נוגדי קרישה למניעת שבץ בראיה מגדרית

ד"ר אבישג לייש-פרקש
מנהלת היחידה לאלקטרופיזיולוגיה וקוצבים
המערך הקרדיולוגי
ביה"ח הציבורי אסותא אשדוד

- ההרצאה בחסות חברת פייזר

AGENDA

- Sex disparities in OAC utilization in patients with NVAF
- Gender differences in residual stroke risk and major bleeding in NVAF patients treated with OAC
- Clinical outcomes (efficacy and safety) in NVAF patients according to sex during anticoagulation with specific NOACs

NVAF= non valvular atrial fibrillation; OAC= oral anticoagulation

Sex disparities in OAC utilization in patients with NVAF

- The prevalence and incidence of AF increase with age and are higher in men than in women of all ages, making the lifetime risk of developing AF higher in men than in women *(1-3)*
- However, women develop AF on average 5 years later and have a higher risk of stroke than men with AF *(4-5)*
- Some studies showed that the risk is higher only in women bearing higher risk ($CHADS_2 \geq 2$) *(6)*
- Also, neurological outcome after stroke in NVAF appears to be worse in women vs. men (7)

1. Friberg L, *J Intern Med* 2013;274:461–468.
2. Heeringa J, *Eur Heart J* 2006;27:949–953
3. Lloyd-Jones DM, *Circulation* 2004;110:1042–1046
4. Humphries KH, *Circulation 2001;103:2370-2365*
5. Emdin CA, *BMJ* 2016;532:h7013
6. Friberg L, BMJ 2012;344:e3522
7. Reid JM, Stroke 2008;39:1090-1095

- Previous studies have shown that OAC treatment is underused for stroke prevention in AF, particularly in women and in patients above 80 years of age *(1,2)*
- An increased use of OAC has been expected with the introduction of non–vitamin K oral anticoagulants (NOACs), with less need for monitoring and fewer drug interactions compared with warfarin

1. Humphries KH, *Circulation 2001;103:2370-2365*
2. Wilke T, *Thromb Haemost 2012;107:1053-1065*

The sex differences observed in 2011 with fewer women using OAC had disappeared in 2015, except in women >80 yo and pts with complicated co-morbidities

Proportions of patients with nonvalvular atrial fibrillation in the Stockholm region 2007 to 2011 and 2011 to 2015 dispensed thromboprophylactic treatment in 2011 and 2015, by sex and age group. No treatment refers to neither oral anticoagulants nor aspirin. Values within parentheses are 95% confidence intervals (CI)

	Oral anticoagulants 2011		Oral anticoagulants 2015	
Age (years)	Men % (95% CI)	Women % (95% CI)	Men % (95% CI)	Women % (95% CI)
0–39	16.8 (14.0–19.7)	8.4 (4.7–12.1)	22.1 (19.3–24.8)	22.5 (16.9–28.0)
40–64	43.3 (41.9–44.6)	37.2 (35.1–39.2)	54.3 (53.0–55.6)	56.6 (54.6–58.6)
65–74	61.9 (60.7–63.1)	58.1 (56.5–59.7)	78.0 (77.1–78.9)	79.4 (78.3–80.6)
75–79	65.4 (63.7–67.1)	64.1 (62.2–66.0)	81.7 (80.6–82.9)	80.7 (79.4–82.1)
80-	50.8 (49.7–51.9)	43.0 (42.1–44.0)	72.2 (71.2–73.2)	66.9 (66.0–67.8)
All	53.2 (52.6–53.9)	47.8 (47.1–48.5)	70.1 (69.6–70.7)	70.5 (69.8–71.1)
	Only aspirin 2011		Only aspirin 2015	
Age (years)	Men % (95% CI)	Women % (95% CI)	Men % (95% CI)	Women % (95% CI)
0–39	9.3 (7.1–11.6)	8.8 (5.0–12.6)	5.4 (3.9–6.9)	4.6 (1.8–7.4)
40–64	27.7 (26.5–28.9)	26.9 (25.0–28.8)	12.4 (11.6–13.3)	10.5 (9.2–11.7)
65–74	26.0 (25.0–27.1)	26.9 (25.5–28.3)	11.1 (10.5–11.8)	8.8 (8.0–9.6)
75–79	25.4 (23.9–27.0)	23.8 (22.1–25.5)	10.5 (9.6–11.4)	10.1 (9.1–11.2)
80-	37.6 (36.6–38.7)	43.0 (42.1–44.0)	17.5 (16.6–18.3)	21.0 (20.2–21.8)
All	29.7 (29.1–30.3)	35.0 (34.3–35.7)	12.9 (12.5–13.3)	15.1 (14.6–15.6)
	No treatment 2011		No treatment 2015	
Age (years)	Men % (95% CI)	Women % (95% CI)	Men % (95% CI)	Women % (95% CI)
0–39	73.9 (70.5–77.2)	82.8 (77.8–87.8)	72.5 (69.6–75.5)	72.9 (67.0–78.8)
40–64	29.1 (27.8–30.3)	36.0 (33.9–38.0)	33.3 (32.1–34.5)	33.0 (31.0–34.9)
65–74	12.1 (11.3–12.9)	15.0 (13.8–16.1)	10.9 (10.3–11.6)	11.8 (10.8–12.7)
75–79	9.2 (8.2–10.2)	12.1 (10.8–13.4)	7.7 (6.9–8.5)	9.1 (8.2–10.1)
80-	11.5 (10.8–12.3)	14.0 (13.3–14.6)	10.4 (9.7–11.1)	12.1 (11.4–12.7)
All	17.0 (16.5–17.5)	17.2 (16.6–17.7)	17.0 (16.6–17.4)	14.5 (14.0–15.0)

Loikas D, AJC 2017;120:1302-8

- Between 2011 and 2015, the number of patients with AF in Stockholm and their use of OAC treatment increased substantially
- The previous sex difference had disappeared, and more patients with complicating co-morbidities were treated in 2015
- These changes occurred following the introduction of NOACs and the replacement of CHADS2 by the CHA2DS2-VASc score.
- This is in line with results from other countries *(1-3)*
- In this study population, the largest improvements over time were observed for women
- Most, but not all, studies performed before NOACs were introduced have shown a lower OAC use in women with AF
- This study found no sex difference in the use of OAC during the latter part of the study (except in pts >80y in whom women were still less treated than men)

1. Barnes GD, *Am J Med* 2015;128:1300–1305, e1302.
2. Brown JD, *Drugs Aging* 2016;33:427–436.
3. Weitz JI, *Clin Ther* 2015;37:2506–2514, e2504.

Possible causes:

1) the additional point in CHA2DS2-VASc for female sex
2) the availability of NOACs and introduction of several NOACs
3) the overall increase of OAC use in patients with numerous co-morbidities
4) By the media focus on the new drugs and the stroke risk of AF

- Regardless of age or the presence of baseline comorbidities, women have 35% higher chances to be prescribed a lower dabigatran dose compared with men, although women have higher baseline risk for stroke (1,2)
- Reason? (Fragility??)

