.41 (1.28–1.56)	<0.001
Diabetes	1.28 (1.19–1.38)	<0.001
Previous stroke	1.15 (1.04–1.27)	0.0075
Hypertension	0.86 (0.80–0.93)	<0.001

CI = confidence interval; OR = odds ratio.

Nelson et al, 2013 AmJCardiol

HF and VKA: the bleeding risk

>4000 pts from the AFFIRM study

Table I. Baseline characteristics

	All patients	No major bleeding	Major bleeding	P
n (%)	4060	3800	260	
Randomized to rhythm control	2033 (50)	1909 (50)	124 (48)	.427
Age (y) (mean ± SD)	69.7 ± 9.0	69.6 ± 9.0	72.3 ± 8.2	<.001*
Women	1594 (39)	1478 (39)	116 (45)	.068
Minority	461 (11)	428 (11)	33 (13)	.482
History of hypertension	2876 (71)	2686 (71)	190 (73)	.412
History of CAD	1551 (38)	1439 (38)	112 (43)	.094
History of CHF	939 (23)	857 (23)	82 (32)	.001*
History of diabetes	813 (20)	748 (20)	65 (25)	.038*
History of stroke or TIA	542 (13)	497 (13)	45 (17)	.052
History of hepatic or renal disease	231 (6)	205 (5)	26 (10)	.002*
Recent history of smoking	496 (12)	471 (12)	25 (10)	.186
Qualifying episode of AF is first episode documented	1391 (36)	1291 (35)	100 (40)	.113
Left atrial enlargement (size >4.0 cm)	2023 (65)	1888 (65)	135 (66)	.724
Left ventricular dysfunction (ejection fraction <50%)	788 (26)	724 (26)	64 (32)	.063
Mitral regurgitation >2+	647 (20)	603 (20)	44 (21)	.799

Di Marco et al, Am Heart J 2005

In summary

Disadvantages of HF patients in therapy with VKA

- Multiple drugs
- More frequent hepatic

and renal dysfunction

- Greater INR lability

HAS-BLED score

Condition	Points
H - Hypertension	1
A - Abnormal renal or liver function (1 point each)	1 or 2
S - Stroke	1
B - Bleeding	1
L - Labile INRs	1
E - Elderly (> 65 years)	1
D - Drugs or alcohol (1 point each)	1 or 2

What about DOACs?

	RE-LY	Rocket-AF	Aristotle	Engage AF TIMI
Agent (mechanism of action)	Dabigatran (direct thrombin inhibitor)	Rivaroxaban (direct inhibitor of activated factor X)	Apixaban (direct inhibitor of activated factor X)	Edoxaban (direct inhibitor of activated factor X)
NOAC dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg or 30 mg once daily In both groups the dose was halved in patients who had any of the following criteria:estimated CrCl 30-50 ml/ min, body weight ≤60 kg or concomitant use of verapamil or quinidine
Patients (n)	18,113	14,264	18,201	21,105
Renal function exclusion CG criteria)	<30 ml/min/1.73 m2	<30 ml/min/1.73 m2	<25 ml/min/1.73 m2	<30 ml/min/1.73 m2
Safety and efficacy of NOAC in comparison to warfarin	150 mg dose:lower rates of stroke and systemic embolism and similar rates of major haemorrhage 110 mg dose:similar rates of stroke and less major bleeding	Similar rates of stroke and major bleeding	Less stroke and major bleeding	Both doses:similar rates of stroke with less major bleeding

DOAC's registration trials: HF subpopulations

Table 2: Baseline characteristics of patients enrolled in major studies of FDA-approved direct-acting oral anticoagulants (DOACs)

Drug	Dabigatran[46]	Rivaroxaban[45]	Apixaban[48]	Edoxaban[47]
HF subgroup, n (%)	4904 (27)	9033 (63)	2736 (15)	8076 (67)
HF definition	NYHA ≥II HF symptoms <6 months screening and prior HF	HF history, or LVEF <40%	LVEF <40% or moderate or severe LV dysfunction	current presence or history of clinical HF Class C or D
Mean LVEF	NR		35 (30-39)	NR
LVEF ≤ 40%	44	34	NR**	NR
Mean age	68.3 ± 10.2	72 (65-78)	68 (60-74)	NR
Male %	67	61	79	NR
Nonischemic HF%	68	70	72	NR
Hypertension%	75	93	75	NR
Diabetes mellitus%	27	42	27	NR
History of stroke/TIA%	17	47	16	NR
Vascular disease%	NR	6.7	NR	NR
Mean $CHADS_2$	2.6 (1.1)	3.7(0.9)	2.22 (1.2)	NR

Zeitler et al, JAFIB 2015

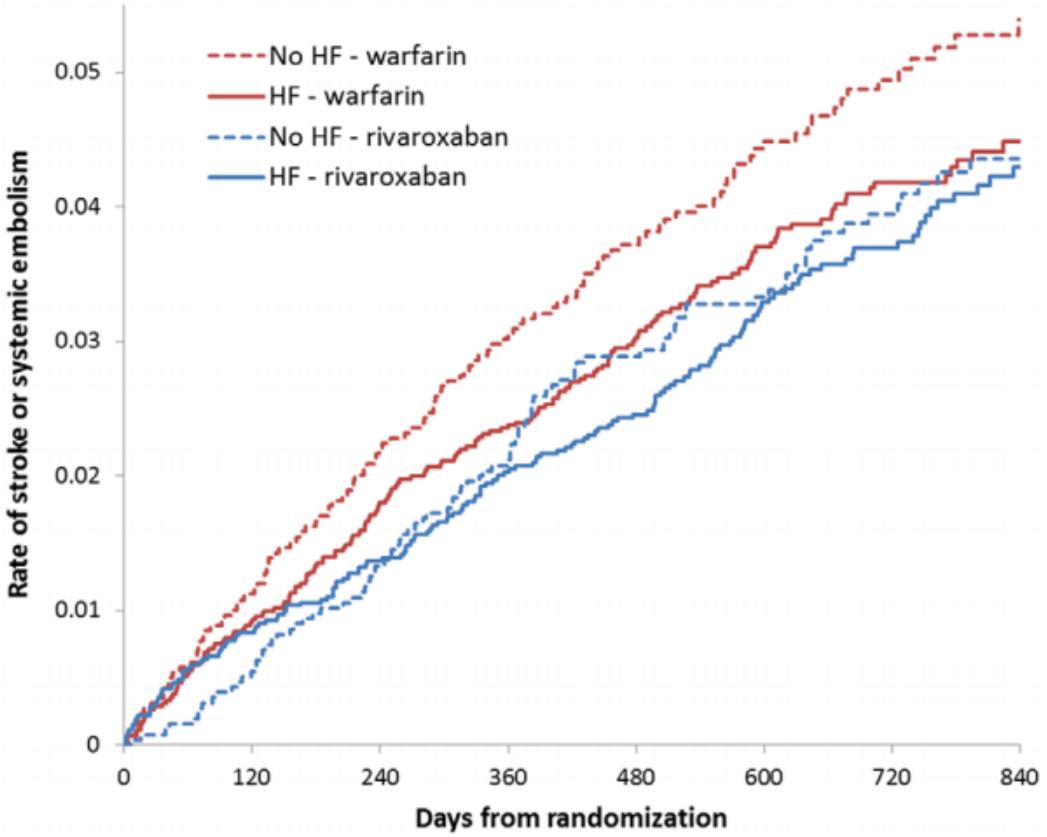
ROCKET AF-HF: impact of HF

Rivaroxaban vs VKA
9033 pts with **HF history or LVEF<40%**
Mean $CHADS_2$ Score 3.5

