הצגת מקרה
High Risk Patient with AF

פרופ מיכאל גליקסון

מרכז דוידאי להפרעות קצב

מרכז הלב ע"ש לבייב

מרכז רפואי שיבא

תל השומר

אפריל 2013

סיפור המקרה

- בת 76 , ברקע יתר לחץ דם ומחלת כלי דם פריפרית המתבטאת בצליעה לסירוגין אחרי 60 מ
- לפני חמש שנים אירוע מוחי שממנו השתקמה לא חיפשו אז AF
- טיפול קבוע בחוסמי בטא , חוסמי ACE
- במדידות לחץ דם שגרתיות לאחרונה שמה לב לאי סדירות הדופק מזה מספר שבועות ככל הנראה
- בבדיקת רופא מטפל היום נמצאה בפרפור פרוזדורים לא מהיר

בדיקות עזר

- אקו (TTE) תקין למעט LVH קל ועליה שמאלית בשטח 28 סמ"ר
- הולטר פרפור בטווח שבין 40 ל 130 ממוצע 64 **הפסקות ליליות עד 3.5 שניות**
- ס"ד , תפקודי בלוטת התריס תקינים
- קראטינין 1.4 EGFR = 45

In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I	B

Recommendations for rate and rhythm control of AF

Recommendations	Class[a]	Level[b]	Ref.[c]
Rate control should be the initial approach in elderly patients with AF and minor symptoms (EHRA score 1).	I	A	86–87, 90

The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B

הערכות סיכונים

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	**Patients (n=7329)**	**Adjusted stroke rate (%/year)[b]**
7	294	9.6%

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

'Hypertension' is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. INR = international normalized ratio. Adapted from Pisters *et al.*[60]

VKA vs NOACS

Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

- Independent of renal function
- Possible to monitor
- Better control when bleeding

- Safer D110, A
- No need for blood testing D,A,R
- No food interactions D,A,R

*** D=Dabigatran; R = Rivaroxaban ; A = Apixaban**

Efficacy and Safety of the Novel Oral Anticoagulants in Atrial Fibrillation

A Systematic Review and Meta-Analysis of the Literature

Francesco Dentali, MD; Nicoletta Riva, MD; Mark Crowther, MD; Alexander G.G. Turpie, MD; Gregory Y.H. Lip, MD; Walter Ageno, MD

- 12 NOAC RCTs were meta analyzed
- Total n = 54875
- NOACS (as compared to Warfarin) significantly reduced :
  - Total mortality
  - CV mortality
  - CVA/systemic embolism
  - Trend toward reduced major bleeding

Circulation 2012

הוראות סל הבריאות בארץ

3. מניעת שבץ ותסחיף סיסטמי בחולים עם פרפור עליות המטופלים ב-warfarin וחוו CVA או TIA עם ביטוי קליני (שטופל או אובחן בבית חולים) במהלך השנה האחרונה (התוויה כלולה בסל);
4. מניעת שבץ ותסחיף סיסטמי בחולים עם פרפור עליות המטופלים ב-Warfarin ושתועד אצלם INR גבוה מ-5 לפחות פעמיים במהלך השנה האחרונה באירועים נפרדים. (התוויה כלולה בסל);
5. מניעת שבץ ותסחיף סיסטמי בחולים עם פרפור עליות ללא מחלה מסתמית ו-CHADS2 score בערך 4 ומעלה (התוויה חדשה).

