DOACs & Kidney Dysfunction

Wednesday | June 28, 2023 | 12pm EST

Presenter

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Moderators

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Direct Oral Anticoagulants Versus Warfarin Across the Spectrum of Kidney Function: Patient-Level Network Meta-Analyses From COMBINE AF

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From Thought Leadership to Clinical Practice

Disclosures

Renato D Lopes, MD MHS PhD

- Research grants or contracts from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, Sanofi-Aventis
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- Funding for consulting or other services from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Novo Nordisk, AstraZeneca

Good News:

Oral anticoagulation with warfarin is very effective at preventing stroke, BUT we can do better

Hart RG, et al. *Ann Intern Med* 1999;131:492-501.
Granger CB, et al. *N Engl J Med* 2011;365:981-992.
Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.
Giugliano RP, et al. *N Engl J Med* 2013;369:2093-2104.
Patel MR, et al. *N Engl J Med* 2011;365:883-891.

Non-Vitamin K Antagonist Oral Anticoagulants ("NOACs")

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Bioavailability	Oral prodrug with poor oral bioavailability (6.5%)	Good oral bioavailability	Good oral bioavailability	Good oral bioavailability
$T_{½}$	12 - 17 hours	6 - 9 hours	12 hours	9 - 11 hours
Dosing	Twice daily	Once or twice daily	Twice daily	Once or twice daily
Time action	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition
Platelet aggregation	No direct effect	No direct effect	No direct effect	No direct effect
Elimination	80% renal	35% renal	25% renal	50% renal

Eriksson BI, et al. *Clin Pharmacokinet.* 2009;48:1-22.


RELY®
Study of stroke prevention
in atrial fibrillation


ROCKET AF


ARISTOTLE™


Engage AF
TIMI 48

Phase 3 Trials of NOAC vs Warfarin

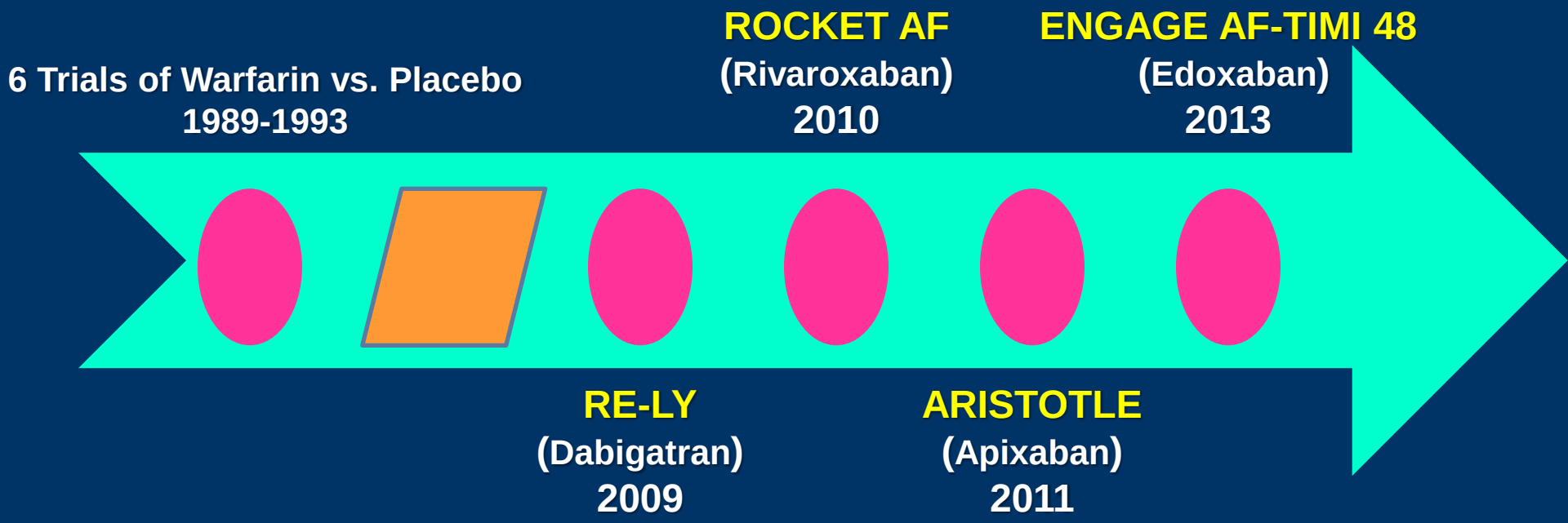
	RELY	ROCKET	ARISTOTLE	ENGAGE-AF
Sample size	18,113	14,266	18,201	21,150
New treatment	Dabigatran 110mg BID Dabigatran 150mg BID	Rivaroxaban 20mg QD	Apixaban 5mg BID	Edoxaban 30mg QD Edoxaban 60mg QD
Design	Non-inferiority PROBE	Non-inferiority Double-blind	Non-inferiority Double-blind	Non-inferiority Double-blind
Patients	AF + CHADS2 ≥ 1	AF + CHADS2 ≥ 2	AF + CHADS2 ≥ 1	AF + CHADS2 ≥ 2
Renal Exclusion	CrCl < 30 ml/min	CrCl < 30 ml/min	CrCl < 25 ml/min	CrCl < 30 ml/min
Primary outcome	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism
Safety outcome	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM

Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger C et al NEJM 2011;
ENGAGE- AF Study Investigators. AHJ 2010

Pivotal Warfarin-Controlled Trials
Stroke Prevention in AF

Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients



Non-Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Atrial Fibrillation

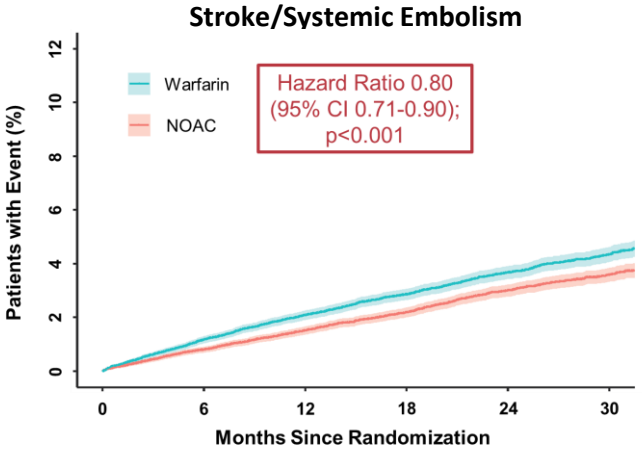
Individual Patient Data from the Pivotal Randomized Trials

(A **CO**llaboration between **M**ultiple institutions to **B**etter **I**nvestigate **N**on-vitamin K antagonist oral anticoagulant us**E** in **A**trial **F**ibrillation)

Kaplan-Meier Curves

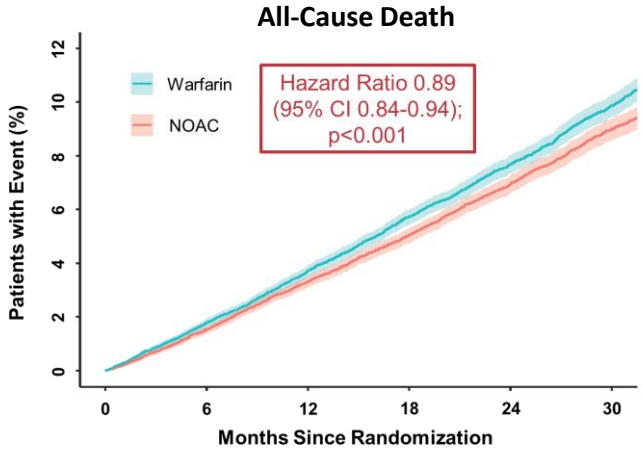
Duke Clinical Research Institute

COMBINE-AF



Number at Risk (number of events)

Warfarin	29229 (0)	28027 (336)	27051 (591)	21654 (786)	15324 (944)	8870 (1031)
NOAC	29312 (0)	28256 (231)	27328 (431)	21907 (602)	15595 (761)	9027 (837)



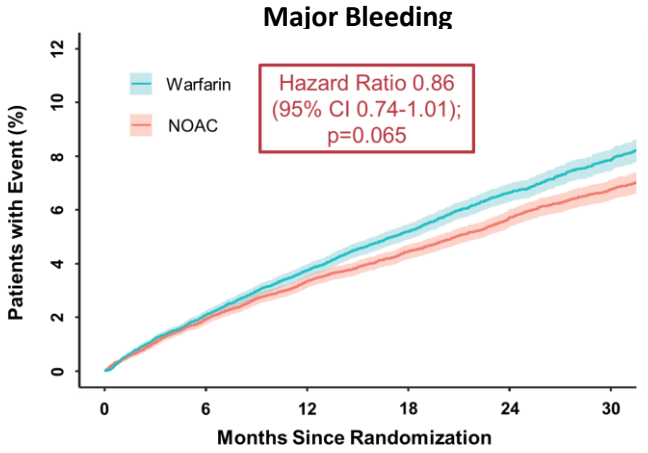
Number at Risk (number of events)

Warfarin	29229 (0)	28302 (512)	27476 (1067)	22120 (1587)	15735 (1987)	9139 (2289)
NOAC	29312 (0)	28462 (442)	27654 (956)	22276 (1404)	15951 (1794)	9271 (2080)

Kaplan-Meier Curves

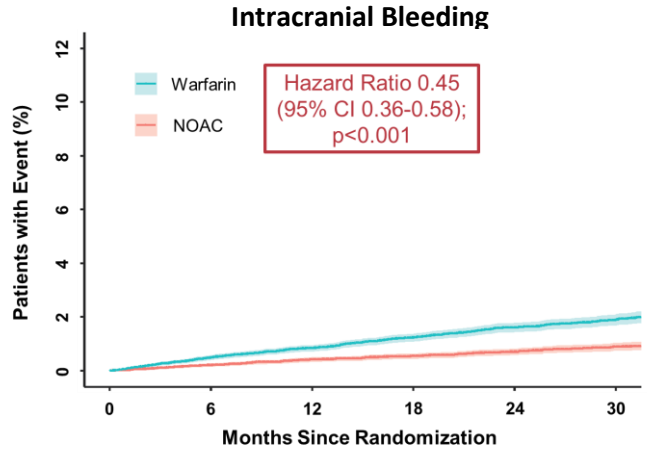
Duke Clinical Research Institute

COMBINE-AF



Number at Risk (number of events)

Warfarin	29187 (0)	25639 (572)	23562 (992)	18382 (1311)	12618 (1555)	7009 (1686)
NOAC	29270 (0)	25375 (521)	23456 (877)	18258 (1117)	12577 (1321)	7050 (1434)



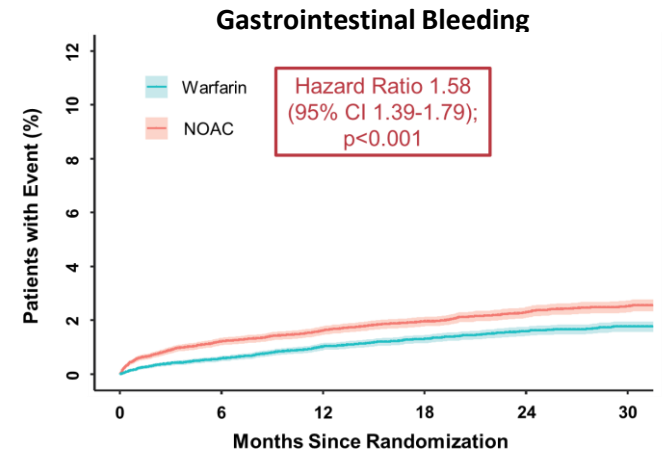
Number at Risk (number of events)