1) Tsadok MA, Circ Cardiovasc Qual Outcomes 2015
2) Larsen TB (Danish population) JACC 2013;61:2264-2273

Gender differences in residual stroke risk and major bleeding in NVAF patients treated with OAC

- Prevalence of AF M>F
- Risk of CVA/SE F>M in nonanticoagulated patients with AF → Female gender is an independent risk factor for CVA/SE → reflected in CHA_2DS_2-VASc
- NOAC theoretically provide a more stable anticoagulant effect → Is this pharmacokinetic advantage translates into an outcome benefit?

CVA= cerebrovascular accident; SE= systemic embolism

Meta-Analysis of Gender Differences in Residual Stroke Risk and Major Bleeding in Patients With Nonvalvular AF Treated With Oral Anticoagulants (Pancholy SB et al. AJC 2014;113:485-490)

- Aim: to analyze gender differences in the residual risk of CVA/SE and major bleeding in AF patients treated with warfarin and NOAC in a pooled sample from randomized trials reported in the published literature

Meta-Analysis of Gender Differences in Residual Stroke Risk and Major Bleeding in Patients With Nonvalvular AF Treated With Oral Anticoagulants (Pancholy SB et al. AJC 2014;113:485-490)

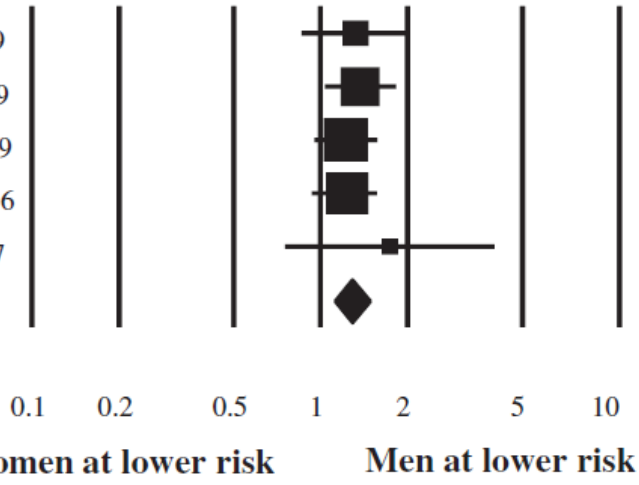
Baseline characteristics of study populations

Study	Study Design	Number of Patients	Patient Characteristic		
			Mean Age (yrs)	Men (%)	$CHADS_2$ Score (%)
BAFTA	RCT, open-label, warfarin vs aspirin	973	81.5	54.4	1–2 (72)
SPORTIF III/V	SPORTIF V, double-blind ximelegatran vs warfarin	SPORTIF III (3,410) and SPORTIF V (3,922)	71	69.2	NA
RE-LY	RCT, blinded, dabigatran vs unblinded warfarin	18,113	71	63.6	2.1 (mean)
ROCKET-AF	RCT, double-blind rivaroxaban vs warfarin	14,264	73	60.3	3.5 (mean)
ARISTOTLE	RCT, double-blind apixaban vs warfarin	18,201	70	64.7	2.1 (mean)
AVERROES	RCT, double-blind, apixiban vs aspirin	5,599	70	58.5	0–2 (72)

ARISTOTLE = Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; AVERROES = Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment: A Randomized Double-blind Trial; BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged Study; RCT = randomized controlled trial; RE-LY = Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET-AF = An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; SPORTIF = Stroke Prevention using ORal Thrombin Inhibitor in atrial Fibrillation.

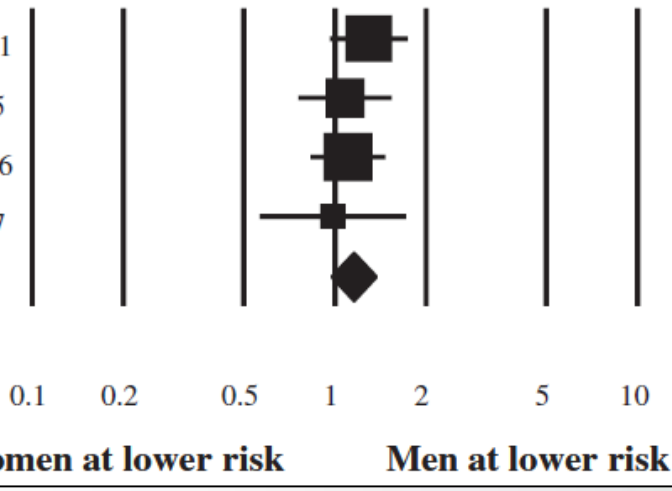
Residual risk of CVA/SE is significantly greater in women compared to men while on warfarin Tx

Study Name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Women	Men	Relative weight
SPORTIF III, V	1.326	0.864	2.035	1.293	0.196	34 / 1116	59 / 2549	10.82
RE-LY 150 mcg	1.374	1.037	1.821	2.213	0.027	90 / 2213	114 / 3809	25.03
ARISTOTLE	1.224	0.953	1.572	1.584	0.113	105 / 3182	160 / 5899	31.72
ROCKET-AF	1.210	0.934	1.567	1.440	0.150	106 / 2768	135 / 4236	29.56
BAFTA	1.738	0.756	3.994	1.302	0.193	14 / 221	10 / 267	2.87
	1.279	**1.111**	**1.473**	**3.428**	**0.001**			



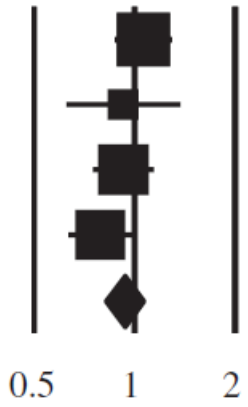
No statistically significant difference in the residual risk of CVA/SE between men and women treated with NOAC

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total: Women	Events / Total: Men	Relative weight
ROCKET-AF	1.294	0.967	1.731	1.735	0.083	86 / 2757	102 / 4201	32.93
RE-LY 150 mcg	1.081	0.760	1.535	0.432	0.666	51 / 2150	85 / 3865	22.61
ARISTOTLE	1.106	0.835	1.465	0.700	0.484	80 / 3234	132 / 5886	35.31
AVERROES	0.985	0.567	1.710	-0.055	0.956	25 / 2321	26 / 2377	9.15
	1.146	**0.970**	**1.354**	**1.601**	**0.109**			