Selection Among NOACS
- General Considerations -

- Efficacy : Dabigatran 150 bid and Apixaban more effective than Warfarin
- Safety : Apixaban and Dabigatran 110 bid safer than Warfarin
- Can this be translated to comparison between NOACs? (different study populations)

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EXPEDITED PUBLICATION

Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

Table 4 Indirect Comparison Using Warfarin as Single Common Comparator, on the Basis of the RE-LY, ROCKET-AF, and ARISTOTLE Trials

	Apixaban ← → Dabigatran 110		Apixaban ← → Dabigatran 150		Apixaban ← → Rivaroxaban		Dabigatran 110 ← → Rivaroxaban		Dabigatran 150 ← → Rivaroxaban	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Efficacy endpoints										
Stroke or systemic embolism	0.88	(0.67–1.15)	1.22	(0.91–1.62)	0.90	(0.71–1.13)	1.02	(0.79–1.32)	**0.74**	**(0.56–0.97)**
Stroke	0.86	(0.65–1.14)	1.23	(0.92–1.66)	0.93	(0.71–1.22)	1.08	(0.81–1.44)	0.75	(0.56–1.02)
Ischemic or uncertain type of stroke	0.83	(0.61–1.13)	1.21	(0.88–1.67)	0.98	(0.72–1.33)	1.18	(0.86–1.62)	0.81	(0.58–1.13)
Hemorrhagic stroke	1.65	(0.81–3.34)	1.96	(0.94–4.08)	0.86	(0.48–1.57)	0.53	(0.25–1.12)	**0.44**	**(0.20–0.96)**
Systemic embolism	NA		NA		**3.78**	**(1.16–12.31)**	NA		NA	
Nondisabling stroke	NA		NA		NA		0.83	(0.53–1.32)	**0.60**	**(0.37–0.97)**
Mortality endpoints										
Death from any cause	0.98	(0.83–1.16)	1.01	(0.85–1.20)	1.05	(0.84–1.30)	1.07	(0.85–1.34)	1.04	(0.82–1.30)
Death from vascular causes	NA		NA		NA		1.01	(0.78–1.31)	0.96	(0.74–1.24)
Other endpoints										
Myocardial infarction	0.68	(0.45–1.03)	0.69	(0.46–1.05)	1.09	(0.74–1.60)	**1.59**	**(1.07–2.37)**	**1.57**	**(1.05–2.33)**
Pulmonary embolism	0.62	(0.17–2.20)	0.48	(0.14–1.68)	NA		NA		NA	
Bleeding endpoints										
Major bleeding	0.86	(0.7–1.06)	**0.74**	**(0.61–0.91)**	**0.66**	**(0.54–0.81)**	**0.77**	**(0.63–0.94)**	0.89	(0.73–1.09)
Major or clinically relevant nonmajor bleeding	NA		NA		**0.66**	**(0.58–0.75)**	NA		NA	
Life-threatening bleeding	NA		NA		NA		1.36	(0.82–2.27)	1.62	(0.97–2.70)
Intracranial bleeding	1.35	(0.79–2.32)	1.05	(0.63–1.76)	0.63	(0.39–1.01)	**0.46**	**(0.27–0.80)**	0.60	(0.35–1.01)
Gastrointestinal bleeding	0.81	(0.57–1.15)	**0.59**	**(0.42–0.83)**	NA		NA		NA	
Extracranial or unclassified bleeding	0.84	(0.67–1.05)	**0.74**	**(0.59–0.92)**	NA		NA		NA	

See Online Table 1 for availability and endpoint definition in original study. How to read: Drug A ←→ Drug B, HR <1.00 means hazard risk of Drug A is smaller than hazard risk of Drug B, indirectly compared via 1 common comparator, warfarin (A ←→ warfarin ←→ B). Comparisons with HR = 1.00 outside 95% confidence interval are in boldface.
NA = not available; other abbreviations as in Table 2.