Warfarin	29187 (0)	25900 (132)	23995 (219)	18854 (306)	13037 (369)	7299 (398)
NOAC	29270 (0)	25624 (55)	23863 (107)	18685 (133)	12986 (159)	7317 (179)

Kaplan-Meier Curves

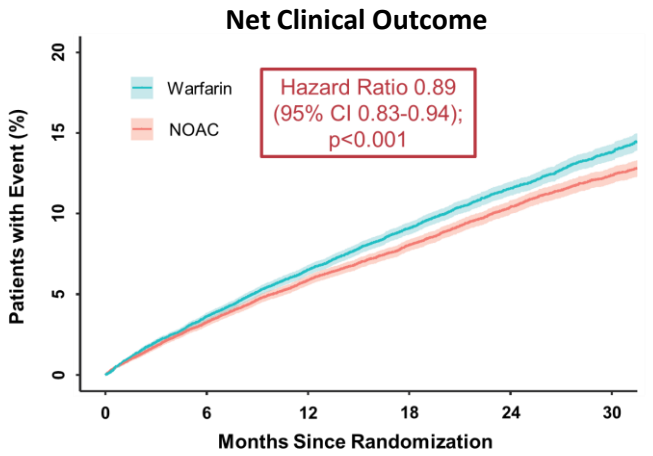
Duke Clinical Research Institute

COMBINE-AF



Number at Risk (number of events)

Warfarin	29187 (0)	25792 (160)	23804 (269)	18677 (330)	12906 (377)	7226 (395)
NOAC	29270 (0)	25393 (335)	23577 (436)	18413 (508)	12791 (564)	7206 (588)



Number at Risk (number of events)

Warfarin	29187 (0)	25567 (999)	23446 (1744)	18260 (2327)	12504 (2758)	6946 (3012)
NOAC	29270 (0)	25323 (890)	23378 (1555)	18178 (2040)	12502 (2445)	6996 (2666)

Net clinical outcome = composite stroke, systemic embolism, major bleeding, all-cause death

ESC European Society of Cardiology

European Heart Journal (2020) **00**, 1–126
doi:10.1093/eurheartj/ehaa612

ESC GUIDELINES

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC)

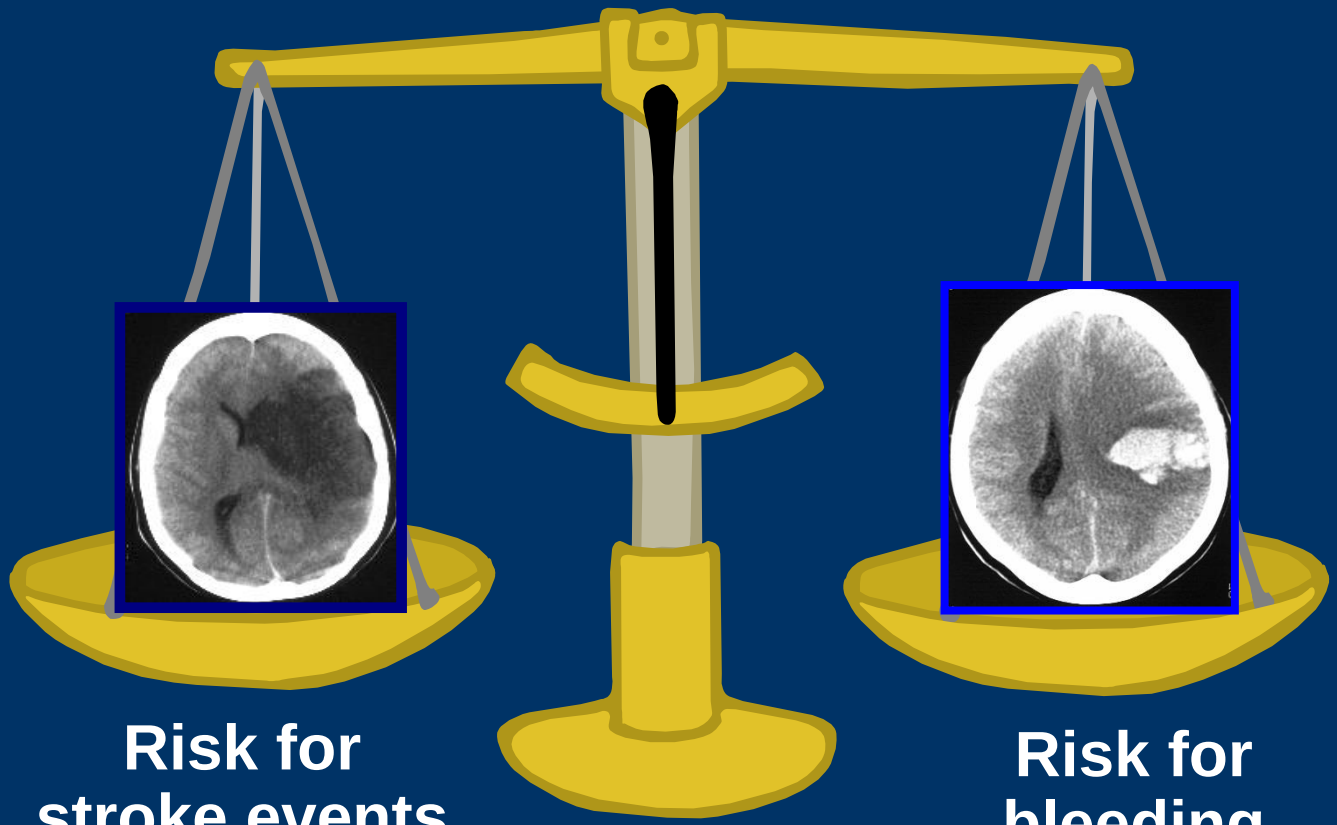
Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Oral Anticoagulation (2020 ESC AF Guidelines)

Recommendations	Class	Level
For stroke prevention in AF patients who are eligible for OAC, **NOACs are recommended in preference to VKAs**. (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis)	I	A
In patients on VKAs with low time in INR therapeutic range (e.g. TTR<70%), recommended options are:		
• Switching to a NOAC but ensuring good adherence and persistence with therapy or	I	B
• Efforts to improve TTR (e.g. education/counselling and more frequent INR checks).	IIa	B
Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF.	III	A

Hindricks et al., European Heart Journal 2020

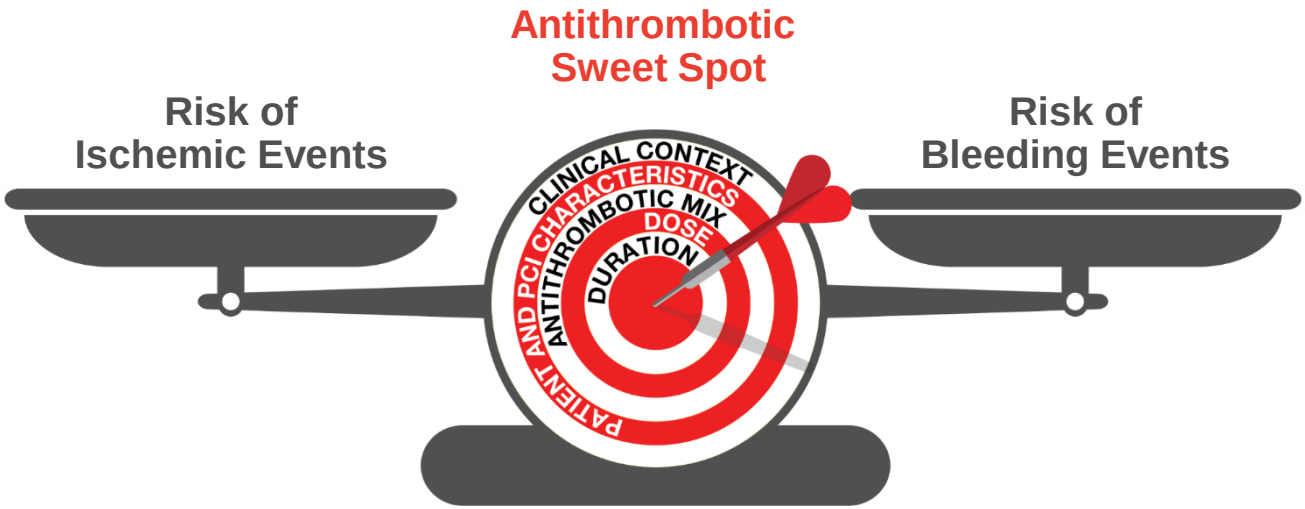
Anticoagulant Therapy in Atrial Fibrillation



Risk for stroke events

Risk for bleeding

Finding the Antithrombotic Sweet Spot



The right combination of antithrombotic agents at the right dose and duration to reduce ischemic events as much as possible at a minimal cost of bleeding

Lopes RD et al. EHJ, 2019

NOACs and Renal Disease

Who Are We Talking About?

- Helen – 84 yo female with…
  - AF, CHA_2DS_2-VASC = 4
  - HTN
  - EF 45%,
  - Weight 75 kg
  - Cr 2.0 mg/dL, CrCl 25 ml/min

- David – 65 yo male with…
  - AF, CHA_2DS_2-VASC = 3
  - HTN
  - Diabetes
  - Weight 70 kg
  - ESRD on HD x 4 years

Non-Vitamin K Antagonist Anticoagulants ("NOACs")

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban*
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Bioavailability	Oral prodrug with poor oral bioavailability (6.5%)	Good oral bioavailability	Good oral bioavailability	Good oral bioavailability
$T_{½}$	12 - 17 hours	6 - 9 hours	~12 hours	9 - 11 hours
Dosing	Twice daily	Once daily	Twice daily	Once daily
Time action	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition
Platelet aggregation	No direct effect	No direct effect	No direct effect	No direct effect
Elimination	80% renal	35% renal	25% renal	50% renal

Eriksson BI, et al. *Clin Pharmacokinet.* 2009;48:1-22.

Phase 3 Trials of "NOACs" vs Warfarin

	RELY	ROCKET	ARISTOTLE	ENGAGE-AF
Sample size	18,113	14,266	18,201	21,150
New treatment	Dabigatran 110 mg BID Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg BID	Edoxaban* 30/15 mg QD Edoxaban* 60/30 mg QD
Design	Non-inferiority PROBE	Non-inferiority Double-blind	Non-inferiority Double-blind	Non-inferiority Double-blind
Patients	AF + CHADS2 ≥ 1	AF + CHADS2 ≥ 2/3	AF + CHADS2 ≥ 1	AF + CHADS2 ≥ 2
Renal Exclusion	CrCl < 30 ml/min	CrCl < 30 ml/min	CrCl < 25 ml/min	CrCl < 30 ml/min
Primary outcome	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism
Safety outcome	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major + CRNM Bleeding Secondary: Major Bleeding	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM

Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger C et al NEJM 2011; Giugliano RP, et al. NEJM 2013

NOAC Dosing Depends Mainly on Renal Function

Drug[*†]	Dose
Dabigatran[1]	• CrCl >30 mL/min: 150 mg PO BID • CrCl 15-30 mL/min: 75 mg PO BID[b] • CrCl <15 mL/min: not recommended
Rivaroxaban[2]	• CrCl >50 mL/min: 20 mg PO once daily • CrCl 15-50 mL/min: 15 mg PO once daily • CrCl <15 mL/min: not recommended
Apixaban[3]	• 5 mg PO BID • Dose adjusted to 2.5 mg PO BID for patients aged ≥80 y, weight ≤60 kg, or SCr ≥1.5 mg/dL • Hemodialysis 5 mg PO BID with dose adjusted to 2.5 mg BID for patients aged ≥80 y or weight ≤60 kg
Edoxaban[4]	• Both doses (30 mg and 60 mg) halved if CrCl 30-50 mL/min, low body weight ≤60 kg or taking concomitant verapamil, quinidine or dronedarone • Patients with CrCL <30 mL/min were excluded from ENGAGE-AF TIMI 48