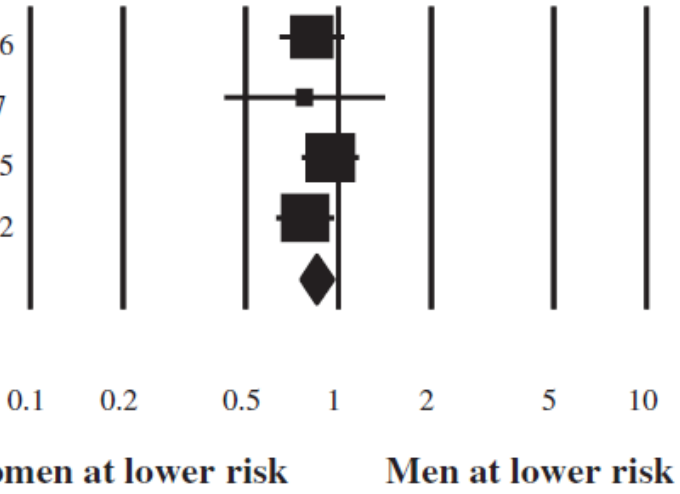
No statistically significant difference in the risk of major bleeding between men and women treated with warfarin

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Bleed / Total: Women	Bleed / Total: Men	Relative weight
ARISTOTLE	1.063	0.875	1.291	0.612	0.541	168 / 3182	294 / 5899	32.08
SPORTIF III, V	0.926	0.628	1.366	-0.386	0.699	37 / 1116	91 / 2549	10.64
RE-LY 150 mcg	0.926	0.753	1.139	-0.726	0.468	148 / 2236	273 / 3840	29.44
ROCKET-AF	0.790	0.637	0.980	-2.146	0.032	133 / 2826	253 / 4299	27.84
	0.926	**0.810**	**1.059**	**-1.123**	**0.261**			



Risk of major bleeding in women with AF treated with NOAC is significantly less compared to men

	Statistics for each study					Bleed / Total		Odds ratio and 95% CI	Relative weight
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Women	Men		
ARISTOTLE	0.819	0.646	1.040	-1.640	0.101	102 / 3234	225 / 5886		27.24
AVERROES	0.777	0.426	1.414	-0.827	0.408	19 / 2321	25 / 2377		4.30
RE-LY 150 mcg	0.942	0.763	1.163	-0.555	0.579	141 / 2150	268 / 3865		34.63
ROCKET-AF	0.780	0.630	0.966	-2.280	0.023	135 / 2819	260 / 4292		33.83
	0.844	**0.745**	**0.955**	**-2.680**	**0.007**				



1) The results of this meta-analysis indicate that women with AF have a significantly greater residual risk of CVA/SE when treated using warfarin prophylaxis compared with men

- The gender difference disappears when a similar analysis is performed on a pooled population treated with NOACs found to be superior to warfarin in published randomized trials

Possible mechanisms:

1) ORBIT-AF registry have found that despite more frequent monitoring, women treated with warfarin spend more time outside the therapeutic anticoagulation range compared with men
2) Pharmacokinetic and pharmacodynamic advantages provided by NOAC resulting in at least a more consistent anticoagulant effect, hence eliminating the outcome disadvantage imparted by subtherapeutic and supra-therapeutic anticoagulation, in a high-risk cohort such as women

ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation)

- 2) The results indicate that the NOAC agents are associated with significantly less major bleeding in the female cohort compared with male cohort

- *Possible mechanism:* unclear, although the absence of wide fluctuations in anticoagulant effect and virtual elimination of extreme spikes in anticoagulant effect might be a potential mechanism responsible for this difference

- *<u>Limitations:</u>*

1) clinical heterogeneity among different trial populations

2) fewer number of trials

3) the results should also not be extrapolated to patients with renal impairment receiving lower doses of NOAC agents as separate outcome data in that cohort were not available

- These observations suggest that women with AF, ordinarily at a greater risk of CVA/SE, continue to have an outcome disadvantage when treated with warfarin prophylaxis, with smaller “net clinical benefit” compared with men. However, if treated with NOAC agents a larger net clinical benefit is expected, in view of equivalent efficacy in preventing CVA/SE and less incidence of major bleeding.

Clinical outcomes (efficacy and safety) in NVAF patients according to sex during anticoagulation with specific NOACs

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2015) **36**, 3268–3275
doi:10.1093/eurheartj/ehv447

CLINICAL RESEARCH
Atrial fibrillation

Clinical outcomes in patients with atrial fibrillation according to sex during anticoagulation with apixaban or warfarin: a secondary analysis of a randomized controlled trial

Dragos Vinereanu[1,2]*, Susanna R. Stevens[3], John H. Alexander[3], Sana M. Al-Khatib[3], Alvaro Avezum[4], Maria Cecilia Bahit[5], Christopher B. Granger[3], Renato D. Lopes[3], Sigrun Halvorsen[6], Michael Hanna[7], Steen Husted[8], Elaine M. Hylek[9], Andrei D. Mărgulescu[1,2], Lars Wallentin[10], and Dan Atar[11]

- Previous results of the large ARISTOTLE trial suggested that efficacy and safety of apixaban when compared with warfarin was consistent in both sexes *(1)*
- According to cohort studies and registries, when compared to men, women with CV disease are *(2)* :

- older
- have more RF for stroke
- more comorbidities
- worse inflammatory and metabolic profiles
- poorer rhythm and rate control
- more severe arrhythmia events

- Thus, difference between sexes might influence the results

ARISTOTLE trial= Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

1) Granger CB, NEJM 2011;365:981-992
2) Michelena HI, Gend Med 2010;7:206-217

Objective

- To assess clinical events and the efficacy and safety of apixaban compared with warfarin according to sex in patients with NVAF enrolled in the ARISTOTLE trial (using various adjustment models).

NVAF, nonvalvular atrial fibrillation.

Vinereanu D, et al. Oral presentation at AHA; 16-20 November, 2013; Dallas, Texas.