A clinical decision aid for the selection of antithrombotic therapy for the prevention of stroke due to atrial fibrillation

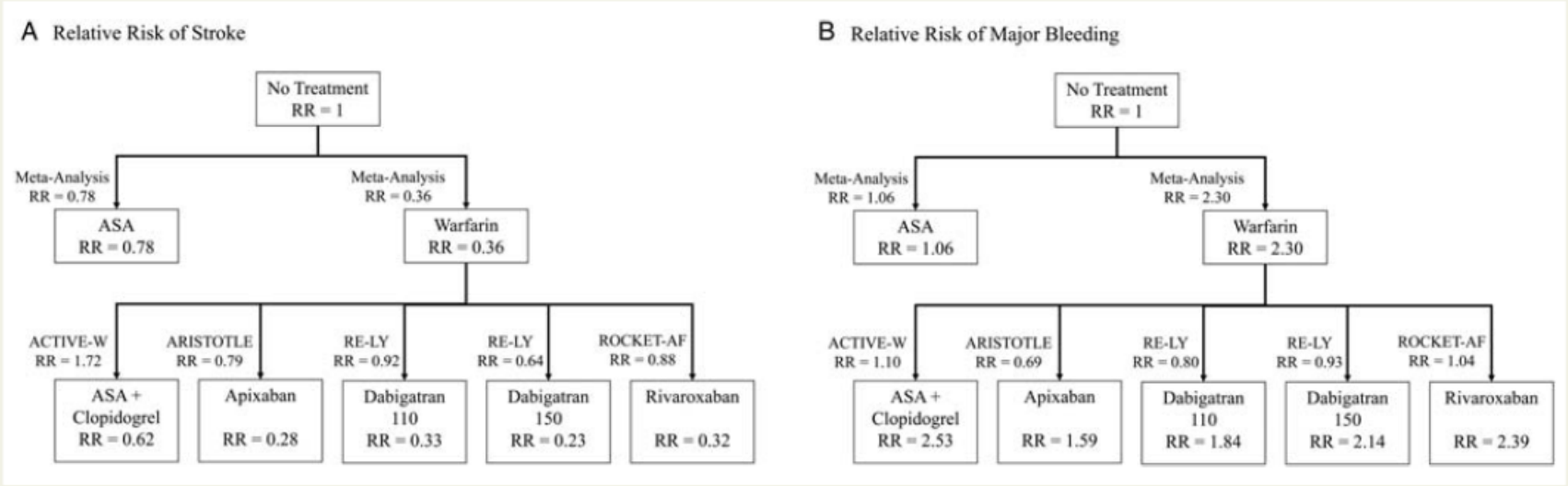


Figure 2 Derivation of relative risks of stroke and major bleeding relative to no treatment. (*A*) Derivation of the risk of stroke relative to no treatment. (*B*) Derivation of the risk of bleeding relative to no treatment. The values next to the arrows are the relative risk values reported in the relevant study. The relative risk values inside each child box are the product of the parent box and the study relative risk. The relative risk values inside each therapy box are utilized by the decision aid to calculate patients' risks of stroke and bleeding with treatment.

LaHaye EHJ 2012

בחירה בין NOACS - המשך

HAS-BLED Score	CHA$_2$DS$_2$VASc Score 0	1	2	3	4	5	6	7	8	9
7		No Treatment	ASA	ASA	ASA	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban
6	No Treatment	No Treatment	ASA	ASA	ASA	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban
5	No Treatment	No Treatment	ASA	ASA	ASA	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban
4	No Treatment	No Treatment	ASA	ASA	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban
3	No Treatment	No Treatment	ASA	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban
2	No Treatment	No Treatment	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban
1	No Treatment	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Apixaban	Dabigatran 150	
0	No Treatment	Apixaban	Apixaban	Apixaban	Dabigatran 150	Dabigatran 150	Dabigatran 150			