[*]For dabigatran, rivaroxaban, and edoxaban, patients with CrCl <30 mL/min were excluded from clinical trials; for apixaban, patients with CrCl <25 mL/min were excluded

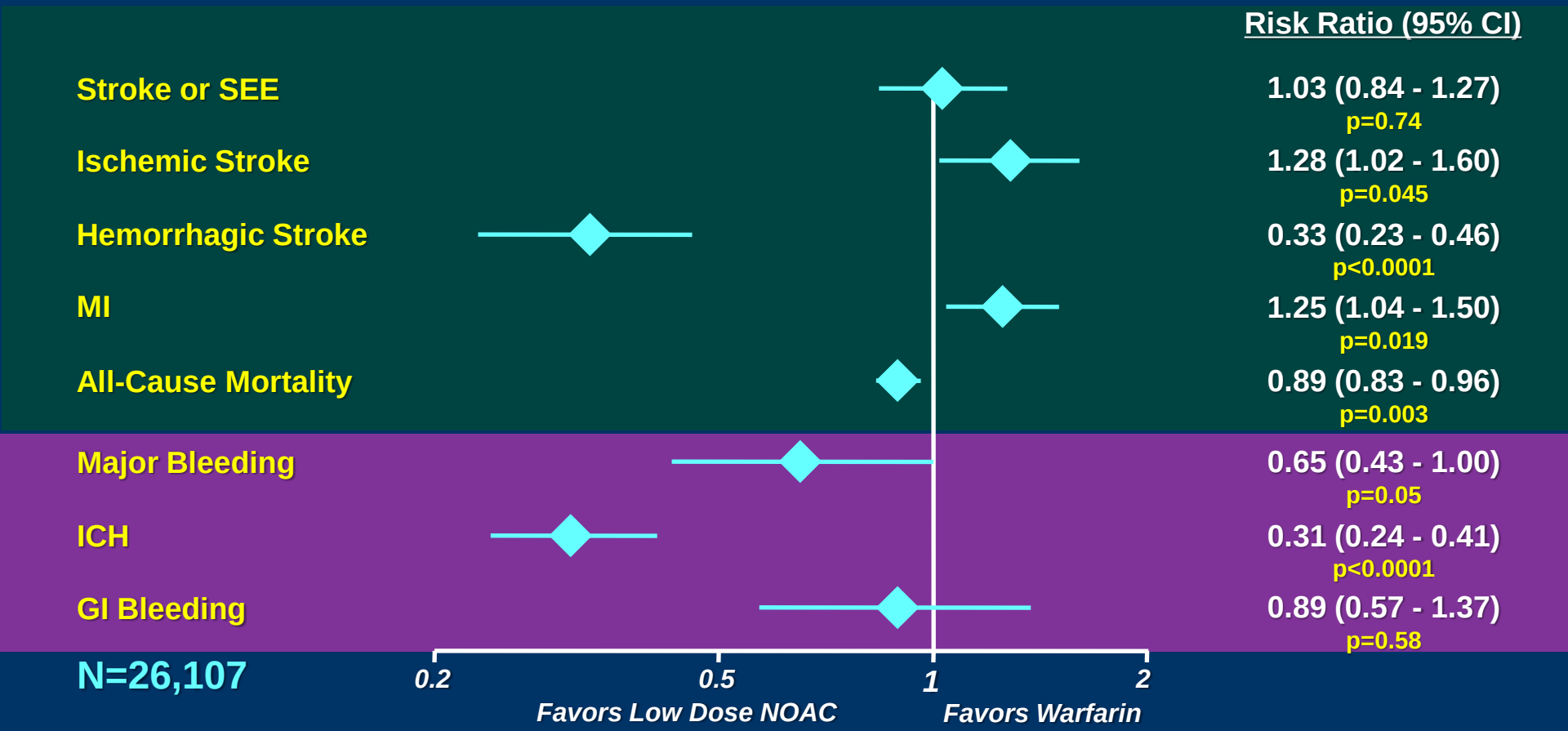
[†]The 75-mg dose of dabigatran was not evaluated in clinical trials, but is an FDA-approved dose

1. Pradaxa® (dabigatran etexilate mesylate) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc.; 11/2012.
2. Xarelto® (rivaroxaban) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 11/2012.
3. Eliquis® (apixaban) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 1/2014.
4. Giugliano RP et al. *N Engl J Med*. 2013; 369:2093-2104.

For individual products please refer to the local label information in your country
Edoxaban approval status and label may vary from country to country

Low Dose Regimens
Efficacy & Safety Outcomes

Dabigatran 110 mg & Edoxaban 30 mg, meta-analysis



P=NS for outcomes except:
Major Bleeding, p=<0.001
GI Bleeding, p=0.01

Ruff CT, et al. *Lancet* 2014;383:955-62.

"Dose-Adjusted" NOACs

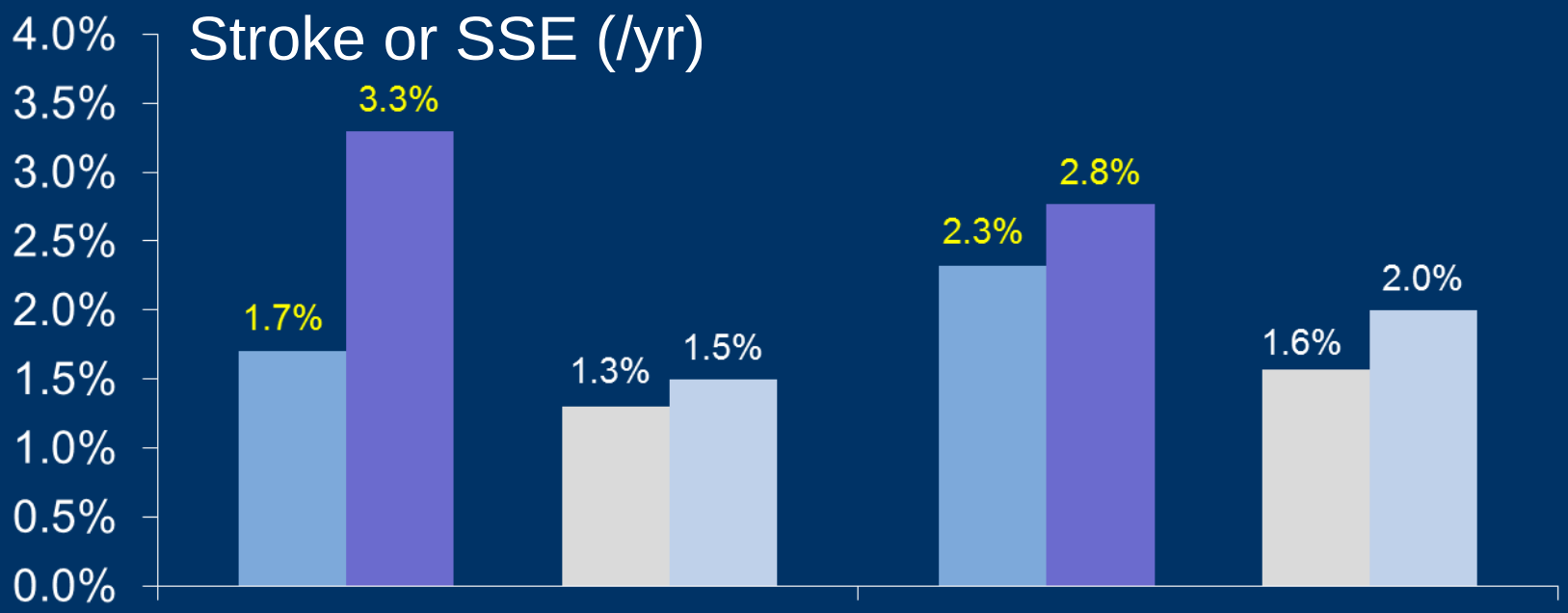
ARISTOTLE

At least 2 of 3….
Age >80 yrs, Cr >1.5 mg/dL, Wt <60 kg

ROCKET AF

Estimate CrCl 30-49 ml/min

Major Bleeding (%/yr)			
3.3 / 6.7	2.1 / 3.0	4.5 / 4.7	3.4 / 3.2



n	831 (5%)	17,370	2,950 (21%)	11,314
dose	2.5 v W	5.0 v W	15 v W	20 v W

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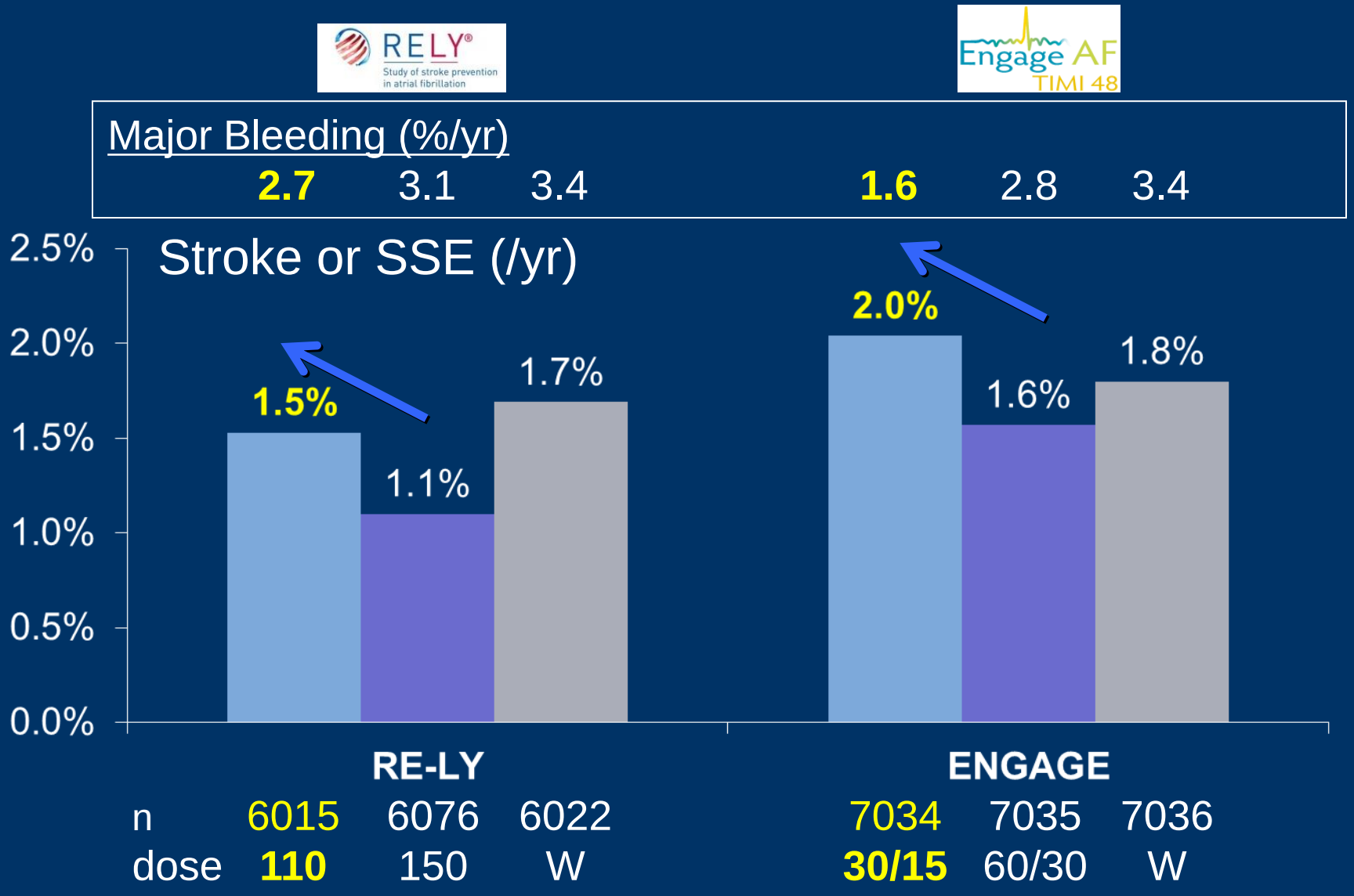
Fox KAA, et al. Eur Heart J 2011;32:2387-2394.
Granger CB, et al. NEJM 2011;365:981-92.