Outcomes by Sex

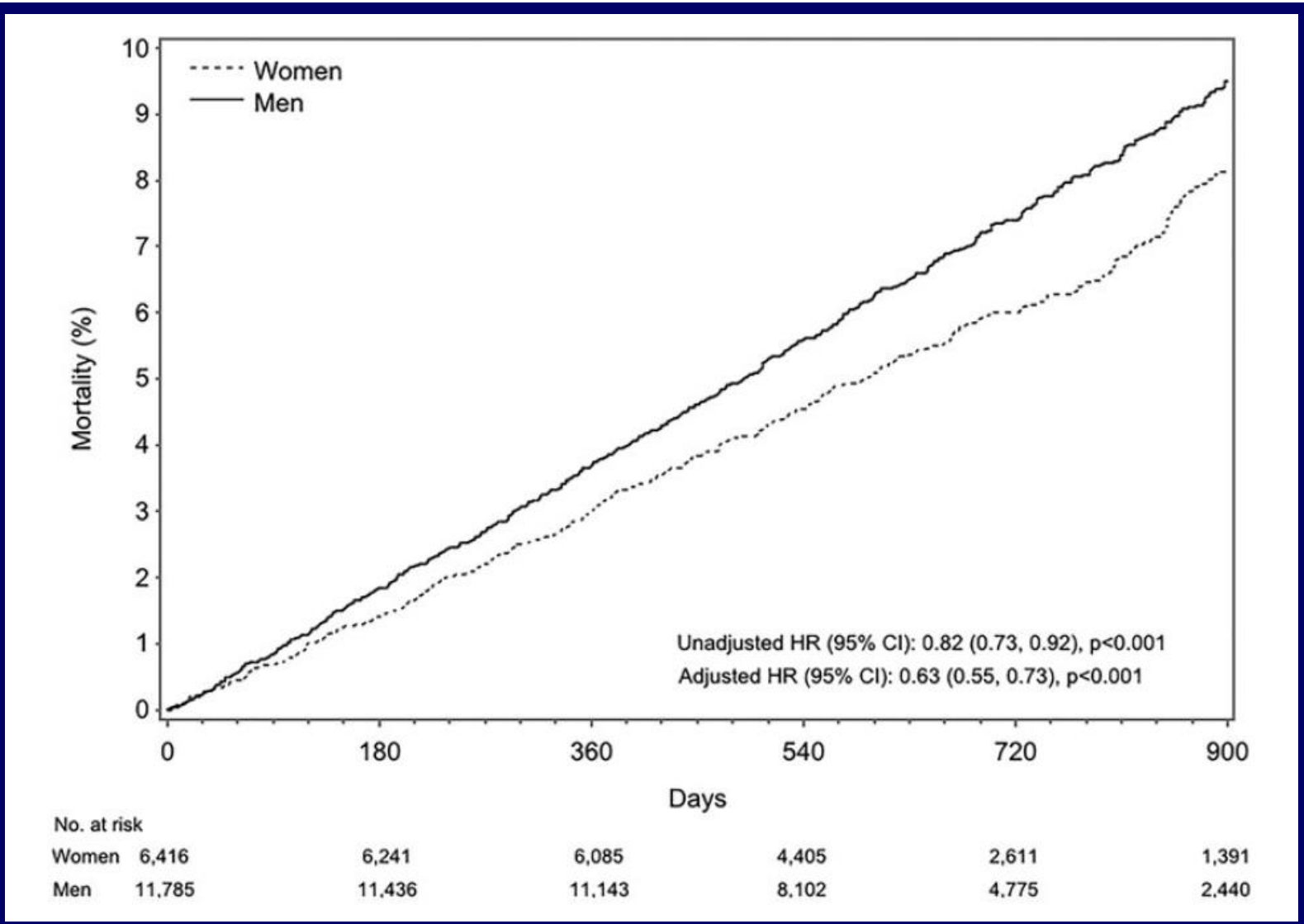
Variable	Rate, men	Rate, women	Adjusted HR (95% CI)	Adjusted *P* value
Stroke or SE	1.35	1.57	0.91 (0.74–1.12)	0.3785
All-cause death	3.98	3.26	0.63 (0.55–0.73)	<0.0001
CV death	2.09	1.58	0.62 (0.51–0.75)	<0.0001
Major bleeding	2.62	2.58	0.86 (0.74–1.01)	0.0660
Major or CRNM bleeding	5.08	4.92	0.89 (0.80–1.00)	0.0493
Study drug discontinuation	12.53	15.31	1.13 (1.05–1.22)	0.0009

- The TTR for warfarin was lower in women than in men (63.8% vs 67.2%; *P*<0.0001)

Gold boxes indicate values that are statistically significant. CI, confidence interval; CRNM, clinically relevant nonmajor; CV, cardiovascular; HR, hazard ratio; SE, systemic embolism; TTR, time in therapeutic range.

Vinereanu D, et al. Oral presentation at AHA; 16-20 November, 2013; Dallas, Texas.

K-M curves for all-cause mortality in women and men



Vinereanu D, et al. Oral presentation at AHA; 16-20 November, 2013; Dallas, Texas.

Major or CRNM Bleeding by Age and Sex

Variable	Men	Women	Adjusted HR (95% CI)	$P_{interaction}$
Major or CRNM bleeding				0.0011
<55	2.47	5.61	2.23 (1.41–3.55)	
55–64	3.21	3.18	0.98 (0.73–1.31)	
65–74	4.98	4.31	0.87 (0.72–1.04)	
75–84	7.80	6.44	0.83 (0.69–0.99)	
85+	10.48	6.63	0.64 (0.40–1.03)	

Gold boxes indicate values that are statistically significant. CI, confidence interval; CRNM, clinically relevant nonmajor; HR, hazard ratio.

Vinereanu D, et al. Oral presentation at AHA; 16-20 November, 2013; Dallas, Texas.

Outcomes by History of Prior Stroke and Sex

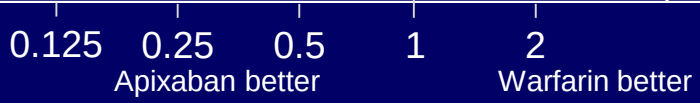
Variable	No prior stroke			Prior stroke			*P* interaction
	Men	Women	Adjusted HR (95% CI)	Men	Women	Adjusted HR (95% CI)	
Stroke or SE	0.99	1.32	1.06 (0.83–1.36)	3.02	2.61	0.70 (0.50–0.97)	0.0355
All-cause death	3.78	3.09	0.62 (0.53–0.73)	4.89	3.94	0.66 (0.51–0.86)	0.6675
CV death	2.01	1.37	0.55 (0.44–0.69)	2.46	2.41	0.85 (0.61–1.20)	0.0273
Major or CRNM bleeding	4.79	4.85	0.92 (0.81–1.05)	6.41	5.20	0.79 (0.62–1.00)	0.2452
Study discontinuation	11.91	14.99	1.16 (1.07–1.26)	15.42	16.57	1.02 (0.88–1.17)	0.0874

Gold boxes indicate values that are statistically significant. CI, confidence interval; CRNM, clinically relevant nonmajor; CV, cardiovascular; HR, hazard ratio; SE, systemic embolism.

Vinereanu D, et al. Oral presentation at AHA; 16-20 November, 2013; Dallas, Texas.

Effect of Treatment: Apixaban vs Warfarin

Endpoint	Rate (%/y) Apixaban	Rate (%/y) Warfarin	Adjusted HR (95% CI)	$P_{Interaction}$
Stroke or SE				0.45
Men	1.22	1.49	0.84 (0.66–1.05)	
Women	1.35	1.81	0.73 (0.54–0.97)	
All-cause death				0.83
Men	3.75	4.22	0.89 (0.78–1.02)	
Women	3.11	3.41	0.87 (0.71–1.06)	
CV death				0.64
Men	1.99	2.20	0.88 (0.73–1.06)	
Women	1.45	1.71	0.81 (0.61–1.08)	
Major bleeding				0.06
Men	2.26	2.98	0.76 (0.64–0.9)	
Women	1.91	3.29	0.56 (0.44–0.72)	
Major or CRNM bleeding				0.48
Men	4.17	6.00	0.69 (0.61–0.79)	
Women	3.88	6.03	0.64 (0.53–0.76)	
Intracranial bleeding				0.76
Men	0.34	0.80	0.43 (0.29–0.64)	
Women	0.33	0.81	0.38 (0.22–0.67)	



CI, confidence interval; CRNM, clinically relevant nonmajor; CV, cardiovascular; HR, hazard ratio; SE, systemic embolism.