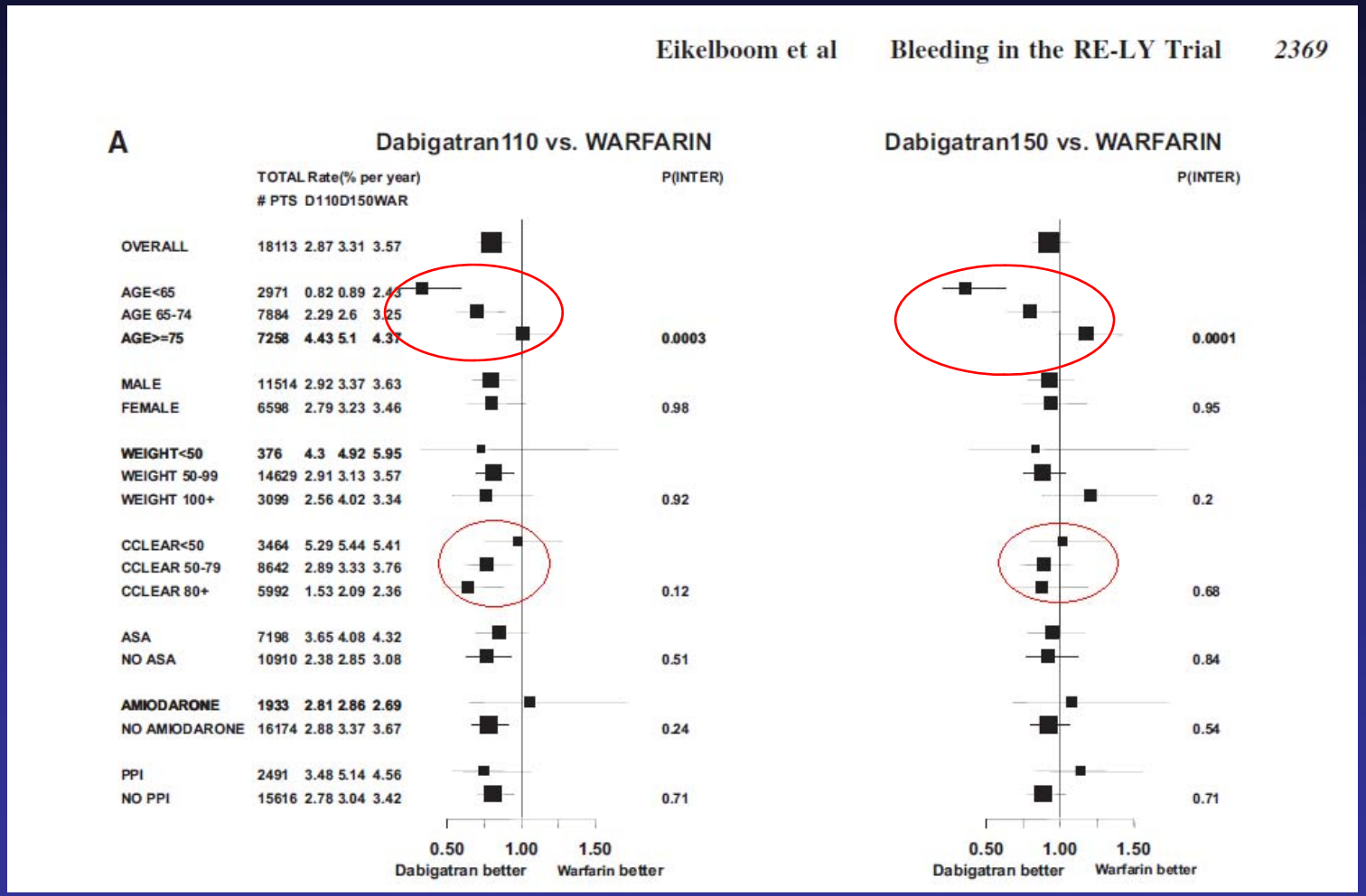
Calculated net risk (= risk for stroke + embolism + severe bleeding) for each therapy .