Outcomes	Heart Failure*	No Heart Failure*	Heart Failure vs No Heart Failure, HR (95% CI)†	*P* Value
Efficacy outcomes				
Stroke or systemic embolization	1.99 (343)	2.32 (232)	0.94 (0.78–1.13)	0.51
Stroke, systemic embolization, or vascular death	5.00 (835)	3.50 (346)	1.28 (1.11–1.47)	0.0006
Stroke	1.84 (317)	2.16 (217)	0.95 (0.78–1.15)	0.57
Systemic embolization	0.17 (30)	0.17 (17)	0.93 (0.48–1.82)	0.84
All-cause death	5.26 (879)	3.37 (335)	1.34 (1.17–1.55)	<0.0001
Vascular death	3.53 (600)	1.75 (176)	1.65 (1.37–1.98)	<0.0001
Myocardial infarction	1.15 (200)	0.71 (72)	1.20 (0.89–1.63)	0.23
Safety outcomes				
Major or NMCR Bleeding	14.12 (1766)	15.73 (1158)	1.00 (0.92–1.08)	0.99
Hemorrhagic stroke	0.29 (41)	0.45 (38)	0.73 (0.45–1.20)	0.22
Intracranial hemorrhage	0.53 (74)	0.77 (65)	0.84 (0.58–1.22)	0.36

Van Diepen, Circ Heart Fail. 2013

ROCKET AF-HF: outcomes by HF and therapy



P=0.62 for interaction

Van Diepen, Circ Heart Fail. 2013

ROCKET AF-HF: outcomes by HF and therapy

	Heart Failure			No Heart Failure			
Outcomes	Rivaroxaban*	Warfarin*	Rivaroxaban vs Warfarin, HR (95% CI)†	Rivaroxaban*	Warfarin*	Rivaroxaban vs Warfarin, HR (95% CI)†	*P* Value for Interaction‡
Efficacy outcomes	(n=4530)	(n=4503)		(n=2551)	(n=2587)		
Stroke or systemic embolization	1.90 (164)	2.09 (179)	0.91 (0.74–1.13)	2.10 (105)	2.54 (127)	0.84 (0.65–1.09)	0.62
Stroke, systemic embolization, or vascular death	4.88 (409)	5.11 (426)	0.97 (0.85–1.11)	3.29 (163)	3.71 (183)	0.89 (0.72–1.10)	0.52
Stroke	1.78 (154)	1.89 (163)	0.94 (0.76–1.17)	1.97 (99)	2.35 (118)	0.85 (0.65–1.11)	0.57
Systemic embolization	0.15 (13)	0.19 (17)	0.78 (0.38–1.61)	0.14 (7)	0.19 (10)	0.72 (0.27–1.88)	0.88
All-cause death	5.05 (423)	5.46 (456)	0.93 (0.82–1.07)	3.20 (159)	3.54 (176)	0.89 (0.71–1.10)	0.68
Vascular death	3.44 (292)	3.63 (308)	0.96 (0.82–1.13)	1.65 (83)	1.84 (93)	0.89 (0.66–1.20)	0.64
Myocardial infarction	1.09 (95)	1.21 (105)	0.94 (0.71–1.24)	0.69 (35)	0.72 (37)	0.94 (0.59–1.49)	0.99
Safety outcomes	(n=4550)	(n=4527)		(n=2561)	(n=2598)		
Major or NMCR bleeding	14.22 (888)	14.02 (878)	1.05 (0.95–1.15)	16.12 (587)	15.35 (571)	1.05 (0.93–1.18)	0.99
Hemorrhagic stroke	0.16 (11)	0.43 (30)	0.38 (0.19–0.76)	0.43 (18)	0.47 (20)	0.91 (0.48–1.73)	0.067
Intracranial hemorrhage	0.40 (28)	0.65 (46)	0.63 (0.40–1.02)	0.64 (27)	0.89 (38)	0.72 (0.44–1.19)	0.71

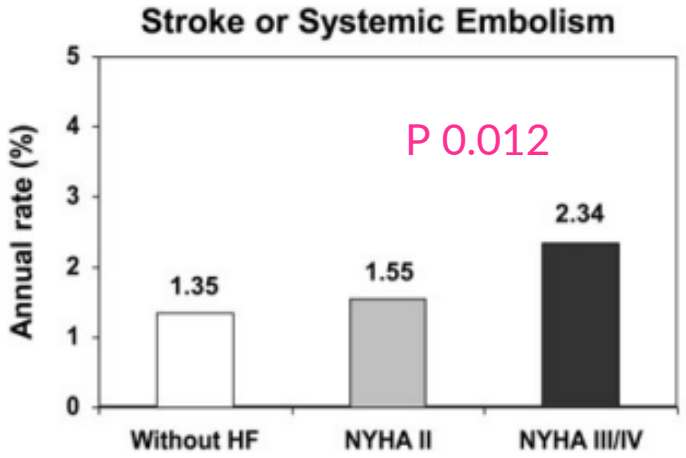
Van Diepen, Circ Heart Fail. 2013

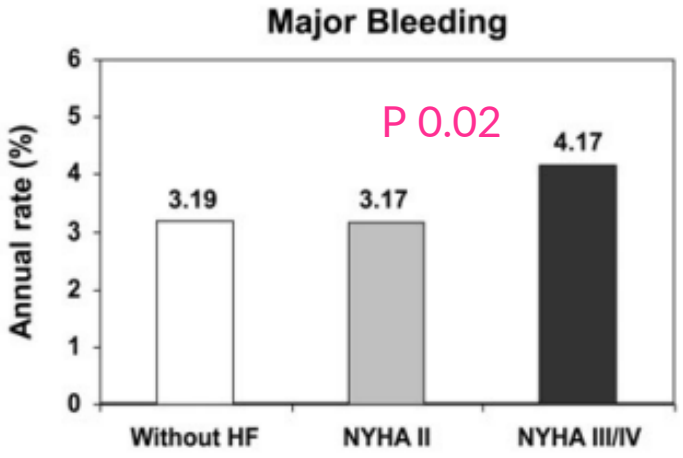
RE-LY: HF subgroup analysis

Definition: NYHA ≥ 2 in the last 6 mo + history of HF

Table 4 Total number and annual rates of outcomes in the study population with and without heart failure and multivariable adjusted hazard ratios