“Low- Dose” NOACs are Less Effective (and Safer)



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Connolly SJ, et al. NEJM 2009;361:1139-51.
Giugliano RP, et al. NEJM 2013;369:2093-104.

Renal Function and Dabigatran

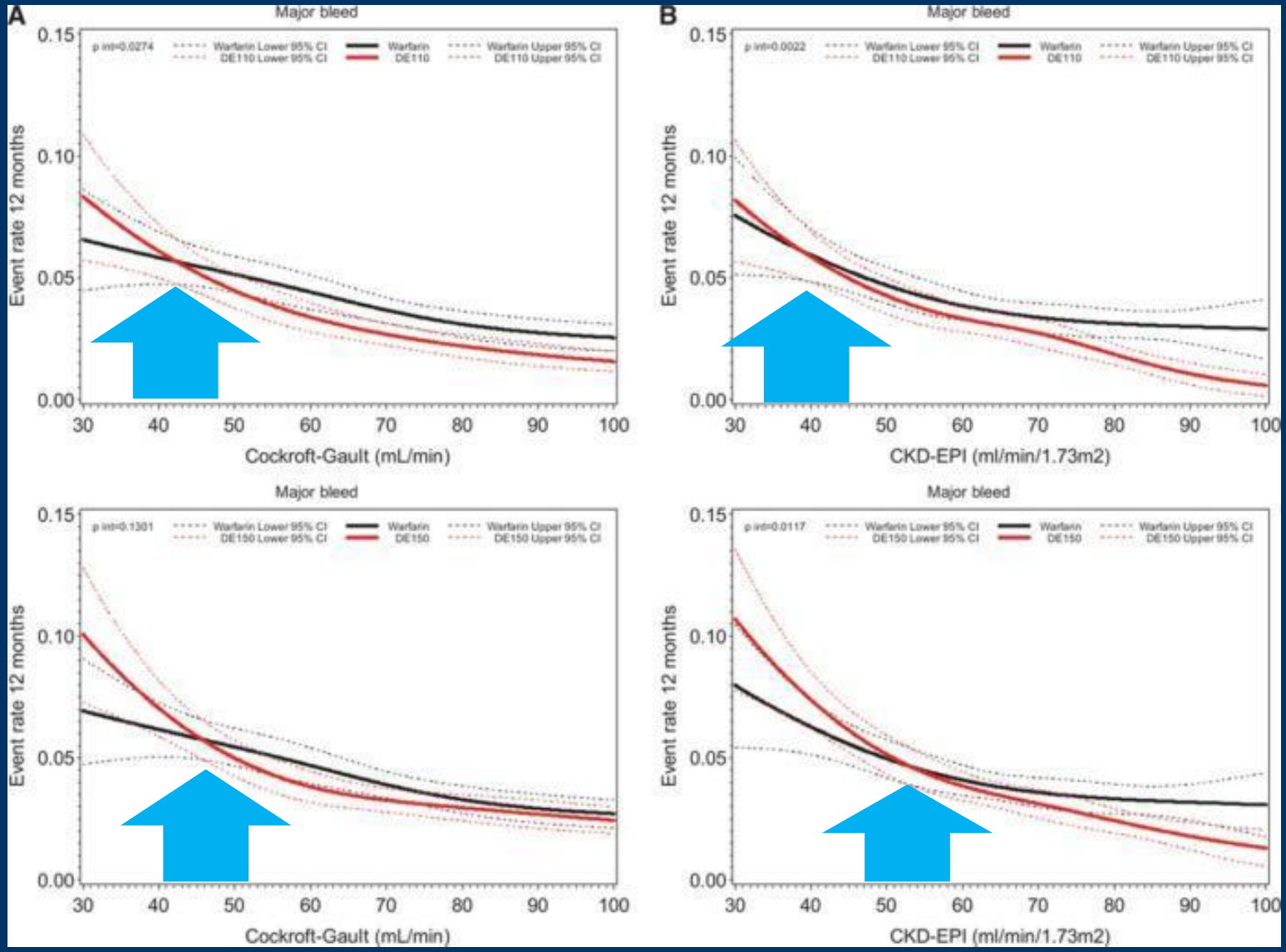
Table 3 Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C_{max}	$t_{1/2}$ (h)
Normal	80	1x	1x	13
Mild	50	1.5x	1.1x	15
Moderate	30	3.2x	1.7x	18

Please refer to the local label information in your country
Dabigatran FDA package insert

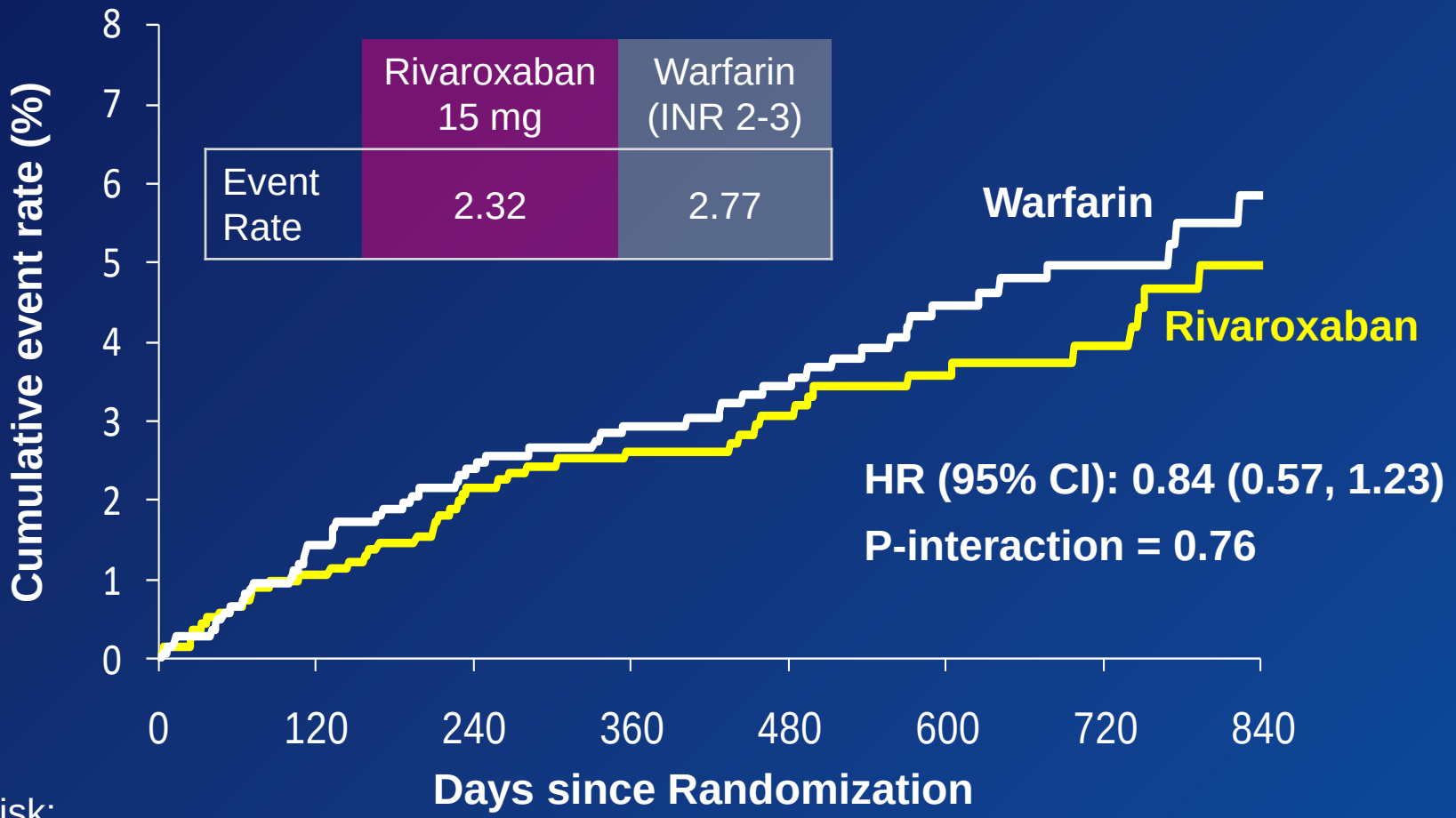
Major Bleeding to Renal Function (CrCl)

Dabigatran 110 mg BID (top) and 150 mg BID (bottom)



Hijazi Z et al. Circulation. 2014;129:961-970

Stroke or non-CNS embolism
CrCl 30–49 mL/min



No. at risk:

Rivaroxaban	1434	1226	1103	1027	806	621	442	275
Warfarin	1439	1261	1140	1052	832	656	455	272

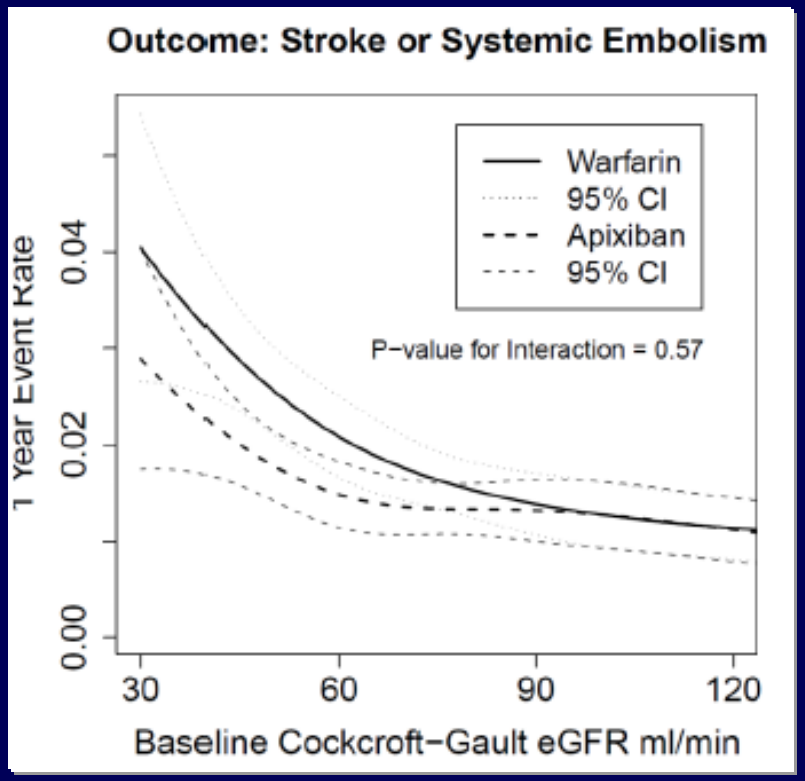
Event rates are % per year

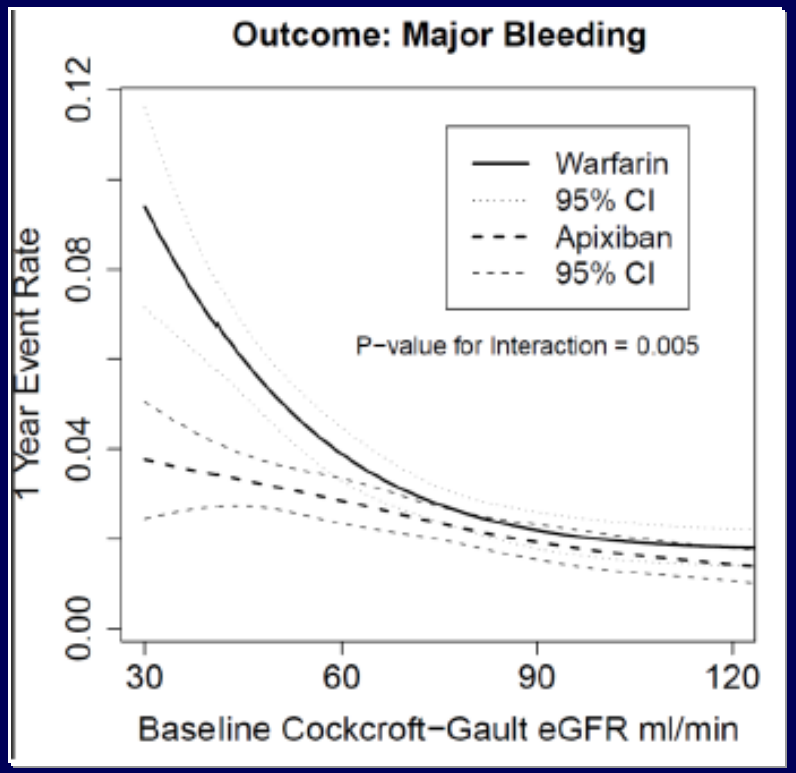
Based on Protocol Compliant on Treatment Population