Assumptions: bleeding ratio = 2, treatment threshold = 0.5 % (NNT = 200) , no funding issues

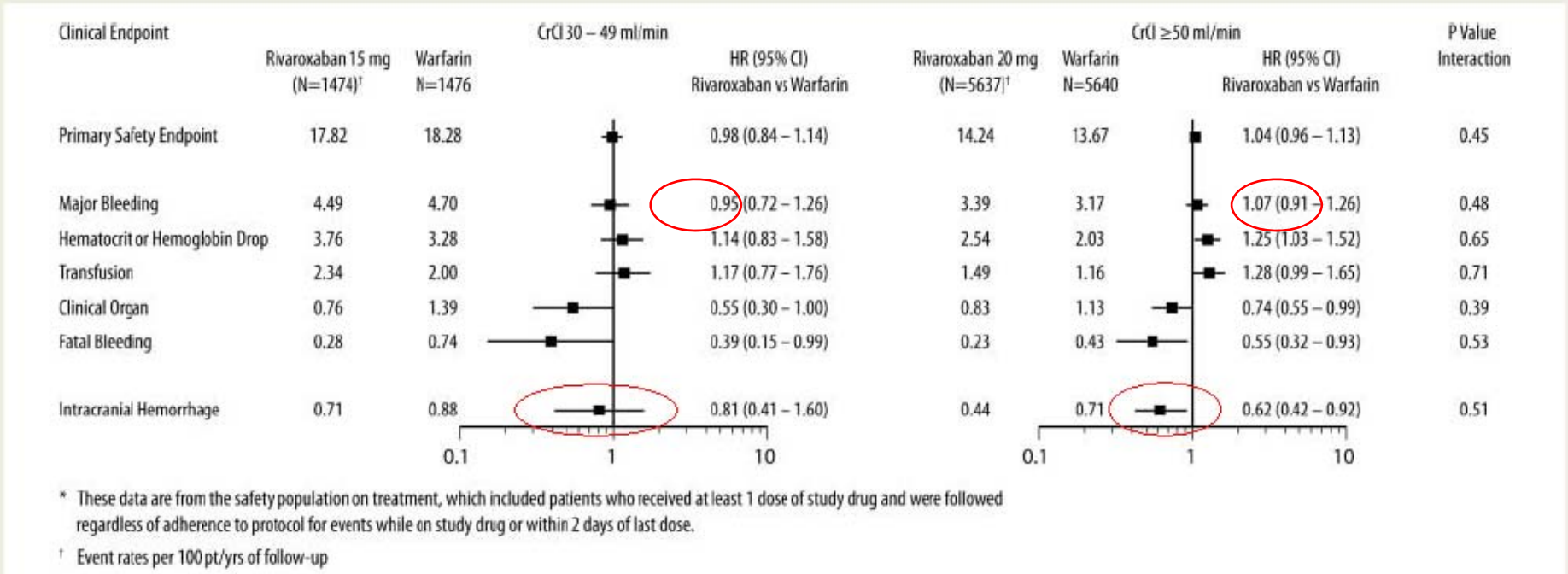
Selection Between NOACS
- Specific Populations -

- Age
- Renal function
- GI bleeding / heartburn
- Side effects
- Compliance to BID dosage

Risk for Major Bleeding in RE-LY



Bleeding in ROCKET-AF (in relation to Renal function)



Clinical Endpoint	CrCl 30 – 49 ml/min			CrCl ≥50 ml/min			P Value
	Rivaroxaban 15 mg (N=1474)†	Warfarin N=1476	HR (95% CI) Rivaroxaban vs Warfarin	Rivaroxaban 20 mg (N=5637)†	Warfarin N=5640	HR (95% CI) Rivaroxaban vs Warfarin	Interaction
Primary Safety Endpoint	17.82	18.28	0.98 (0.84 – 1.14)	14.24	13.67	1.04 (0.96 – 1.13)	0.45
Major Bleeding	4.49	4.70	0.95 (0.72 – 1.26)	3.39	3.17	1.07 (0.91 – 1.26)	0.48
Hematocrit or Hemoglobin Drop	3.76	3.28	1.14 (0.83 – 1.58)	2.54	2.03	1.25 (1.03 – 1.52)	0.65
Transfusion	2.34	2.00	1.17 (0.77 – 1.76)	1.49	1.16	1.28 (0.99 – 1.65)	0.71
Clinical Organ	0.76	1.39	0.55 (0.30 – 1.00)	0.83	1.13	0.74 (0.55 – 0.99)	0.39
Fatal Bleeding	0.28	0.74	0.39 (0.15 – 0.99)	0.23	0.43	0.55 (0.32 – 0.93)	0.53
Intracranial Hemorrhage	0.71	0.88	0.81 (0.41 – 1.60)	0.44	0.71	0.62 (0.42 – 0.92)	0.51