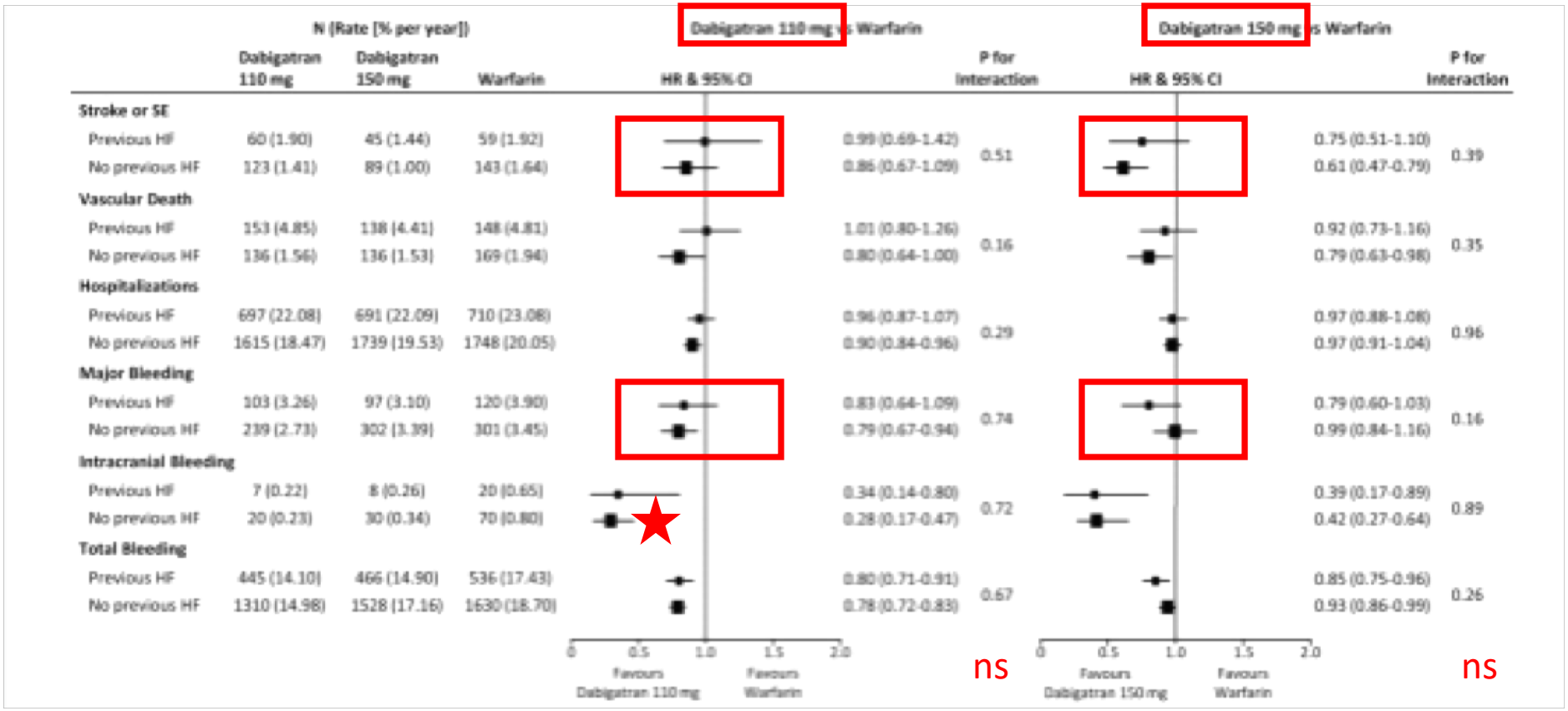
Outcomes	With HF (n = 4904)	Without HF (n = 13 209)	Adjusted hazard ratio (95% CI)	P-value
Stroke or systemic embolism	164 (1.75)	355 (1.35)	1.08 (0.89–1.31)	0.46
Vascular death	439 (4.69)	441 (1.67)	2.26 (1.96–2.61)	<0.0001
Hospitalization	2098 (22.41)	5102 (19.35)	1.13 (1.07–1.20)	<0.0001
Major bleeding	320 (3.42)	842 (3.19)	0.96 (0.83–1.10)	0.53
Intracranial bleeding	35 (0.37)	120 (0.46)	0.72 (0.49–1.06)	0.10





Ferreira et al, Eur J Heart Fail 2013

RE-LY HF: outcomes



Ferreira et al, Eur J Heart Fail 2013

ARISTOTELE subanalysis

14.671 pts

8728 patients

no symptomatic HF and an EF >40%

3207 patients

Symptomatic HF and an EF >40% (study definition of HF-PEF)

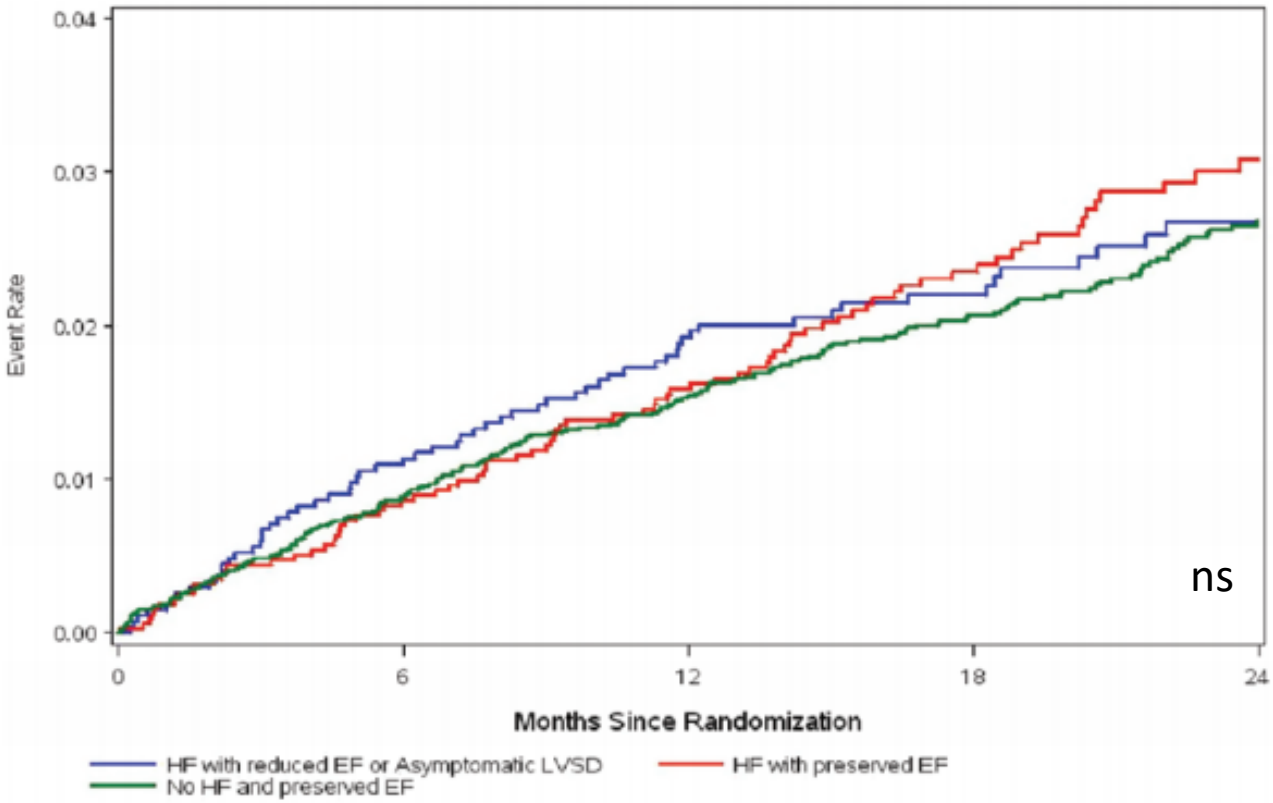
2736 patients

EF ≤40% (moderate or severe LV dysfunction)