Fox KAA, Eur Heart J 2011

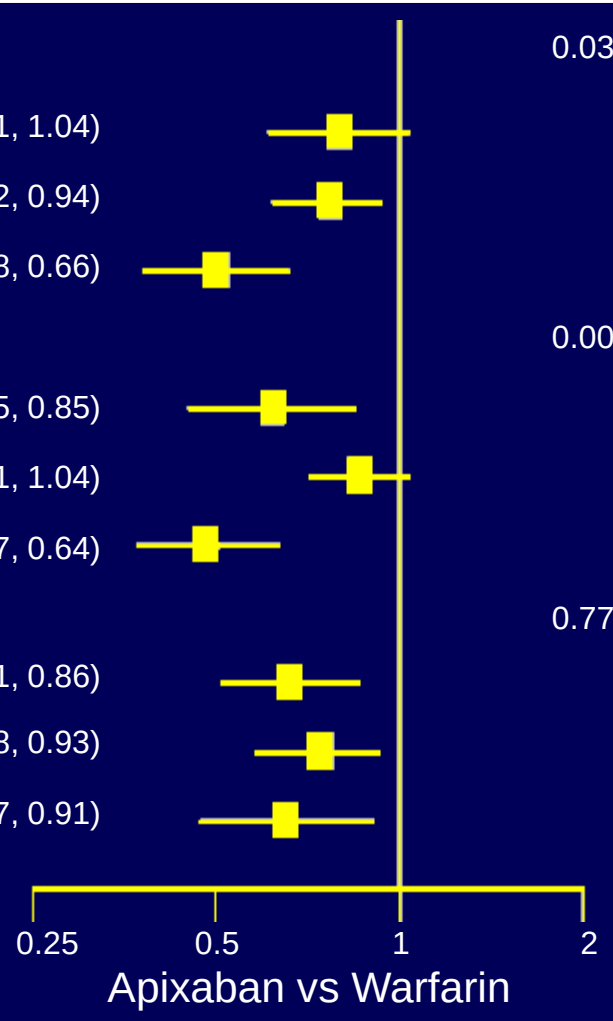
ROCKET AF

Renal Function





Apixaban versus Warfarin: Effect on Major Bleeding According to Kidney Function



	Apixaban %/yr (n)	Warfarin %/yr (n)	Hazard Ratio (95% CI)	P Value for interaction
Cockcroft-Gault eGFR ml/min				0.030
>80	1.46 (96)	1.84 (119)	0.80 (0.61, 1.04)	
>50-80	2.45 (157)	3.21 (199)	0.77 (0.62, 0.94)	
≤50	3.21 (73)	6.44 (142)	0.50 (0.38, 0.66)	
CKD-EPI eGFR ml/min				0.004
>80	1.42 (64)	2.30 (100)	0.62 (0.45, 0.85)	
>50-80	2.21 (190)	2.58 (219)	0.86 (0.71, 1.04)	
≤50	3.28 (73)	6.78 (143)	0.48 (0.37, 0.64)	
Cystatin C eGFR ml/min				0.775
>80	1.45 (99)	2.19 (146)	0.66 (0.51, 0.86)	
>50-80	2.67 (120)	3.62 (162)	0.74 (0.58, 0.93)	
≤50	3.56 (60)	5.47 (85)	0.65 (0.47, 0.91)	

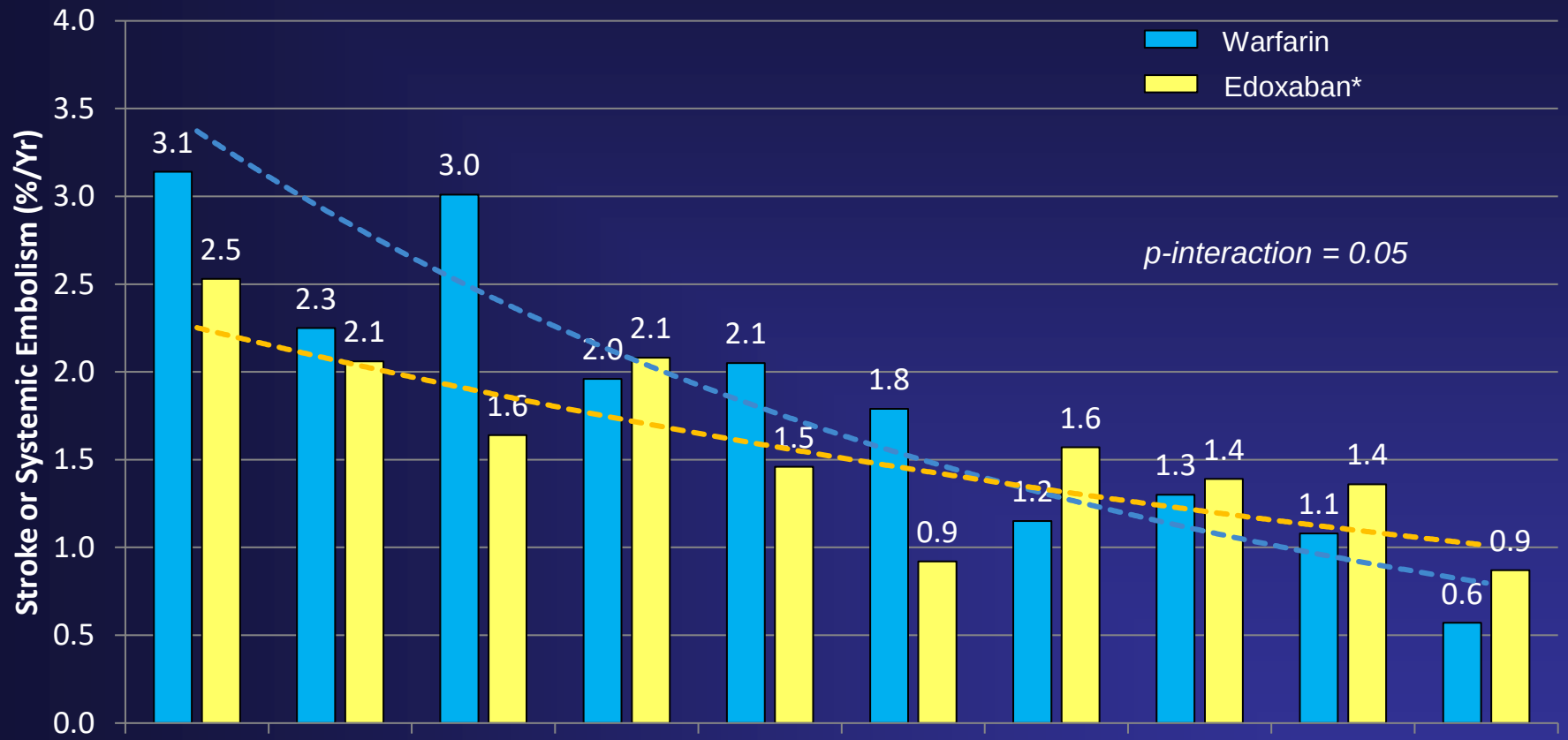
Duke Clinical Research Institute

Hohnloser S. Eur Heart J. 2012 Nov;33(22):2821-30

UCR UPPSALA CLINICAL RESEARCH CENTER

Stroke or SE by CrCl Decile

Intention-to-treat Overall Study Period



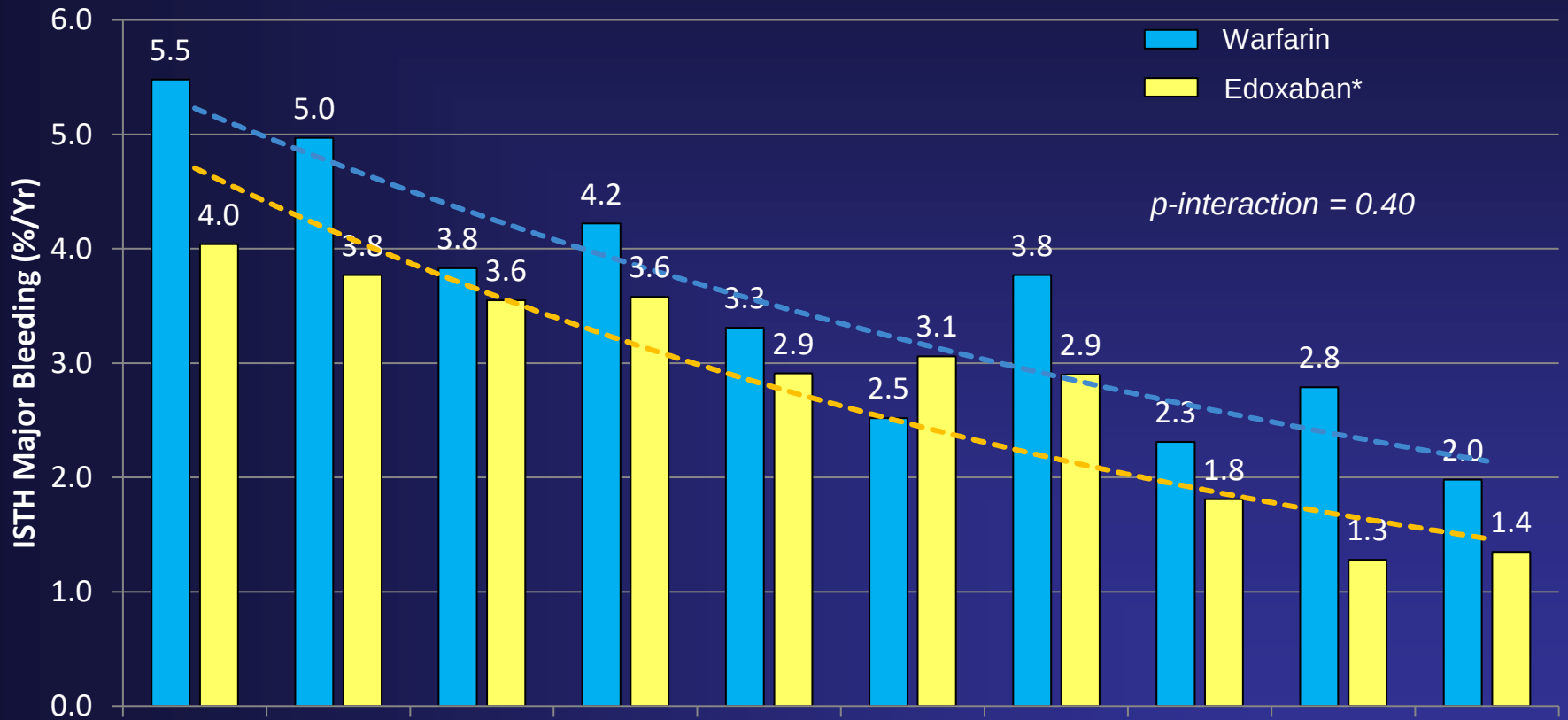
Decile	1	2	3	4	5	6	7	8	9	10
CrCl (mL/min)	≤42.8	42.9-50.5	50.6-57.2	57.3-63.6	63.4-70.3	70.4-77.8	77.9-86.6	86.7-98.0	98.1-117.1	≥117.2
ITT (N=)	1429	1412	1418	1375	1389	1431	1436	1366	1379	1436