* These data are from the safety population on treatment, which included patients who received at least 1 dose of study drug and were followed regardless of adherence to protocol for events while on study drug or within 2 days of last dose.

† Event rates per 100 pt/yrs of follow-up

Figure 3 Safety endpoints.

K.A.A. Fox *et al.*

Primary efficacy results for apixaban were consistent across major subgroups in ARISTOTLE

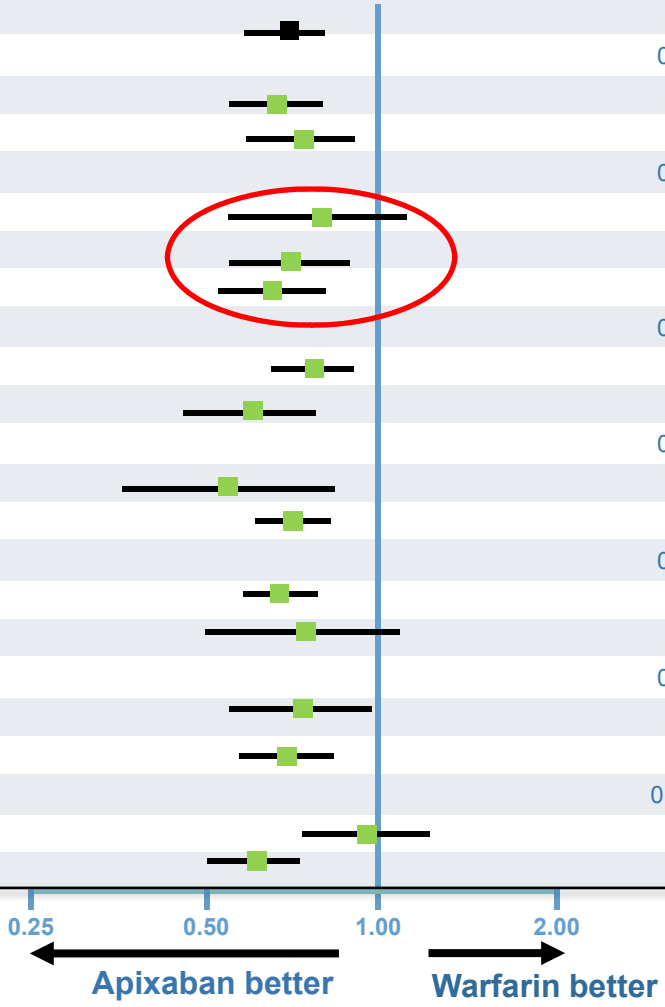
Characteristics	No. of patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
All patients	**18,201**	**212 (1.27)**	**265 (1.60)**		
Prior warfarin/VKA					**0.39**
Yes	10,401	102 (1.1)	138 (1.5)		
No	7,800	110 (1.5)	127 (1.8)		
Age					**0.12**
< 65 yrs	5,471	51 (1.0)	44 (0.9)		
65 to < 75 yrs	7,052	82 (1.3)	112 (1.7)		
≥ 75 yrs	5,678	79 (1.6)	109 (2.2)		
Sex					**0.60**
Male	11,785	132 (1.2)	160 (1.5)		
Female	6,416	80 (1.4)	105 (1.8)		
Weight					**0.26**
≤ 60 kg	1,985	34 (2.0)	52 (3.2)		
> 60 kg	16,154	177 (1.2)	212 (1.4)		
Type of AF					**0.70**
Permanent/Persistent	15,412	191 (1.4)	235 (1.7)		
Paroxysmal	2,786	21 (0.8)	30 (1.1)		
Prior stroke or TIA					**0.71**
Yes	3,436	73 (2.5)	98 (3.2)		
No	14,765	139 (1.0)	167 (1.2)		
Diabetes mellitus					**0.71**
Yes	4,547	57 (1.4)	75 (1.9)		
No	13,654	155 (1.2)	190 (1.5)		

Primary efficacy endpoint: stroke or systemic embolism

Adapted from Granger et al. N Engl J Med 2011;365:981-92.