McMurray et al, Circ Heart Fail 2013

ARISTOTELE subanalysis

Composite primary outcome: stroke + SE



McMurray et al, Circ Heart Fail 2013

Treatment effect by HF/LVSD: efficacy and safety endpoints

	Rate (n)			
	Apixaban	Warfarin	HR (95% CI)	Interaction *P* Value
Stroke or systemic embolism*				
LVSD	0.99 (24)	1.80 (43)	0.55 (0.34–0.91)	0.21
HF-PEF	1.51 (44)	1.54 (45)	0.98 (0.65–1.49)	
No LVSD/no HF	1.16 (95)	1.58 (129)	0.74 (0.57–0.96)	
Stroke				
LVSD	0.91 (22)	1.67 (40)	0.54 (0.32–0.91)	0.22
HF-PEF	1.37 (40)	1.40 (41)	0.98 (0.63–1.51)	
No LVSD/no HF	1.09 (89)	1.54 (125)	0.71 (0.54–0.93)	
ISTH major bleeding				
LVSD	2.77 (61)	3.41 (74)	0.81 (0.58–1.14)	0.50
HF-PEF	1.95 (52)	3.17 (82)	0.62 (0.44–0.88)	
No LVSD/no HF	2.17 (162)	2.83 (210)	0.77 (0.62–0.94)	
ISTH major bleeding: intracranial				
LVSD	0.18 (4)	0.73 (16)	0.25 (0.08–0.73)	0.23
HF-PEF	0.15 (4)	0.76 (20)	0.20 (0.07–0.58)	
No LVSD/no HF	0.38 (29)	0.81 (61)	0.47 (0.30–0.73)	

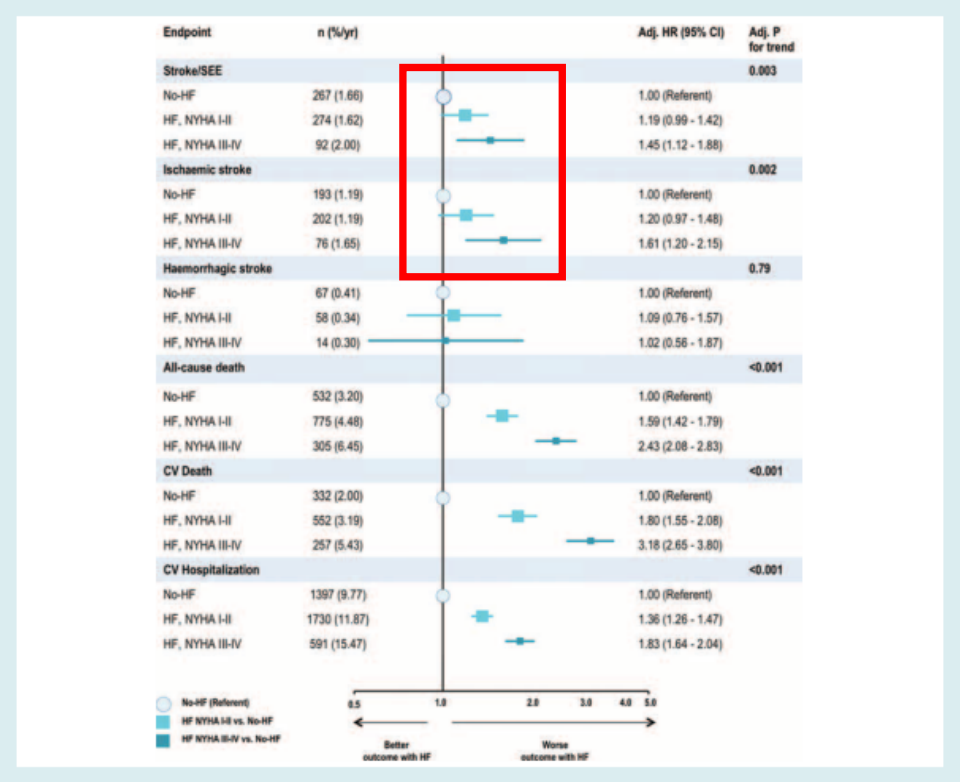
*"Apixaban was **superior** to warfarin with respect to both efficacy and safety outcomes in all patient groups, with the greatest absolute benefit in the highest risk patients with LVSD".*

McMurray et al, Circ Heart Fail 2013

ENGAGE AF-HF: outcomes by HF degree

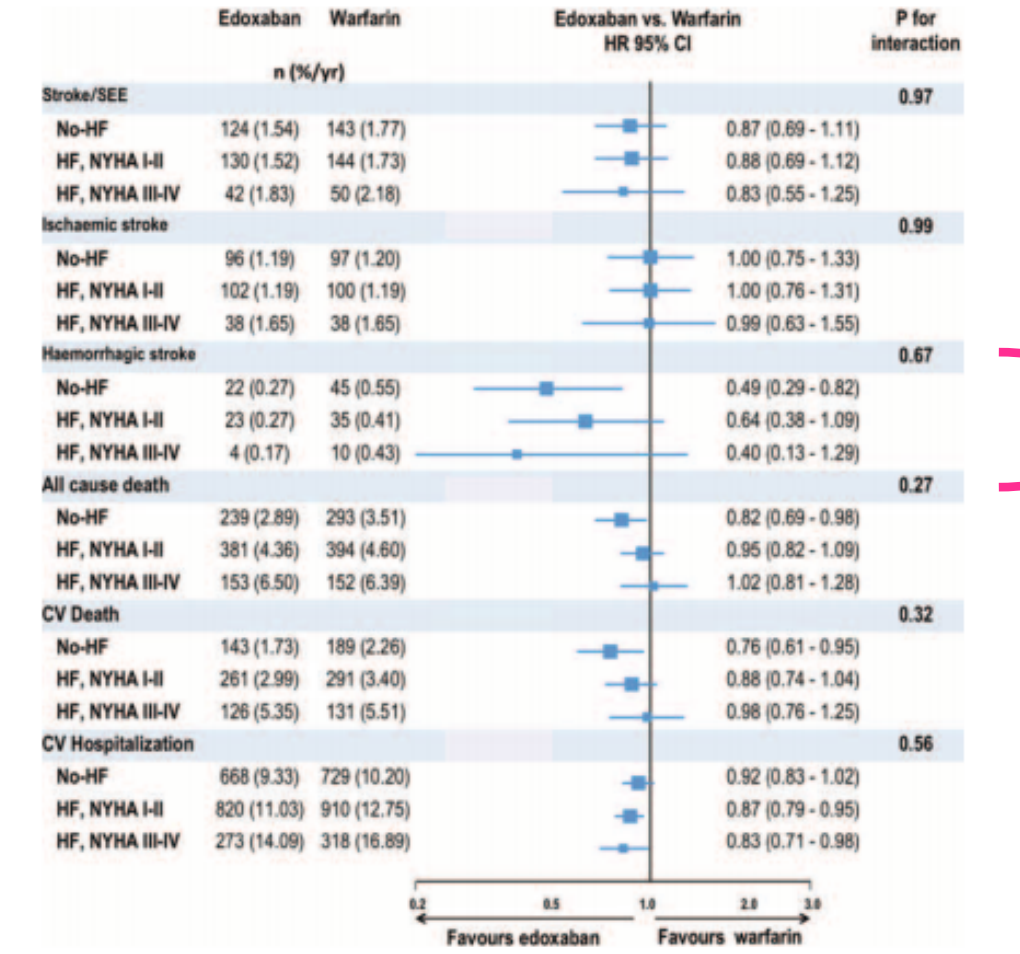
HDER only!