Vinereanu D, et al. Oral presentation at AHA; 16-20 November, 2013; Dallas, Texas.

Conclusions

- In ARISTOTLE, women had lower rates of all-cause mortality, CV mortality, and bleeding than men but had similar rates of stroke or SE
  - The risk of recurrent stroke or SE was 30% lower in women than in men who had experienced a previous stroke
  - The lower rate of bleeding in women was observed mainly in women aged ≥75 years
- The efficacy and safety benefits of apixaban compared with warfarin were consistent in men and women

CV, cardiovascular; SE, systemic embolism.

Vinereanu D, et al. Oral presentation at AHA; 16-20 November, 2013; Dallas, Texas.

Clinical outcomes (efficacy and safety) in NVAF patients according to sex during anticoagulation with specific NOACs

Sex Differences in Dabigatran Use, Safety, And Effectiveness In a Population-Based Cohort of Patients With Atrial Fibrillation

Meytal Avgil Tsadok, PhD; Cynthia A. Jackevicius, PharmD, MSc; Elham Rahme, PhD; Karin H. Humphries, DSc; Louise Pilote, MD, PhD

Background—Sex differences were observed with regard to warfarin treatment in patients with atrial fibrillation, with women having a higher risk of stroke compared with men. We aimed to compare sex differences in use, safety, and effectiveness of dabigatran.

Methods and Results—We conducted a population-based cohort study of patients with atrial fibrillation using administrative data in Quebec, Canada, 1999 to 2013. Men and women who filled a prescription for dabigatran (110 and 150 mg bid) were compared with matched warfarin users with respect to their rates of stroke, bleeding, and myocardial infarction events, using propensity score analysis. The cohort comprised 31 786 women (50.4%) and 31 324 men (49.6%). Women had a higher baseline stroke risk and lower baseline bleeding risk compared with men. Women filled more prescriptions for the lower dabigatran dose compared with men (adjusted OR, 1.35; 95% confidence interval, 1.24–1.48). In multivariable analyses adjusted for propensity scores, dabigatran use was associated with a lower risk of bleeding compared with warfarin in men (*P* for interaction=0.008). Dabigatran was associated with a trend toward lower risk of stroke in women treated with the 150-mg dose (HR, 0.79; 95% confidence interval, 0.56–1.04), but was not associated with a difference in the risk of myocardial infarction compared with warfarin in either sex.

Conclusions—In real-life practice, women are more frequently treated with low-dose dabigatran, yet a trend toward lower stroke rates in women taking high-dose dabigatran was observed. Men benefit from lower bleeding rates with dabigatran compared with warfarin. **(*Circ Cardiovasc Qual Outcomes*. 2015;8:00-00. DOI: 10.1161/CIRCOUTCOMES.**

Background

- The efficacy and safety of dabigatran was investigated in the clinical trial setting in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, but the low enrollment of women (37%) precludes sex-specific conclusions *(1)*
- In a study assessing sex differences in the pharmacokinetic and pharmacodynamic profiles of the 150 mg bid dabigatran dose in 18 women and 18 men (≥65 years), the results demonstrated a trend toward increased dabigatran plasma concentrations in women compared with men *(2)*
- ***Aim: to compare sex differences in use, safety, and effectiveness of dabigatran***

1) Connolly SJ,NEJM 2009;361:1139-1151
2) Stangier J. Clin Pharmacokinet. 2008;47:47-59

Table 1. Patterns of Dabigatran and Warfarin Use and Baseline Characteristics by Sex

	Men (n=31 324)	Women (n=31 786)	*P* Value
Patients Characteristic			
AF as a main diagnosis, %	28.7	34.2	<0.001
Age, y, mean (SD)	76.3 (9.3)	80.3 (8.8)	<0.001
Age ≥65 y, %	90.0	94.7	<0.001
Age ≥75 y, %	59.1	75.4	<0.001
Rural setting, %	24.5	20.6	<0.001
Comorbidities, %			
Hypertension	72.9	79.7	<0.001
Coronary artery disease	56.0	42.5	<0.001
Congestive heart failure	35.6	34.5	0.003
Hyperlipidemia	56.9	47.2	<0.001
Diabetes mellitus	32.2	26.8	<0.001
Chronic obstructive pulmonary disease	26.5	22.4	<0.001
Valvular heart disease	25.0	31.5	<0.001
History of myocardial infarction	24.9	15.1	<0.001
Acute or chronic renal disease	29.8	27.0	<0.001
Vascular disease	17.4	12.9	<0.001
History of stroke	10.5	12.2	<0.001
Any malignancy	12.2	8.8	<0.001
History of bleeding event	12.5	8.2	<0.001
Liver disease	5.9	5.1	<0.001
CHA_2DS_2-VASc score, mean (SD)	2.6 (1.4)	3.9 (1.3)	<0.001
Low risk (0 for men and 1 for women), %	6.2	3.5	<0.001
Moderate risk (only for men), %	15.6	…	…
High risk (≥2), %	78.3	96.5	<0.001
Modified HAS-BLED score, mean (SD)	2.6 (1.1)	2.5 (1.0)	0.018
Low, moderate risk (0–2), %	50.4	52.3	<0.001
High risk (≥3), %	49.6	47.7	<0.001

- Women had a higher crude stroke incidence
- Women had lower crude bleeding incidence
- No sex differences in crude incidence stroke in both dabigatran doses
- With dabigatran 110 mg dose, women had lower crude rates of bleeding

Table 2. Crude Incidence Rates of Outcomes per 100 Person-Years, by Sex and Warfarin and Dabigatran Use*

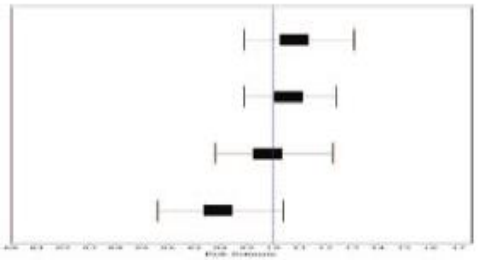
	Warfarin All			Dabigatran 110			Dabigatran 150		
	Men (n=22 978)	Women (n=24 214)	*P* Value	Men (n=4019)	Women (n=4907)	*P* Value	Men (n=4327)	Women (n=2665)	*P* Value
Stroke events	2.43 (660)	2.95 (842)	<0.001	2.83 (128)	3.05 (174)	0.556	1.74 (90)	1.76 (58)	1.000
Bleeding events	8.43 (2190)	6.56 (1826)	<0.001	7.47 (327)	6.38 (355)	0.043	4.54 (228)	4.40 (142)	0.821
MI events	1.20 (327)	1.11 (322)	0.395	1.42 (65)	1.09 (63)	0.151	1.06 (55)	0.54 (18)	0.013