Apixaban provided generally consistent major bleeding results across subgroups in ARISTOTLE

Characteristics	No. of patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
All patients	**18,140**	**327 (2.13)**	**462 (3.09)**		
Prior warfarin/VKA					0.50
Yes	10,376	185 (2.1)	274 (3.2)		
No	7,764	142 (2.2)	188 (3.0)		
Age					0.64
< 65 yrs	5,455	56 (1.2)	72 (1.5)		
65 to < 75 yrs	7,030	120 (2.0)	166 (2.8)		
≥ 75 yrs	5,655	151 (3.3)	224 (5.2)		
Sex					0.08
Male	11,747	225 (2.3)	294 (3.0)		
Female	6,393	102 (1.9)	168 (3.3)		
Weight					0.22
≤ 60 kg	1,978	36 (2.3)	62 (4.3)		
> 60 kg	16,102	290 (2.1)	398 (3.0)		
Type of AF					0.75
Permanent/Persistent	15,361	283 (2.2)	402 (3.2)		
Paroxysmal	2,776	44 (1.9)	60 (2.6)		
Prior stroke or TIA					0.71
Yes	3,422	77 (2.8)	106 (3.9)		
No	14,718	250 (2.0)	356 (2.9)		
Diabetes mellitus					0.003
Yes	4,526	112 (3.0)	114 (3.1)		
No	13,614	215 (1.9)	348 (3.1)		



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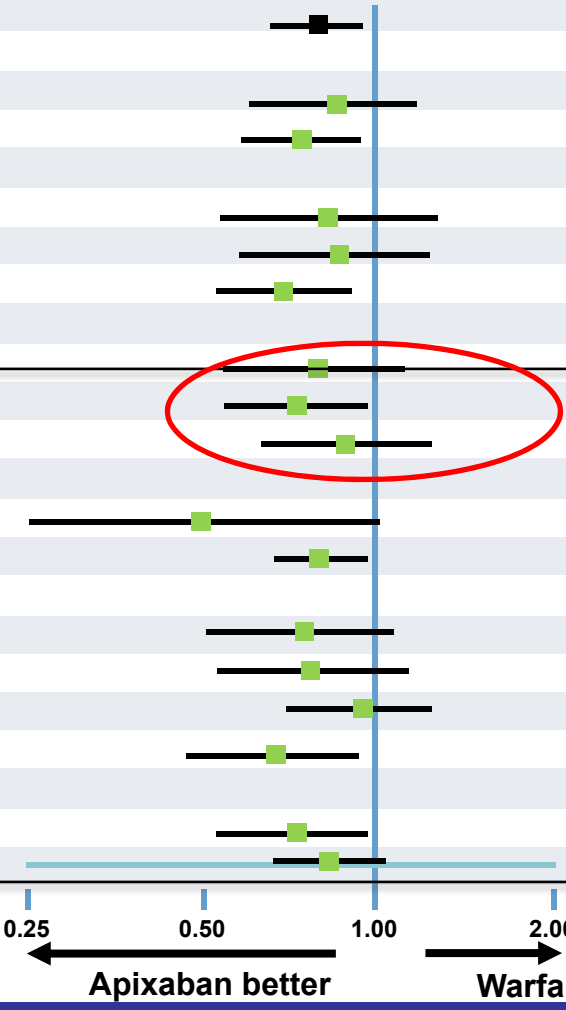
Primary efficacy results for apixaban were consistent across major subgroups in ARISTOTLE