Previous history or presence of HF stage C/D (ACC/AHA definition)



Magnani et al, European Journal of Heart Failure 2016

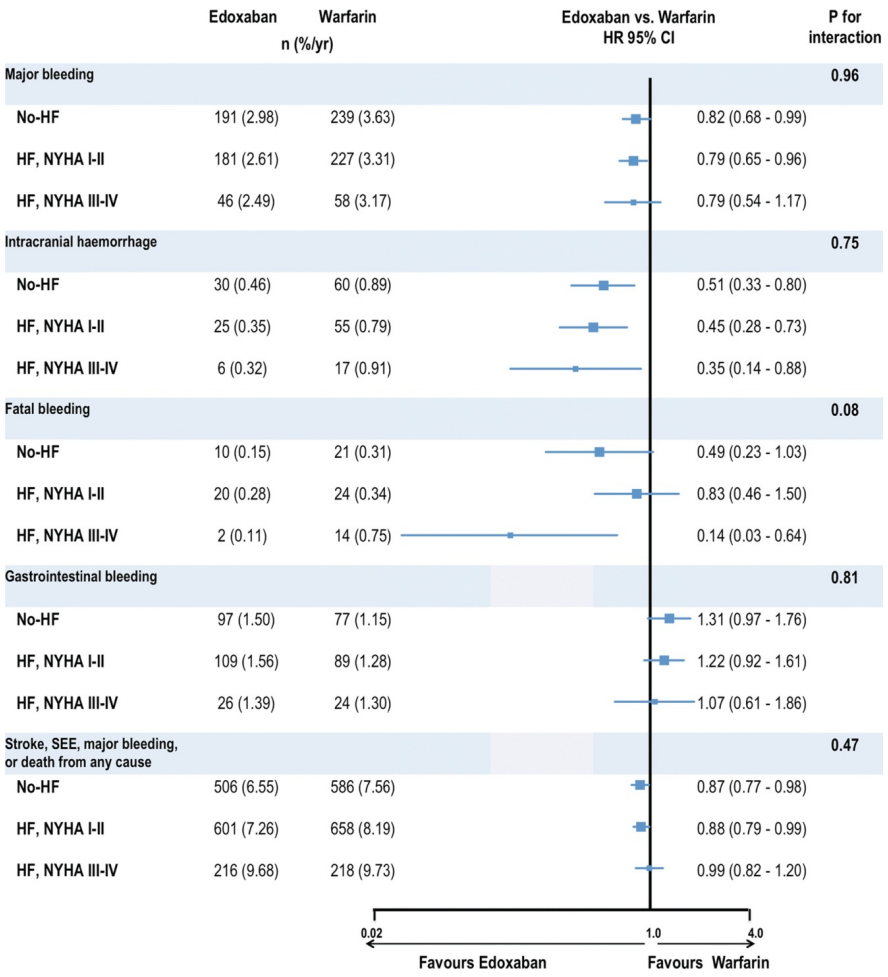
ENGAGE AF-HF: outcomes by HF and therapy



All p<0.05

Magnani et al, European Journal of Heart Failure 2016

ENGAGE AF-HF: outcomes by HF and therapy



p p 0.04

p p 0.02

All p<0.05

Magnani et al,
European Journal of Heart Failure 2016

Overall results

Table 2: Baseline characteristics of patients enrolled in major studies of FDA-approved direct-acting oral anticoagulants (DOACs)

Drug	Dabigatran[46]	Rivaroxaban[45]	Apixaban[48]	Edoxaban[47]
HF subgroup, n (%)	4904 (27)	9033 (63)	2736 (15)	8076 (67)
Efficacy	No significant interaction between treatment effect of dabigatran (110mg or 150mg) and the presence of HF.	No significant interaction between the primary efficacy endpoint and the presence of heart failure for those taking rivaroxaban versus warfarin.	No evidence of treatment heterogeneity according to the presence of heart failure.	No interaction between reduction in stroke or systemic embolism and the presence of HF.