**Edoxaban 60mg or 30mg if dose-reduced for CrCl≤50, weight ≤60kg or P-gp use*

Bohula, AHA Nov 2015, Orlando, FL

Major Bleeding by CrCl Decile

Safety Population



Decile	1	2	3	4	5	6	7	8	9	10
CrCl (mL/min)	≤42.8	42.9-50.5	50.6-57.2	57.3-63.6	63.4-70.3	70.4-77.8	77.9-86.6	86.7-98.0	98.1-117.1	≥117.2
Safety (N=)	1420	1407	1414	1365	1385	1427	1433	1361	1378	1434

**Edoxaban 60mg or 30mg if dose-reduced for CrCl≤50, weight ≤60kg or P-gp use*

Bohula, AHA Nov 2015, Orlando, FL

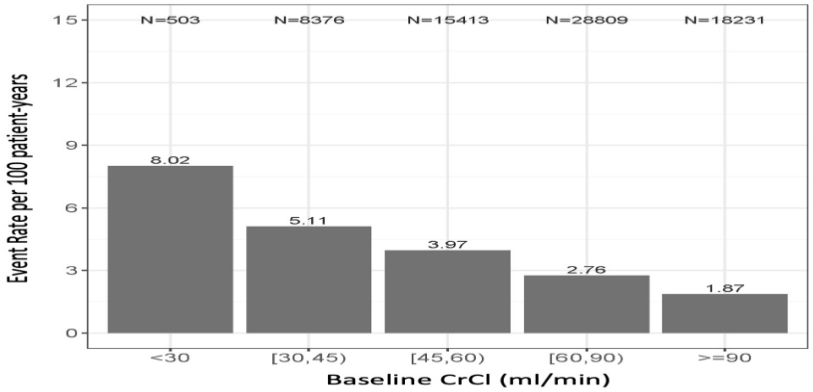
Circulation

ORIGINAL RESEARCH ARTICLE

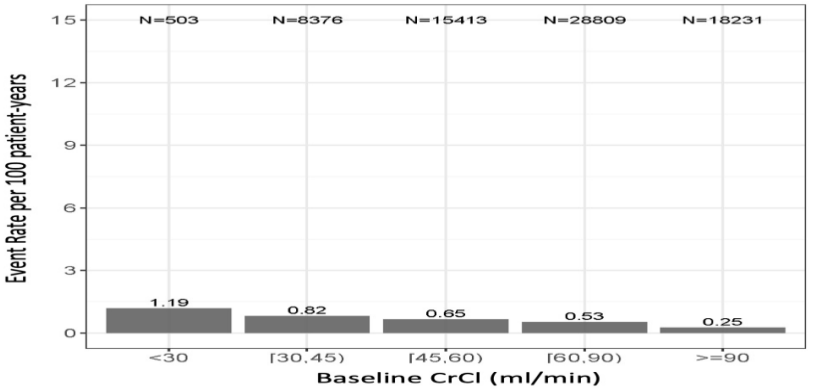
Direct Oral Anticoagulants Versus Warfarin Across the Spectrum of Kidney Function: Patient-Level Network Meta-Analyses From COMBINE AF

Josephine Harrington, MD; Anthony P. Carnicelli, MD; Kaiyuan Hua, MS; Lars Wallentin, MD, PhD; Manesh R. Patel, MD; Stefan H. Hohnloser, MD; Robert P. Giugliano, MD, ScM; Keith A.A. Fox, MB, ChB; Ziad Hijazi, MD, MPH; Renato D. Lopes, MD, MHS, PhD; Sean D. Pokorney, MD, MBA; Hwanhee Hong, PhD; Christopher B. Granger, MD

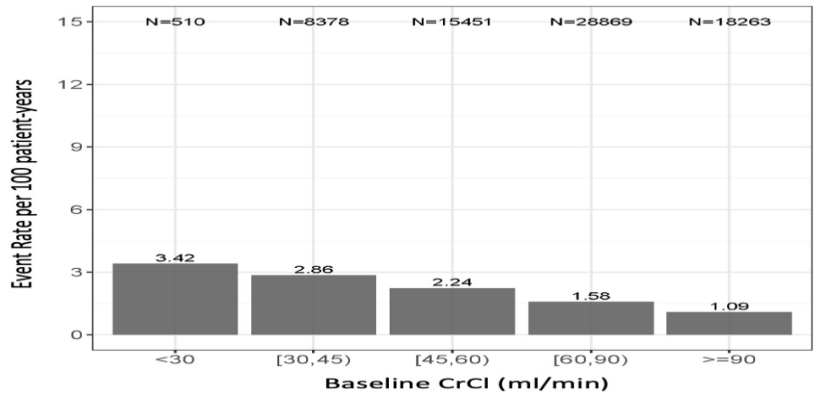
Major Bleeding



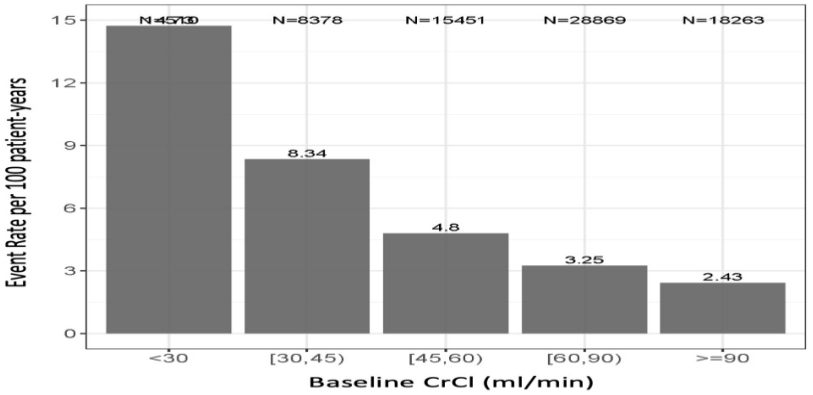
Intracranial Hemorrhage

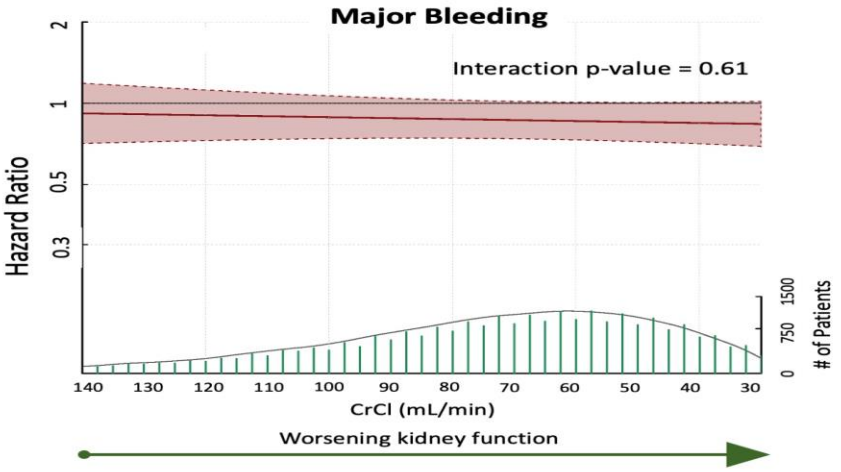


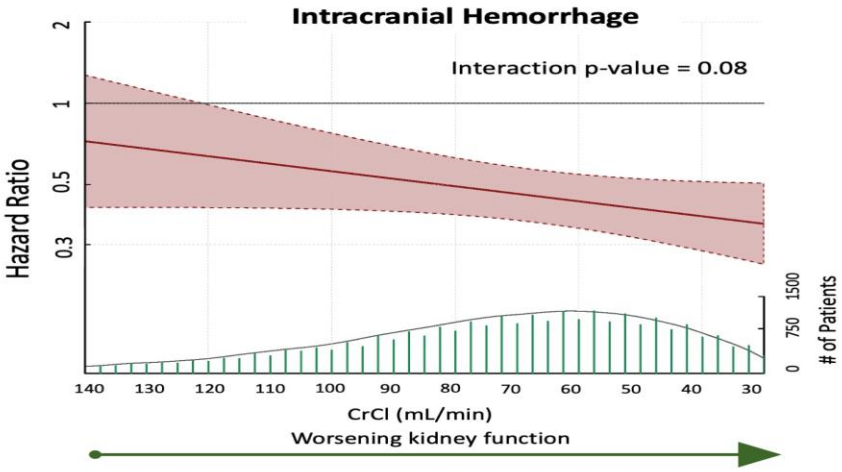
Stroke/Systemic Embolism

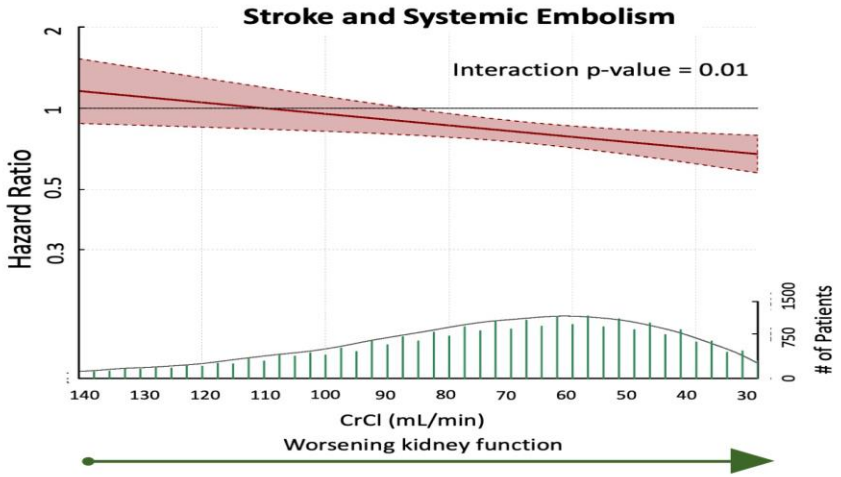


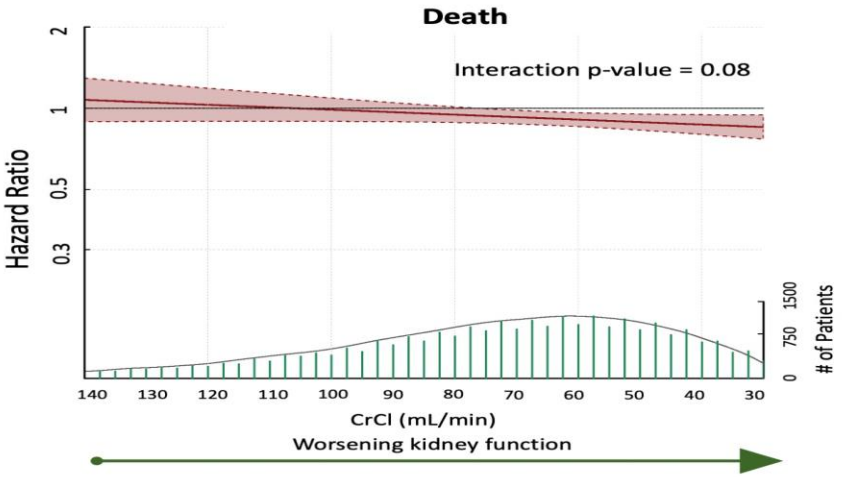
Death




Major Bleeding
Interaction p-value = 0.61
Hazard Ratio
2
1
0.5
0.3
140 130 120 110 100 90 80 70 60 50 40 30
CrCl (mL/min)
Worsening kidney function
0 750 1500
# of Patients