Characteristics	No. of patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
All patients	**18,201**	**212 (1.27)**	**265 (1.60)**		
Heart failure					0.50
Yes	5,541	70 (1.4)	79 (1.6)		
No	12,660	142 (1.2)	186 (1.6)		
$CHADS_2$ score					0.45
≤ 1	6,183	44 (0.7)	51 (0.9)		
2	6,516	74 (1.2)	82 (1.4)		
≥ 3	5,502	94 (1.9)	132 (2.8)		
Level of renal impairment					0.72
Severe or Moderate	3,017	54 (2.1)	69 (2.7)		
Mild	7,587	87 (1.2)	116 (1.7)		
No impairment	7,518	70 (1.0)	79 (1.1)		
Apixaban dose					0.22
2.5 mg BID or placebo	831	12 (1.7)	22 (3.3)		
5 mg BID or placebo	17,370	200 (1.3)	243 (1.5)		
Geographic region					0.44
North America	4,474	42 (1.0)	56 (1.3)		
Latin America	3,468	43 (1.4)	52 (1.8)		
Europe	7,343	75 (1.1)	77 (1.1)		
Asian Pacific	2,916	52 (2.0)	80 (3.1)		
ASA use at randomisation					0.44
Yes	5,632	70 (1.3)	94 (1.9)		
No	12,569	142 (1.2)	171 (1.5)		



Primary efficacy endpoint: stroke or systemic embolism

Adapted from Granger et al. N Engl J Med 2011;365:981-92.

Apixaban provided generally consistent major bleeding results across subgroups in ARISTOTLE

Characteristics	No. of patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
All patients	**18,140**	**327 (2.13)**	**462 (3.09)**		
Heart failure					0.30
Yes	5,527	87 (1.9)	137 (3.1)		
No	12,613	240 (2.2)	325 (3.1)		
$CHADS_2$ score					0.40
≤ 1	6,169	76 (1.4)	126 (2.3)		
2	6,492	125 (2.3)	163 (3.0)		
≥ 3	5,479	126 (2.9)	173 (4.2)		
Level of renal impairment					0.03
Severe or Moderate	3,005	73 (3.2)	142 (6.4)		
Mild	7,565	157 (2.5)	199 (3.2)		
No impairment	7,496	96 (1.5)	119 (1.8)		
Apixaban dose					0.21
2.5 mg BID or placebo	826	20 (3.3)	37 (6.7)		
5 mg BID or placebo	17,314	307 (2.1)	425 (3.0)		
Geographic region					0.16
North America	4,463	106 (2.8)	137 (3.6)		
Latin America	3,460	60 (2.1)	94 (3.5)		
Europe	7,313	110 (1.7)	135 (2.2)		
Asian Pacific	2,904	51 (2.1)	96 (4.1)		
ASA use at randomisation					0.40
Yes	5,608	129 (2.7)	164 (3.7)		
No	12,532	198 (1.9)	298 (2.8)		

Adapted from Granger et al. N Engl J Med 2011;365:981-92.

סיכום

- ל NOACS יתרון על פני VKA במרבית האוכלוסיות
- דביגטרן במינון 110 2X בטוח יותר מקומדין , אך יתרון זה הולך לאיבוד עם עלית הגיל וירידת התפקוד הכלייתי
- דביגטרן במינון 150 X 2 יעיל יותר מקומדין במניעת אירועים אמבוליים אך הסיכון שבו עולה משמעותית עם הגיל, ועם איס"ק כליות
- לריברוקסבן פרופיל יעילות ובטיחות דומה לקומדין , שאינו משתנה באופן בולט עם הירידה בתפקוד הכליה (התאמת מינון)
- לאפיקסבן פרופיל יעילות ובטיחות טוב יותר מקומדין, שאינו מושפע לרעה מתפקוד כליתי או גיל (התאמת מינון)