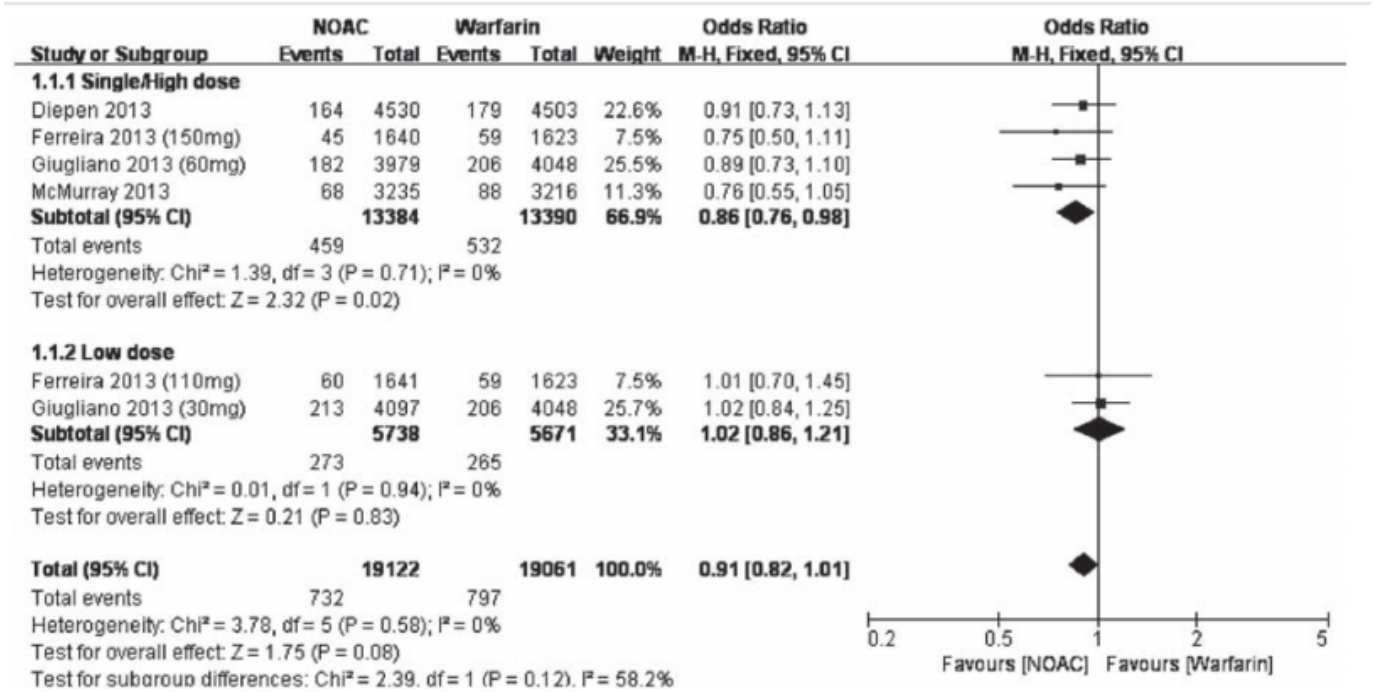
Zeitler et al, JAFIB 2015

AF +HF metanalysis

RCT: RE-LY, ARISTOTELE, ROCKET-AF, ENGAGE-AF

Primary efficacy outcome: stroke/SE

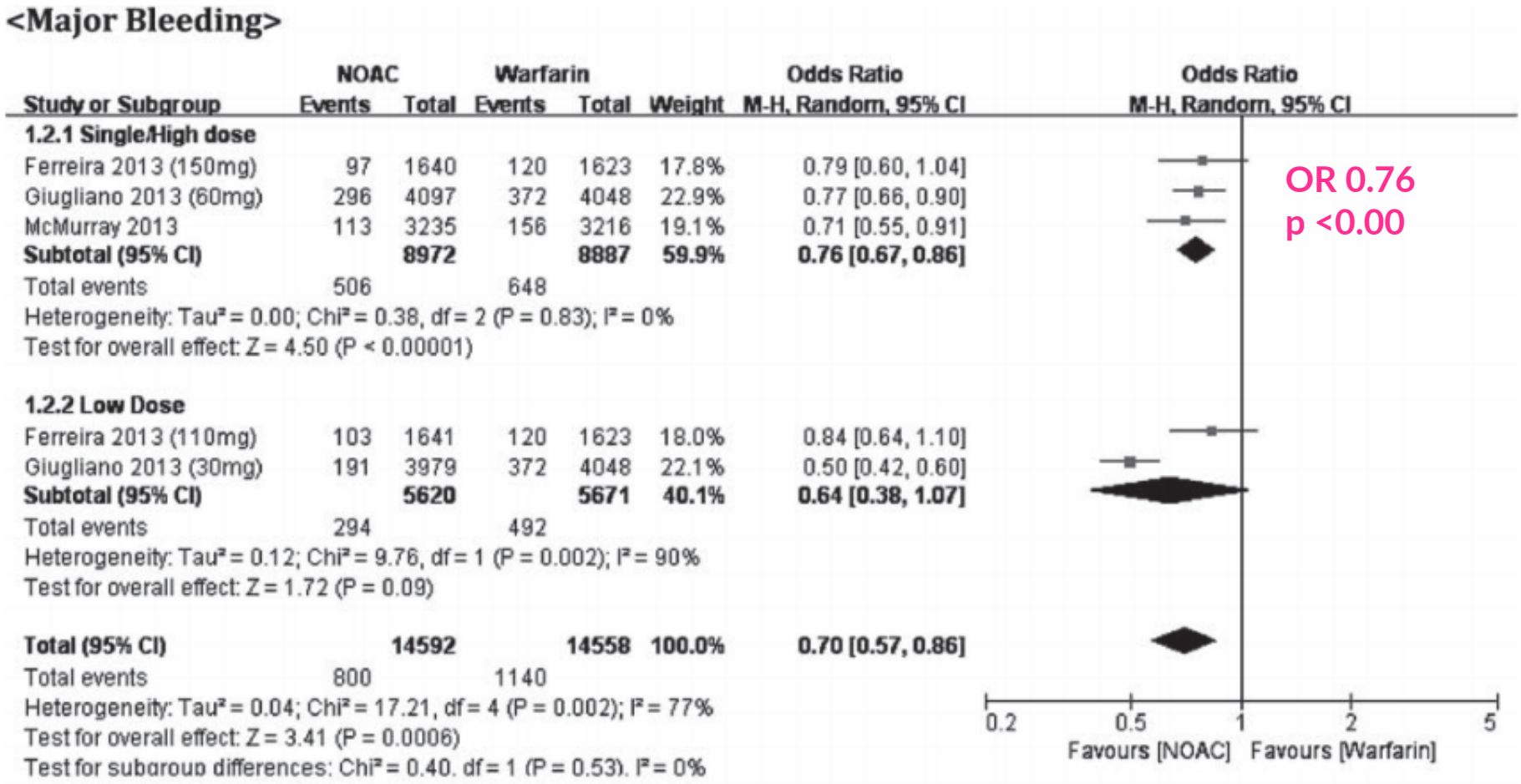
19122 NAO vs 13390 VKA



OR 0.86
p 0.02

Xiong et al, European Journal of Heart Failure 2015

AF +HF metanalysis: SAFETY



OR 0.76
p <0.00

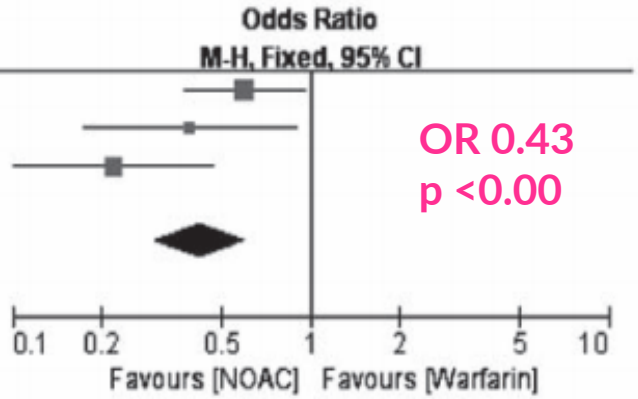
Xiong et al, European Journal of Heart Failure 2015

AF +HF metanalysis: SAFETY

<Intracranial Haemorrhage>

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Diepen 2013	28	4530	46	4503	45.0%	0.60 [0.38, 0.97]
Ferreira 2013 (150mg)	8	1640	20	1623	19.6%	0.39 [0.17, 0.89]
McMurray 2013	8	3235	36	3216	35.4%	0.22 [0.10, 0.47]
Total (95% CI)		**9405**		**9342**	**100.0%**	**0.43 [0.30, 0.61]**
Total events	44		102			

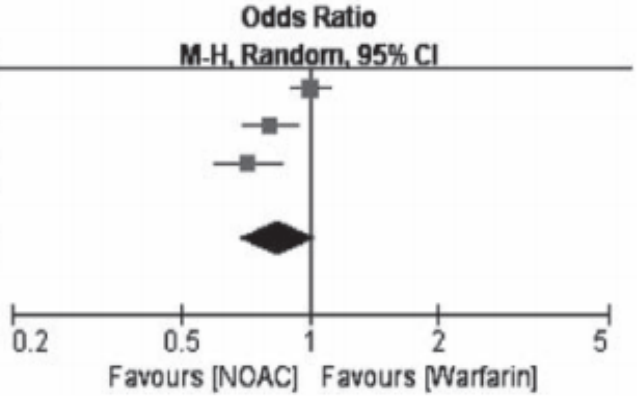
Heterogeneity: Chi² = 5.00, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 4.72 (P < 0.00001)