MI indicates myocardial infarction

- Dabigatran was not associated with differences in the risk of stroke vs. warfarin in both sexes regardless of dabigatran dose
- There was a trend for women having a lower risk for stroke with dabigatran 150 vs. warfarin
- In men, dabigatran was associated with lower rates of bleeding, at both doses (P value for interaction between dabigatran use and sex was p=0.008) for the outcome of bleeding

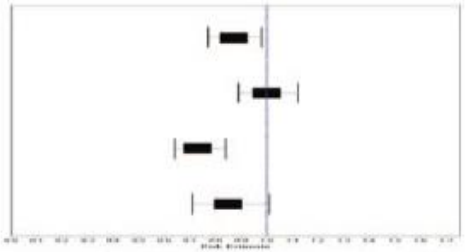
A Stroke/TIA outcome

Dabigatran Dose	Sex	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
110 mg	Men	1.15 (0.95, 1.39)	1.08 (0.89, 1.31)
	Women	1.03 (0.87, 1.21)	1.06 (0.89, 1.24)
150 mg	Men	0.72 (0.58, 0.89)	0.98 (0.78, 1.23)
	Women	0.60 (0.46, 0.78)	0.79 (0.56, 1.04)



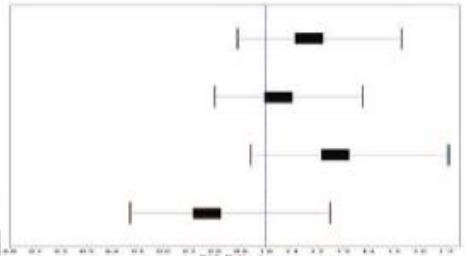
B Bleeding outcome

Dabigatran Dose	Sex	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
110 mg	Men	0.88 (0.78, 0.99)	0.87 (0.77, 0.98)
	Women	0.97 (0.86, 1.09)	1.00 (0.89, 1.12)
150 mg	Men	0.54 (0.47, 0.62)	0.73 (0.64, 0.84)
	Women	0.67 (0.57, 0.80)	0.85 (0.71, 1.01)



C Myocardial Infarction outcome

Dabigatran Dose	Sex	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
110 mg	Men	1.18 (0.91, 1.54)	1.17 (0.89, 1.53)
	Women	0.97 (0.74, 1.27)	1.05 (0.80, 1.38)
150 mg	Men	0.89 (0.67, 1.18)	1.27 (0.94, 1.71)
	Women	0.49 (0.30, 0.78)	0.77 (0.47, 1.25)



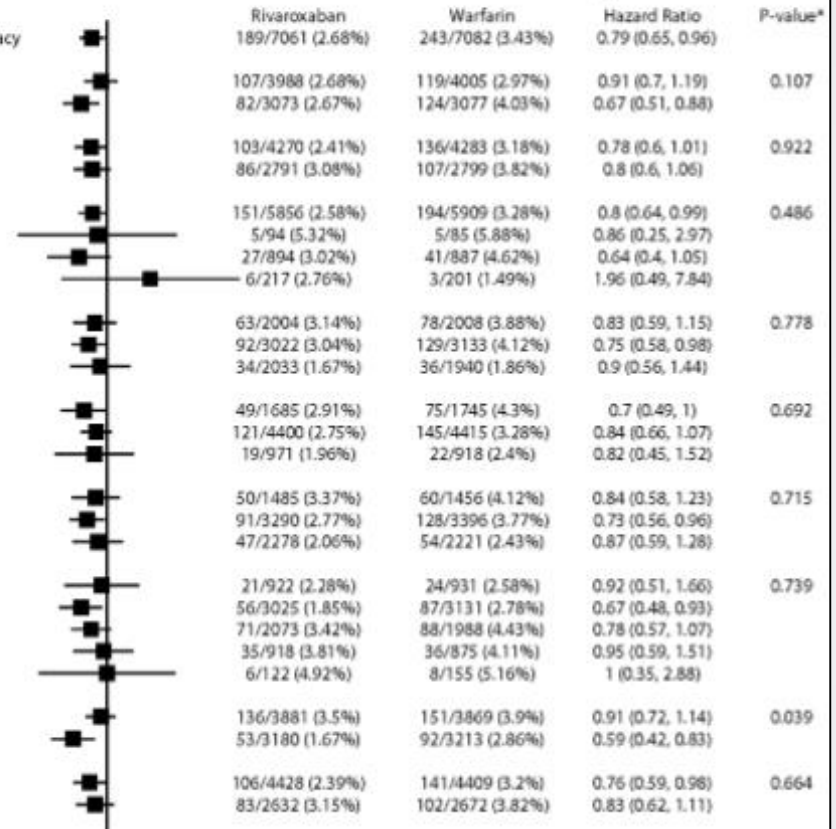
Conclusion:

- In everyday practice, women with AF are mainly treated with dabigatran 110mgX2; However they tend to gain more stroke protection with the higher dabigatran dose
- Men using dabigatran benefit from lower bleeding rates compared with warfarin

Clinical outcomes (efficacy and safety) in NVAF patients according to sex during anticoagulation with specific NOACs

The effect of rivaroxaban, as compared with warfarin, in both efficacy and safety analyses was consistent across all pre-specified groups in the ROCKET-AF study