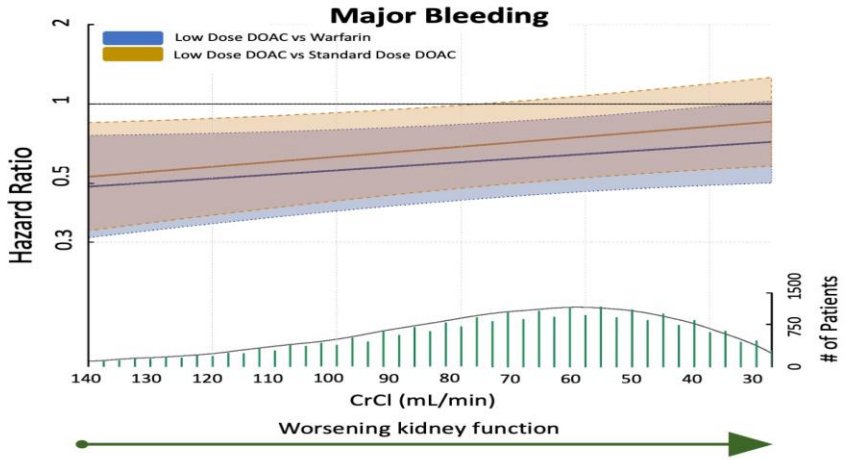

Intracranial Hemorrhage
Interaction p-value = 0.08
Hazard Ratio
2
1
0.5
0.3
140 130 120 110 100 90 80 70 60 50 40 30
CrCl (mL/min)
Worsening kidney function
0 750 1500
# of Patients

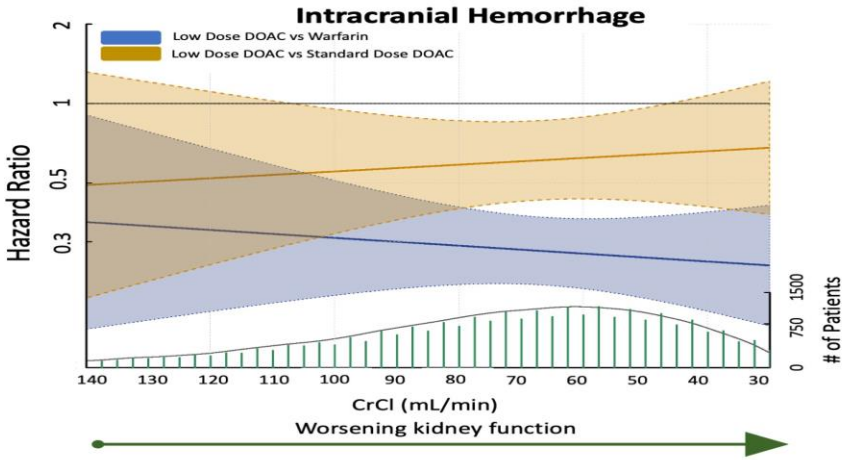

Stroke and Systemic Embolism
Interaction p-value = 0.01
Hazard Ratio
2
1
0.5
0.3
140 130 120 110 100 90 80 70 60 50 40 30
CrCl (mL/min)
Worsening kidney function
0 750 1500
# of Patients

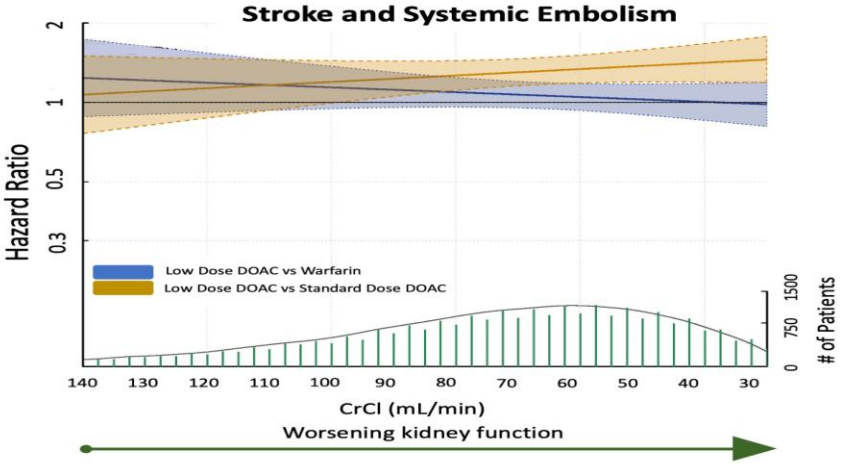

Death
Interaction p-value = 0.08
Hazard Ratio
2
1
0.5
0.3
140 130 120 110 100 90 80 70 60 50 40 30
CrCl (mL/min)
Worsening kidney function
0 750 1500
# of Patients

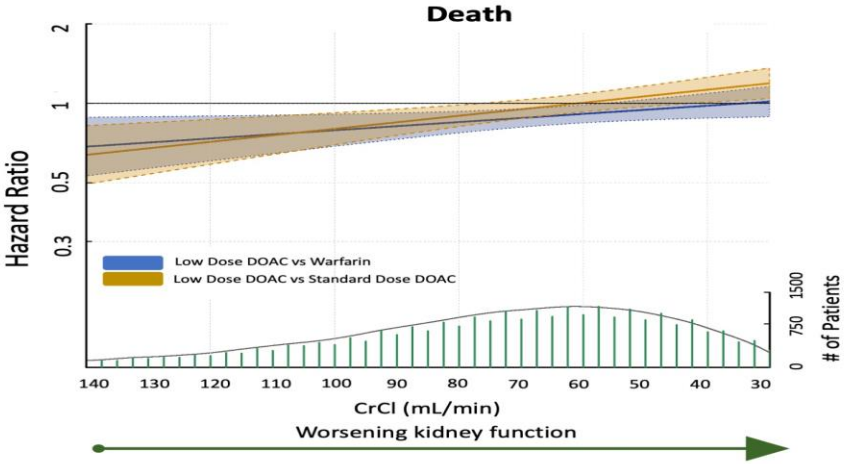
Standard Dose vs Low Dose

weight. Standard-dose DOACs were defined as the standard dose used in ROCKET AF or ARISTOTLE (with trial protocol–specified dose adjustment based on age, weight, and kidney function) and as the DOAC randomization arm with the higher dosing regimen in RE-LY (150 mg of dabigatran twice daily) or ENGAGE AF-TIMI 48 (60 mg of edoxaban once daily or 30 mg once daily for patients meeting trial criteria for dose adjustment). Lower-dose DOACs were defined as the DOAC randomization arm with the lower dosing regimen in RE-LY (110 mg of dabigatran twice daily) or ENGAGE AF-TIMI 48 (30 mg of edoxaban once daily or 15 mg once daily for patients meeting trial criteria for dose adjustment).


Major Bleeding
Low Dose DOAC vs Warfarin
Low Dose DOAC vs Standard Dose DOAC
Hazard Ratio
2
1
0.5
0.3
140 130 120 110 100 90 80 70 60 50 40 30
CrCl (mL/min)
Worsening kidney function
0 750 1500
# of Patients


Intracranial Hemorrhage
Low Dose DOAC vs Warfarin
Low Dose DOAC vs Standard Dose DOAC
Hazard Ratio
2
1
0.5
0.3
140 130 120 110 100 90 80 70 60 50 40 30
CrCl (mL/min)
Worsening kidney function
0 750 1500
# of Patients

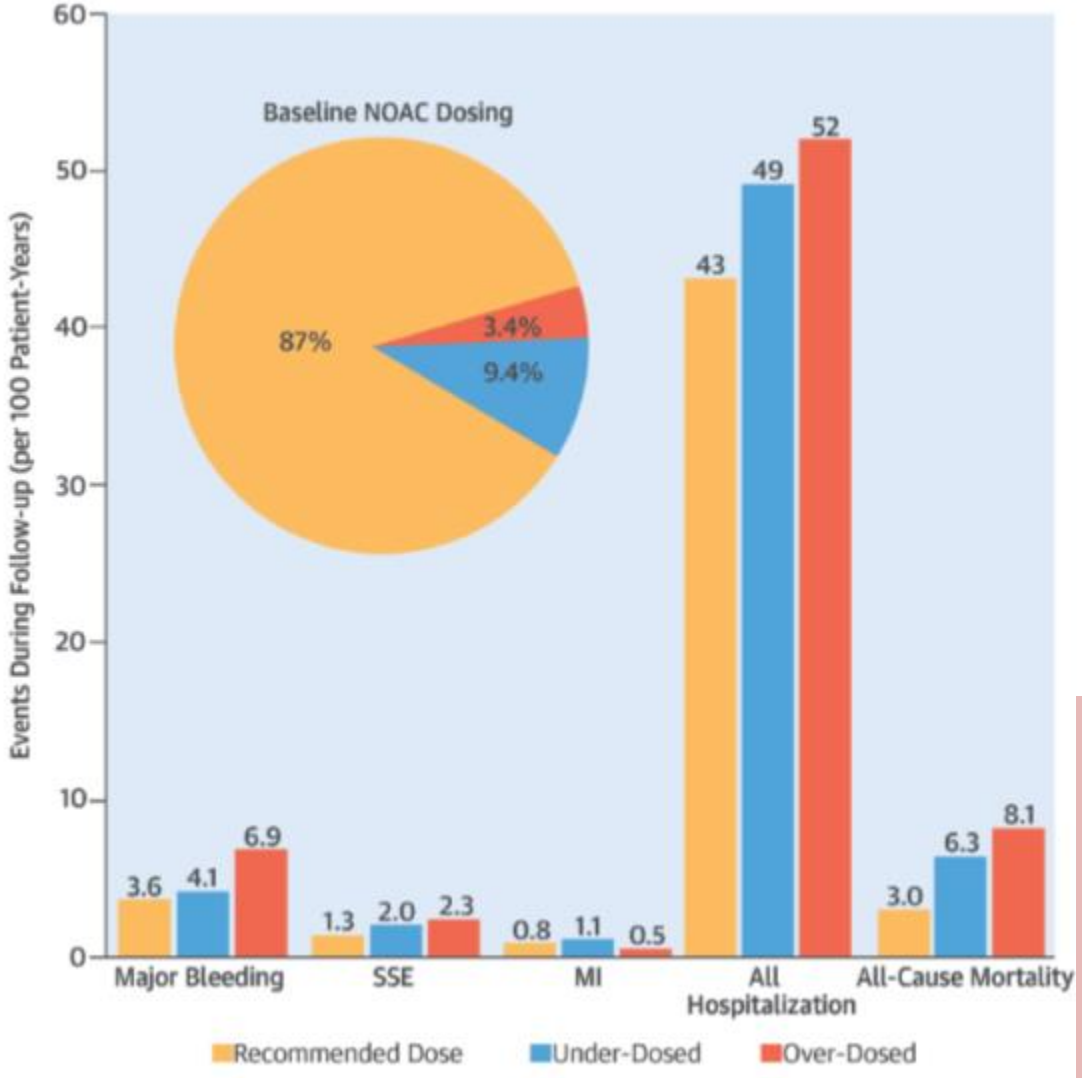

Stroke and Systemic Embolism
Low Dose DOAC vs Warfarin
Low Dose DOAC vs Standard Dose DOAC
Hazard Ratio
2
1
0.5
0.3
140 130 120 110 100 90 80 70 60 50 40 30
CrCl (mL/min)
Worsening kidney function
0 750 1500
# of Patients