<All-bleeding>

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Random, 95% CI
Diepen 2013	888	4530	878	4503	36.4%	1.01 [0.91, 1.12]
Ferreira 2013 (150mg)	466	1640	536	1623	33.2%	0.80 [0.69, 0.93]
McMurray 2013	216	3235	292	3216	30.5%	0.72 [0.60, 0.86]
Total (95% CI)		**9405**		**9342**	**100.0%**	**0.84 [0.69, 1.04]**
Total events	1570		1706			

Heterogeneity: Tau² = 0.03; Chi² = 12.52, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 1.62 (P = 0.10)



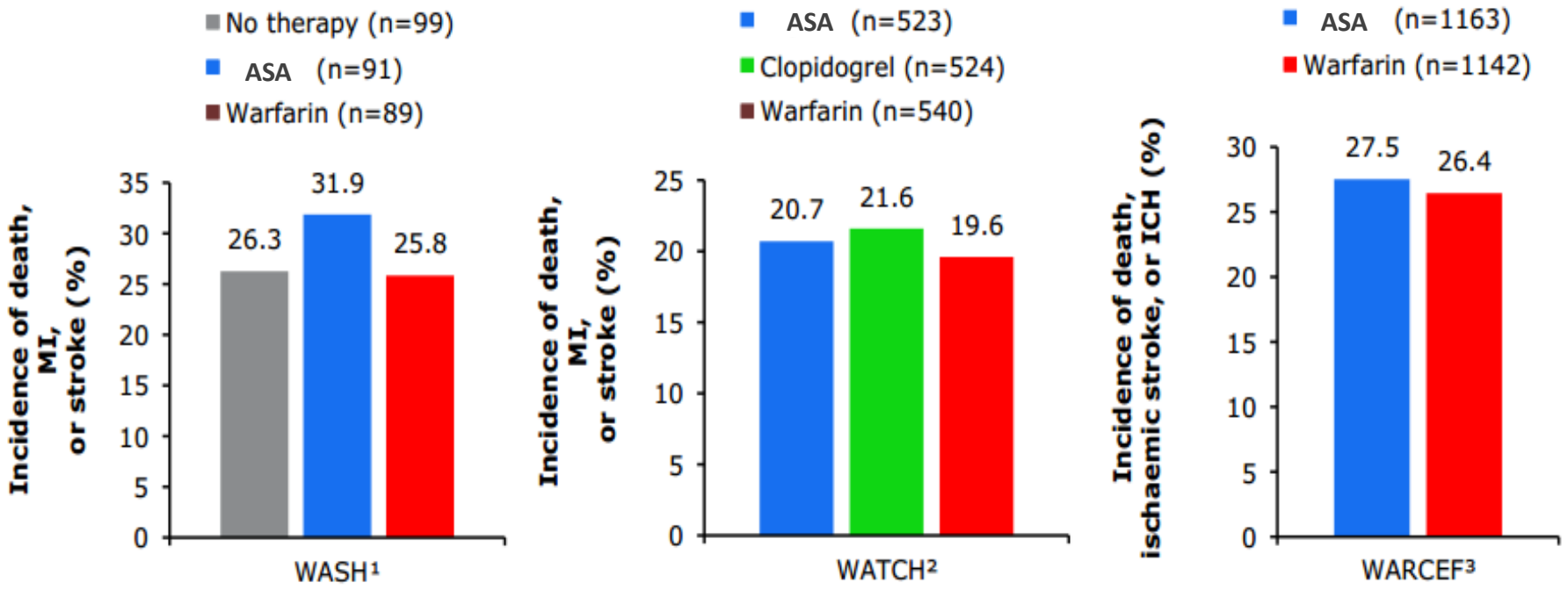
Xiong et al, European Journal of Heart Failure 2015

Heart failure and sinus rhythm?

Rationale:

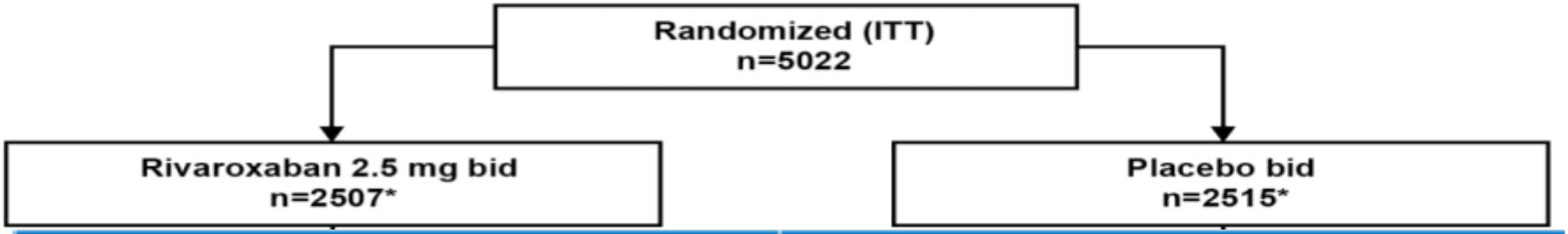
- deceleration of peripheral and intracardiac blood flow due to peripheral congestion and impaired cardiac contractility
- prolonged bed rest in severely ill cases
- endothelial dysfunction (impaired NO response)
- the presence of coagulation defects as, for example, in the case of ventricular assist devices
- **increased risk for misdiagnosed atrial fibrillation**

Warfarin has failed to demonstrate improved outcomes in pts with HF and SR



1. Cleland JGF, et al. *Am Heart J.* 2004.
2. Massie BM, et al. *Circulation.* 2009
3. Homma S *et al*, *N Engl J Med.* 2012.

COMMANDER HF



Key Inclusion Criteria

- Chronic HF (>3mths) with reduced LVEF (≤40%)
- Within 21 days after an episode of hospitalization for worsening HF
- Elevated plasma BNP (≥200 pg/mL) or NT-proBNP (≥800 pg/mL) during the index event
- CAD (Hx MI, Revasc, angiogram, ECG+Echo)
- Receiving appropriate guidelines medical treatment†
- No anticoagulation

Key Exclusion Criteria

- Bleeding risk, AF, acute MI
- Planned cardiac surgery within 28 days (eg, PCIs and EP devices)
- History of severe valvular disease, chronic episodes of ventricular tachycardia, severe peptic ulcer disease, or HIV
- eGFR <20 mL/min
- Prior stroke (within 90 days)
- Anemia (Hb<8 g/dL) or severe thrombocytopenia (platelets <50,000/µL)