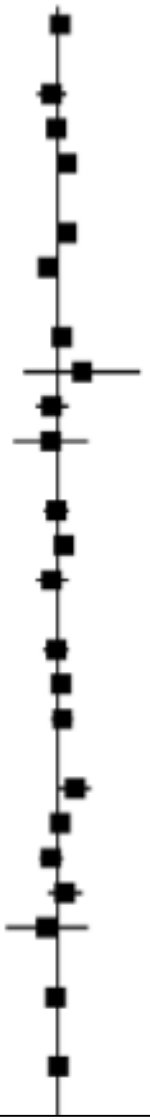
Online Figure 4
Safety on Treatment



		Rivaroxaban	Warfarin	Hazard Ratio	P-value*
Overall Efficacy		189/7061 (2.68%)	243/7082 (3.43%)	0.79 (0.65, 0.96)	
Age	<75	107/3988 (2.68%)	119/4005 (2.97%)	0.91 (0.7, 1.19)	0.107
	≥75	82/3073 (2.67%)	124/3077 (4.03%)	0.67 (0.51, 0.88)	
Sex	Male	103/4270 (2.41%)	136/4283 (3.18%)	0.78 (0.6, 1.01)	0.922
	Female	86/2791 (3.08%)	107/2799 (3.82%)	0.8 (0.6, 1.06)	
Race	White	151/5856 (2.58%)	194/5909 (3.28%)	0.8 (0.64, 0.99)	0.486
	Black	5/94 (5.32%)	5/85 (5.88%)	0.86 (0.25, 2.97)	
	Asian	27/894 (3.02%)	41/887 (4.62%)	0.64 (0.4, 1.05)	
	Other	6/217 (2.76%)	3/201 (1.49%)	1.96 (0.49, 7.84)	
Weight (kg)	≤70	63/2004 (3.14%)	78/2008 (3.88%)	0.83 (0.59, 1.15)	0.778
	70–≤90	92/3022 (3.04%)	129/3133 (4.12%)	0.75 (0.58, 0.98)	
	>90	34/2033 (1.67%)	36/1940 (1.86%)	0.9 (0.56, 1.44)	
BMI (kg/m²)	≤25	49/1685 (2.91%)	75/1745 (4.3%)	0.7 (0.49, 1)	0.692
	25–≤35	121/4400 (2.75%)	145/4415 (3.28%)	0.84 (0.66, 1.07)	
	>35	19/971 (1.96%)	22/918 (2.4%)	0.82 (0.45, 1.52)	
CrCl (mL/min)	<50	50/1485 (3.37%)	60/1456 (4.12%)	0.84 (0.58, 1.23)	0.715
	50–80	91/3290 (2.77%)	128/3396 (3.77%)	0.73 (0.56, 0.96)	
	>80	47/2278 (2.06%)	54/2221 (2.43%)	0.87 (0.59, 1.28)	
CHADS2	2	21/922 (2.28%)	24/931 (2.58%)	0.92 (0.51, 1.66)	0.739
	3	56/3025 (1.85%)	87/3131 (2.78%)	0.67 (0.48, 0.93)	
	4	71/2073 (3.42%)	88/1988 (4.43%)	0.78 (0.57, 1.07)	
	5	35/918 (3.81%)	36/875 (4.11%)	0.95 (0.59, 1.51)	
	6	6/122 (4.92%)	8/155 (5.16%)	1 (0.35, 2.88)	
Prior Stroke/TIA/ Non-CNS Systemic Embolism	Yes	136/3881 (3.5%)	151/3869 (3.9%)	0.91 (0.72, 1.14)	0.039
	No	53/3180 (1.67%)	92/3213 (2.86%)	0.59 (0.42, 0.83)	
Congestive Heart Failure	Yes	106/4428 (2.39%)	141/4409 (3.2%)	0.76 (0.59, 0.98)	0.664
	No	83/2632 (3.15%)	102/2672 (3.82%)	0.83 (0.62, 1.11)	

Patel M, 2011- Supplementary appendix to ROCKET-AF. NEJM 365 (10)

Online Figure 5



Major and Non-Major Clinically Relevant Bleeding While on Treatment		Rivaroxaban	Warfarin	HR (95% CI)	P-value*
Overall		1475 (20.74)	1449 (20.34)	1.03 (0.96, 1.11)	
Age	<65	241 (14.64)	260 (15.83)	0.93 (0.78, 1.11)	0.118
	65 to 75	541 (19.48)	556 (19.99)	0.98 (0.87, 1.10)	
	>75	693 (25.78)	633 (23.43)	1.12 (1.00, 1.25)	
Sex	Male	970 (22.60)	898 (20.89)	1.12 (1.02, 1.22)	0.004
	Female	505 (17.91)	551 (19.50)	0.89 (0.79, 1.01)	
Race	White	1210 (20.49)	1178 (19.79)	1.05 (0.97, 1.13)	0.591
	Black	19 (20.21)	13 (15.29)	1.35 (0.66, 2.75)	
	Asian	210 (23.49)	220 (24.80)	0.93 (0.77, 1.13)	
	Other	36 (16.59)	38 (18.91)	0.92 (0.58, 1.44)	
BMI (kg/m^2)	≤25	349 (20.54)	374 (21.26)	0.98 (0.85, 1.14)	0.310
	25 to ≤35	921 (20.78)	865 (19.47)	1.08 (0.98, 1.18)	
	>35	205 (21.03)	209 (22.72)	0.93 (0.77, 1.13)	
CrCl (mL/min)	<50	336 (22.37)	342 (23.17)	0.98 (0.84, 1.14)	0.735
	50 to 80	725 (21.88)	719 (21.09)	1.04 (0.93, 1.15)	
	>80	412 (18.01)	388 (17.40)	1.06 (0.92, 1.21)	
CHADS2	2	241 (26.11)	208 (22.32)	1.24 (1.03, 1.50)	0.121
	3	632 (20.74)	636 (20.15)	1.03 (0.92, 1.15)	
	4	389 (18.64)	402 (20.12)	0.92 (0.80, 1.06)	
	5	187 (20.11)	165 (18.77)	1.09 (0.89, 1.35)	
	6	26 (21.14)	38 (24.05)	0.87 (0.53, 1.44)	
Prior Stroke/TIA/Non-CNS Systemic Embolism		723 (18.51)	739 (19.00)	0.97 (0.88, 1.08)	0.118
Congestive Heart Failure		864 (19.39)	859 (19.36)	1.01 (0.92, 1.11)	0.587

15

Patel M, 2011- Supplementary appendix to ROCKET-AF. NEJM 365 (10)

J Am Coll Cardiol. 2014 March 11; 63(9): 891–900. doi:10.1016/j.jacc.2013.11.013.

Factors Associated With Major Bleeding Events:

Insights From the ROCKET AF Trial (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)

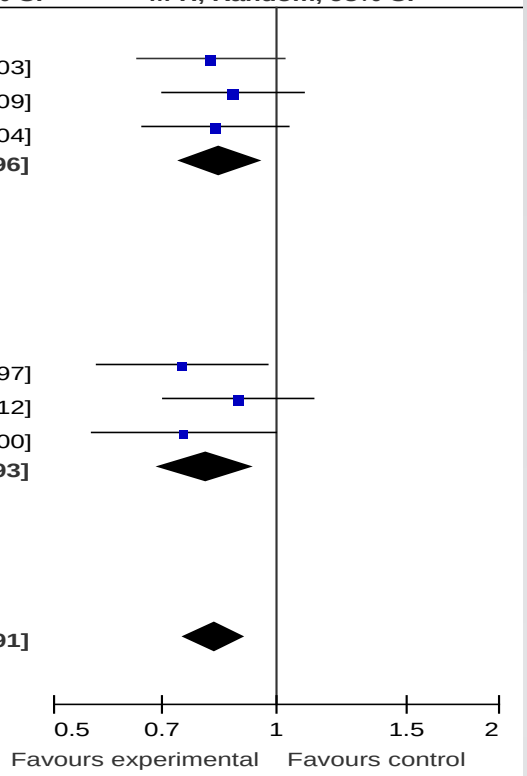
Multivariable Model Predicting Major Bleeding in the ROCKET AF Cohort

Independent Predictor	HR	95% CIs	Chi-Square	p Value
Age (per 5-yr increase)	1.17	1.12–1.23	53.0	<0.0001
Sex (female vs. male)	0.82	0.70–0.95	6.7	0.009
DBP <90 mm Hg (per 5-mm Hg increase)	0.92	0.89–0.96	17.7	<0.0001
DBP ≥90 mm Hg (per 5-mm Hg increase)	1.28	1.11–1.47	12.0	0.0005
History of COPD	1.29	1.05–1.58	5.8	0.016
History of GI bleeding	1.88	1.44–2.45	21.9	<0.0001
Prior use of aspirin	1.42	1.23–1.64	22.8	<0.0001
Anemia at baseline	1.88	1.59–2.22	53.8	<0.0001