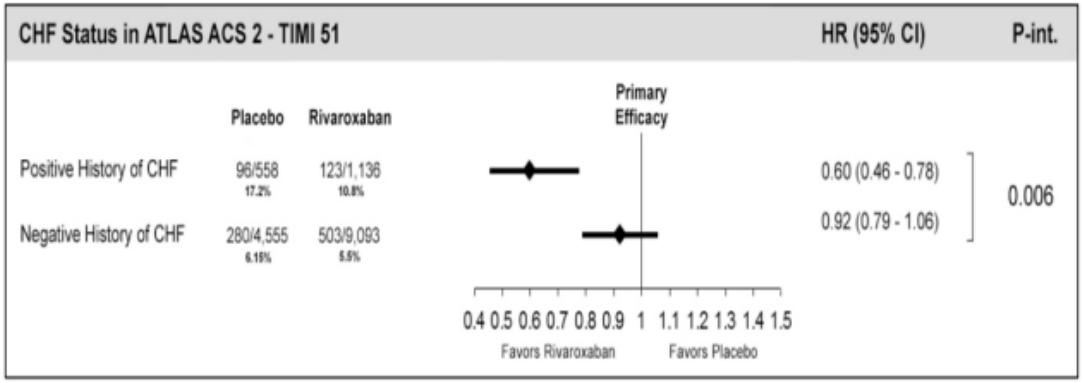
Zannad NEJM 2018

Rationale for the Commander HF design

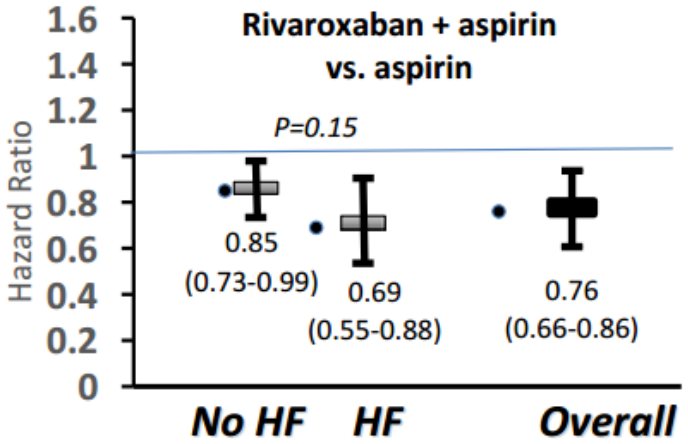
ATLAS ACS 2-TIMI 51

Figure 1.

Primary Efficacy Endpoint among Subjects with History of CHF vs. Patient Without Prior History of CHF



COMPASS

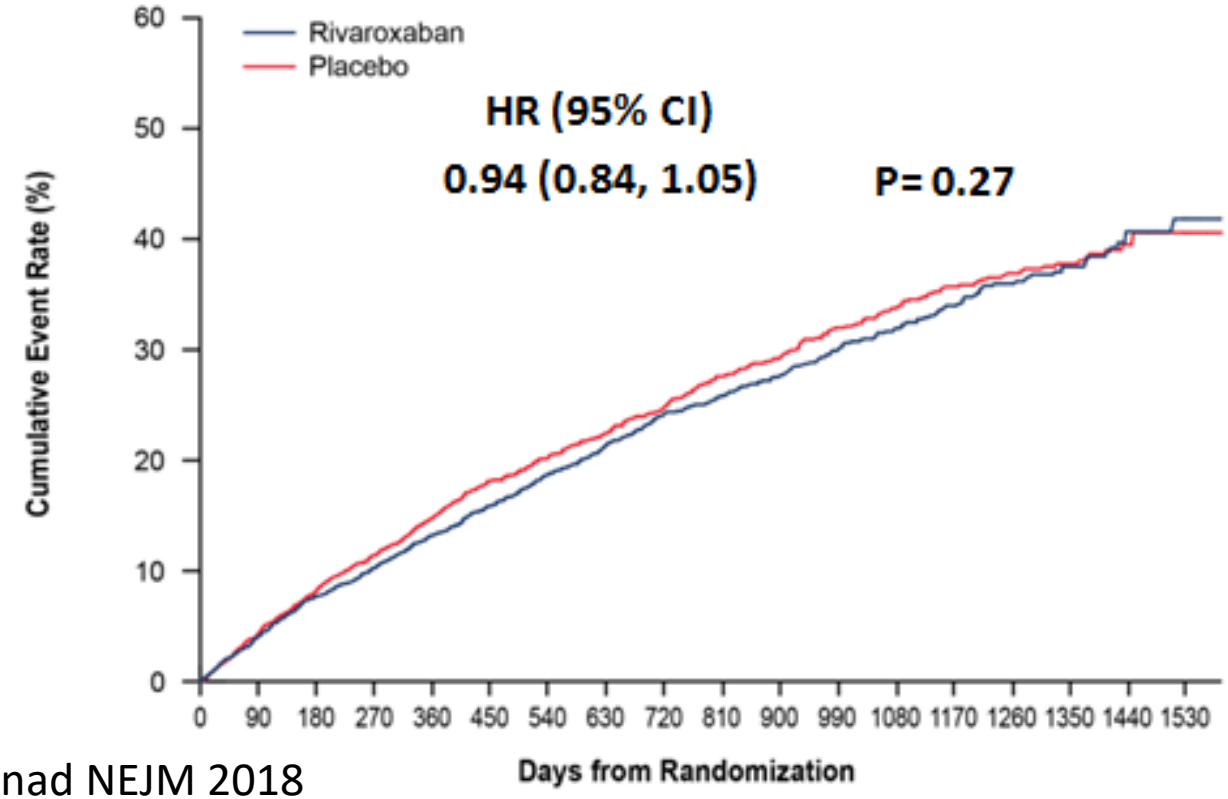


Korjian et al, AJCC2018

Branch et al, Circulation 2019

COMMANDER HF

Primary Efficacy Outcome
(ITT, All-cause mortality, MI, or stroke)



Zannad NEJM 2018

COMMANDER HF: safety outcomes

	Rivaroxaban (N=2499)		Placebo (N=2509)		Rivaroxaban vs. Placebo	P value
Outcomes	n (%)	Event Rate/ (100 pt-yr)	n (%)	Event Rate/ (100 pt-yr)	HR (95% CI)	Log-rank P value
Principal safety (composite)	18 (0.7)	0.44	23 (0.9)	0.55	0.80 (0.43, 1.49)	0.484
Fatal bleeding	9 (0.4)	0.22	9 (0.4)	0.22	1.03 (0.41, 2.59)	0.951
Bleeding in critical space with potential for permanent disability	13 (0.5)	0.32	20 (0.8)	0.48	0.67 (0.33, 1.34)	0.253
ISTH major bleeding	82 (3.3)	2.04	50 (2.0)	1.21	1.68 (1.18, 2.39)	0.003
ISTH: HGB decreases ≥2g/dL	55 (2.2)	1.37	30 (1.2)	0.73	1.87 (1.20, 2.91)	0.005
ISTH: transfusions ≥2 Units	31 (1.2)	0.77	18 (0.7)	0.43	1.74 (0.98, 3.12)	0.058
ISTH: critical bleeding sites	25 (1.0)	0.62	23 (0.9)	0.56	1.12 (0.63, 1.97)	0.699
ISTH: fatal outcome	3 (0.1)	0.07	7 (0.3)	0.17	0.45 (0.12, 1.72)	0.228
Bleeding requiring hospitalization	61 (2.4)	1.52	48 (1.9)	1.16	1.30 (0.89, 1.90)	0.170

In patients with recent worsening of chronic HF and reduced ejection fraction who also have underlying CAD and are not in AF, low-dose rivaroxaban, when added to guideline-based therapy, does not improve the composite of all-cause mortality, MI, or stroke, nor does it favorably influence HF rehospitalization

Take home messages

- Thromboembolic risk increases with the worsening of HF
- In patients with both NVAF and HF all DOACs demonstrated the same efficacy/safety profile showed in the overall populations
- To date in patients with HF without AF the anticoagulation therapy did not prove benefit in prevention of ischemic events and death

Grazie per l'attenzione