- The principal safety endpoint was similar in the rivaroxaban and warfarin groups (14.9 vs. 14.5 events/100 patient-years; hazard ratio: 1.03; 95% confidence interval: 0.96 to 1.11)
- A multivariable model examining factors associated with major bleeding derived from the ROCKET AF cohort showed that female sex and DBP <90 mm Hg were associated with a decreased risk for major bleeding

Subgroup analyses for all strokes and systemic embolic events

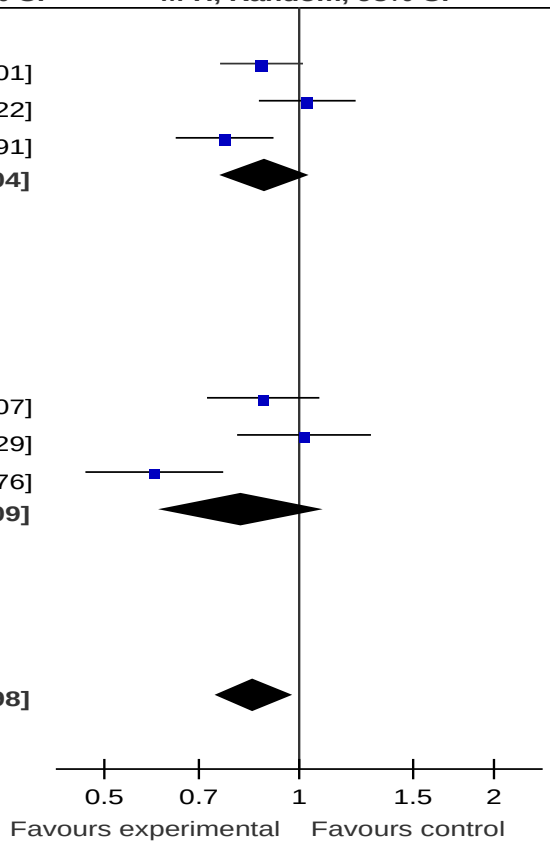
Study or Subgroup	NEW ANTICOAGULANT Events	Total	WARFARIN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.3.1 MALE						
01. RE-LY	188	7705	114	3809	18.4%	0.82 [0.65, 1.03]
02. ROCKET-AF	143	4279	164	4287	19.9%	0.87 [0.70, 1.09]
03. ARISTOTLE	132	5886	160	5899	18.6%	0.83 [0.66, 1.04]
Subtotal (95% CI)		**17870**		**13995**	**56.9%**	**0.84 [0.74, 0.96]**
Total events	463		438			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.64 (P = 0.008)						
8.3.2 FEMALE						
01. RE-LY	130	4385	88	2213	13.7%	0.75 [0.57, 0.97]
02. ROCKET-AF	126	2802	142	2803	17.6%	0.89 [0.70, 1.12]
03. ARISTOTLE	80	3234	105	3182	11.8%	0.75 [0.56, 1.00]
Subtotal (95% CI)		**10421**		**8198**	**43.1%**	**0.80 [0.69, 0.93]**
Total events	336		335			
Heterogeneity: Tau² = 0.00; Chi² = 1.22, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 2.89 (P = 0.004)						
Total (95% CI)		**28291**		**22193**	**100.0%**	**0.82 [0.75, 0.91]**
Total events	799		773			
Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 3.89 (P = 0.0001)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%						



Gómez-Outes et al., Thrombosis 2013. Supplementary materials

Subgroup analyses for major bleeding

Study or Subgroup	NEW ANTICOAGULANT Events	Total	WARFARIN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.5.1 MALE						
01. RE-LY	483	7705	273	3809	19.3%	0.87 [0.76, 1.01]
02. ROCKET-AF	260	4292	253	4299	17.9%	1.03 [0.87, 1.22]
03. ARISTOTLE	225	5886	294	5899	17.8%	0.77 [0.65, 0.91]
Subtotal (95% CI)		**17883**		**14007**	**55.0%**	**0.88 [0.75, 1.04]**
Total events	968		820			
Heterogeneity: Tau² = 0.01; Chi² = 5.87, df = 2 (P = 0.05); I² = 66%						
Test for overall effect: Z = 1.53 (P = 0.13)						
8.5.2 FEMALE						
01. RE-LY	258	4385	148	2213	16.4%	0.88 [0.72, 1.07]
02. ROCKET-AF	135	2819	133	2826	14.5%	1.02 [0.81, 1.29]
03. ARISTOTLE	102	3234	168	3182	14.1%	0.60 [0.47, 0.76]
Subtotal (95% CI)		**10438**		**8221**	**45.0%**	**0.81 [0.61, 1.09]**
Total events	495		449			
Heterogeneity: Tau² = 0.05; Chi² = 10.40, df = 2 (P = 0.006); I² = 81%						
Test for overall effect: Z = 1.37 (P = 0.17)						
Total (95% CI)		**28321**		**22228**	**100.0%**	**0.85 [0.74, 0.98]**
Total events	1463		1269			
Heterogeneity: Tau² = 0.02; Chi² = 17.02, df = 5 (P = 0.004); I² = 71%						
Test for overall effect: Z = 2.22 (P = 0.03)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						



Gómez-Outes et al., Thrombosis 2013. Supplementary materials

SUMMARY

- ***Sex disparities in OAC utilization in patients with NVAF:***

- Lifetime risk of AF M>F and earlier
- Risk of stroke F>M and worse outcome
- Previous sex differences in OAC use had disappeared since the introduction of NOACS (except >80y)

- ***Gender differences in residual stroke risk and major bleeding in NVAF patients treated with OAC:***

- Residual risk of CVA/SE on warfarin F>M but no difference on NOACs
- F=M in risk of major bleeding on warfarin but F<M on NOACs
- Thus, women with AF and warfarin have smaller net clinical benefit vs. men; However if treated with NOACS they have larger net clinical benefit vs. men

- ***Clinical outcomes (efficacy and safety) in NVAF patients according to sex during anticoagulation with specific NOACs***
- **APIXABAN**: women vs. men had:
- lower rates of all-cause mortality, CV mortality, and bleeding
- similar rates of stroke/SE;
- 30% lower risk of recurrent stroke/SE after a previous stroke
- lower rate of bleeding if ≥75 years of age
- **DABIGATRAN:** No differences in the risk of stroke vs. warfarin in both sexes regardless of dabigatran dose; in men- lower bleeding rates vs. warfarin
- In everyday practice, women with AF are mainly treated with dabigatran 110mgX2; However they tend to gain more stroke protection with the higher dabigatran dose
- **RIVAROXABAN:** The principal safety endpoint was similar in all subgroups
- A multivariable model showed that female sex was associated with a decreased risk for major bleeding

תודה!

בית החולים האוניברסיטאי
אסותא אשדוד
קהילה שיש לה בית חולים

מקבוצת מכבי

avishagl@assuta.co.il