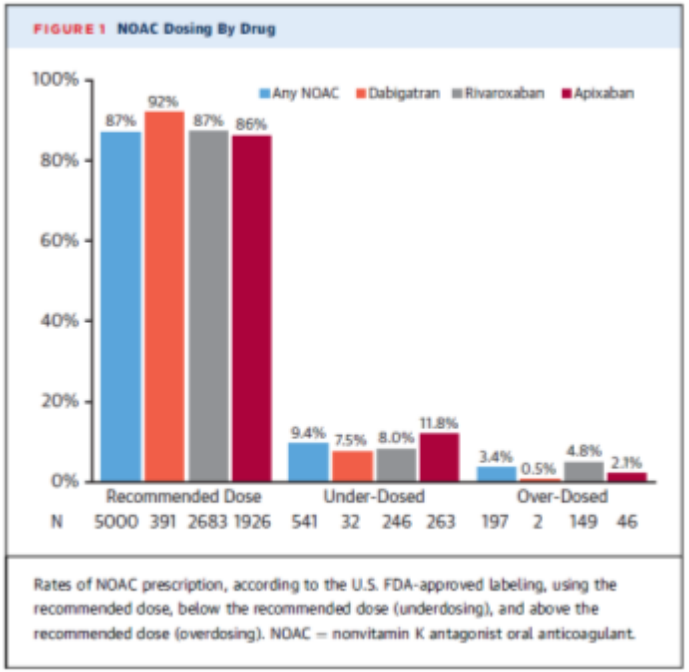

Death
Low Dose DOAC vs Warfarin
Low Dose DOAC vs Standard Dose DOAC
Hazard Ratio
2
1
0.5
0.3
140 130 120 110 100 90 80 70 60 50 40 30
CrCl (mL/min)
Worsening kidney function
0 750 1500
# of Patients

Conclusion

CONCLUSIONS: Standard-dose DOACs are safer and more effective than warfarin down to a CrCl of at least 25 mL/min. Lower-dose DOACs do not significantly lower the incidence of bleeding or ICH compared with standard-dose DOACs but are associated with a higher incidence of S/SE and death. These findings support the use of standard-dose DOACs over warfarin in patients with kidney dysfunction.

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry.





- **A significant minority (almost 1 in 8) of U.S. patients in the community received NOAC doses inconsistent with labeling.**
- **NOAC over- and underdosing are associated with increased risk for adverse events.**

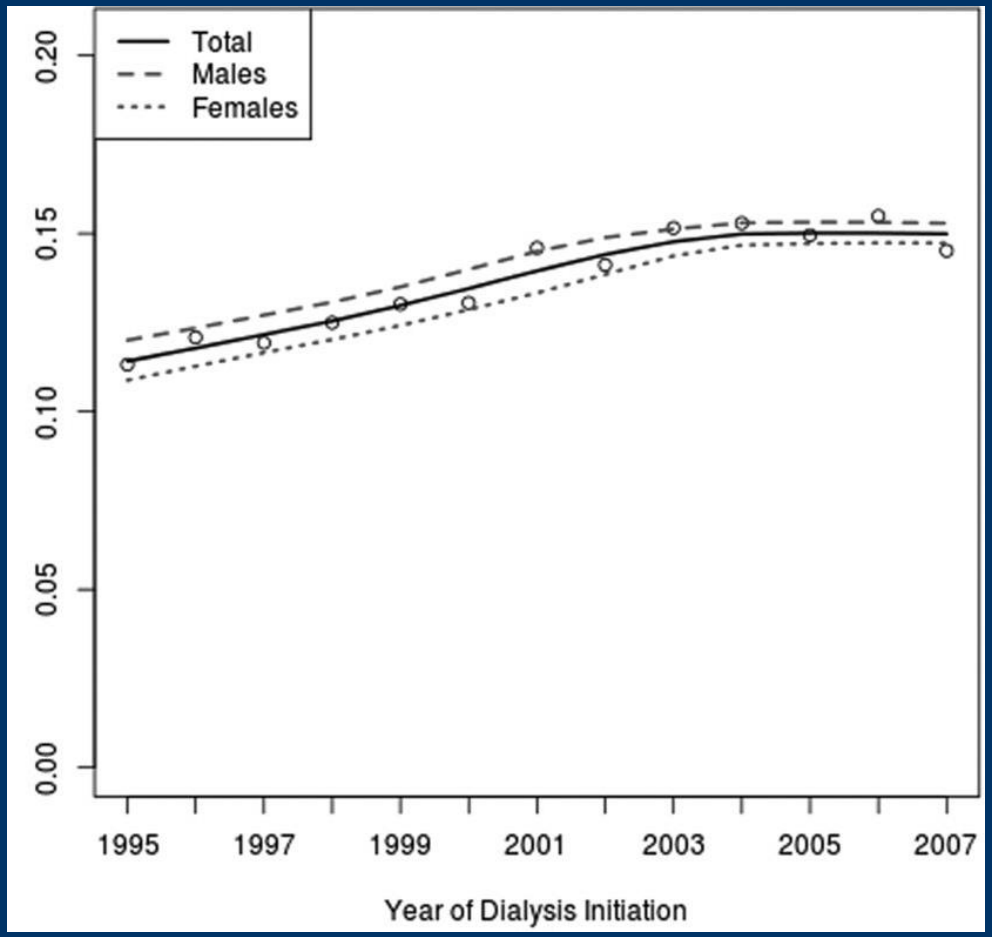
Steinberg BA et al. JACC 2016

Hemodialysis

- Prothrombotic
- Coagulopathic

Incidence of AF in ESRD

- Medicare patients initiating dialysis 1995-2007 without prior AF in last 2 years (N=258,605)
- 29% developed AF prior to death or kidney transplantation
- Probability of developing AF within 1-year of dialysis increased:
  - 11.3% (1995)-14.5% (2007)



Goldstein *Circulation* 2012

CKD and 6-month Mortality

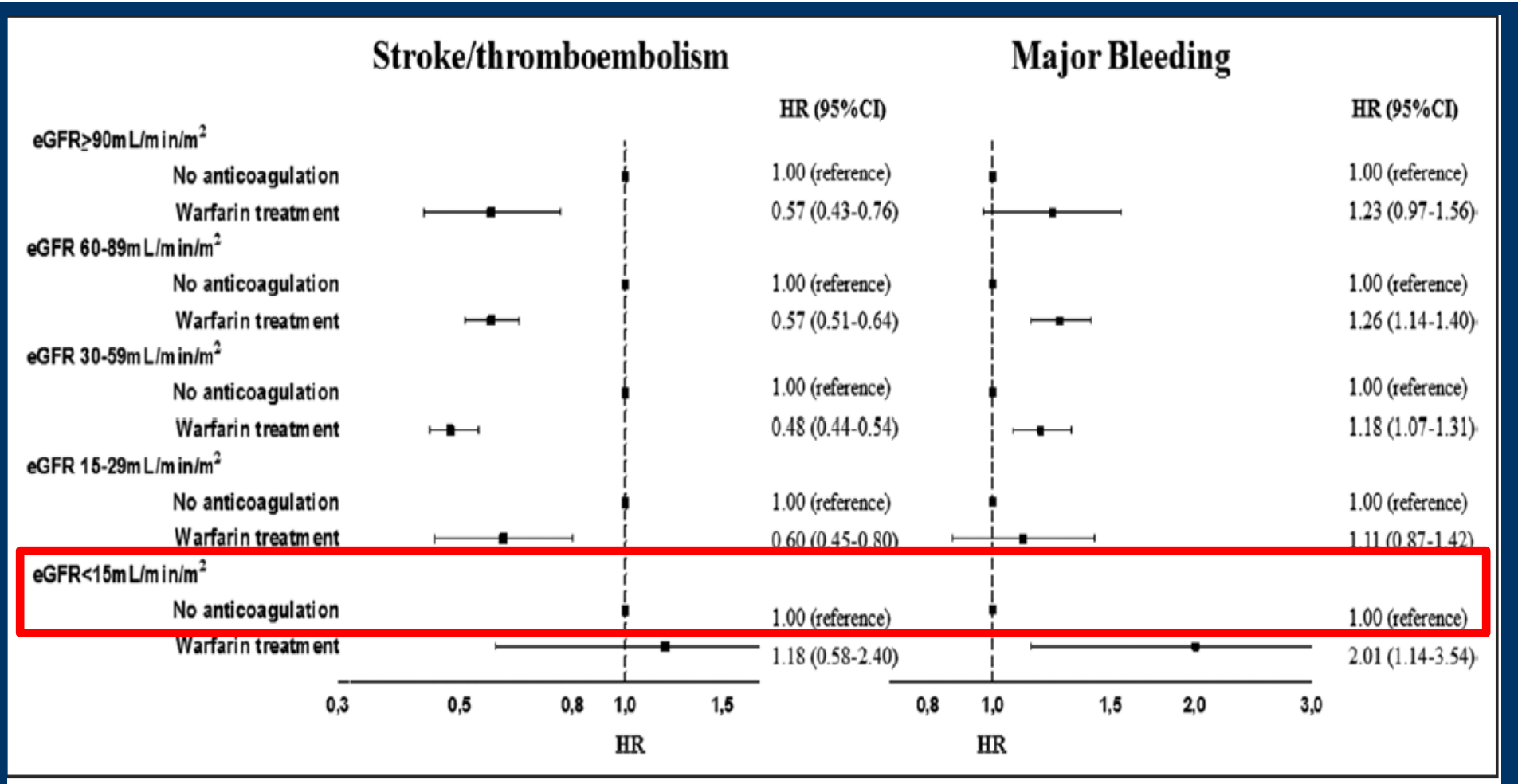
Variable	Regression Coefficient	aOR (95% CI)	*P*	Points
Age category				
65-69 y	0	1.00 (reference)		0
70-74 y	0.0675	1.07 (0.76-1.50)	0.7	0
75-79 y	0.0191	1.02 (0.72-1.43)	0.9	0
≥80 y	0.4493	1.57 (1.13-2.17)	0.007	2
eGFR				
0-9.9 mL/min/1.73 m^2	0	1.00 (reference)		0
10-14.9 mL/min/1.73 m^2	0.2846	1.33 (0.97-1.82)	0.08	1
≥15 mL/min/1.73 m^2	0.9590	2.61 (1.98-3.44)	<0.001	3
Atrial fibrillation				
No	0	1.00 (reference)		0
Yes	0.5694	1.77 (1.36-2.29)	<0.001	2
Congestive heart failure				
No	0	1.00 (reference)		0
Yes	0.4336	1.54 (1.19-2.01)	0.001	2
Lymphoma				
No	0	1.00 (reference)		0
Yes	1.3019	3.68 (2.30-5.89)	<0.001	5
Metastatic cancer				
No	0	1.00 (reference)		0
Yes	0.9671	2.63 (1.53-4.52)	<0.001	3
Hospitalization in prior 6 mo				
No	0	1.00 (reference)		0
Yes	0.4310	1.54 (1.21-1.96)	<0.001	2

Wick *AJKD* 2016

Renal Function and the Risk of Stroke and Bleeding in Patients With Atrial Fibrillation

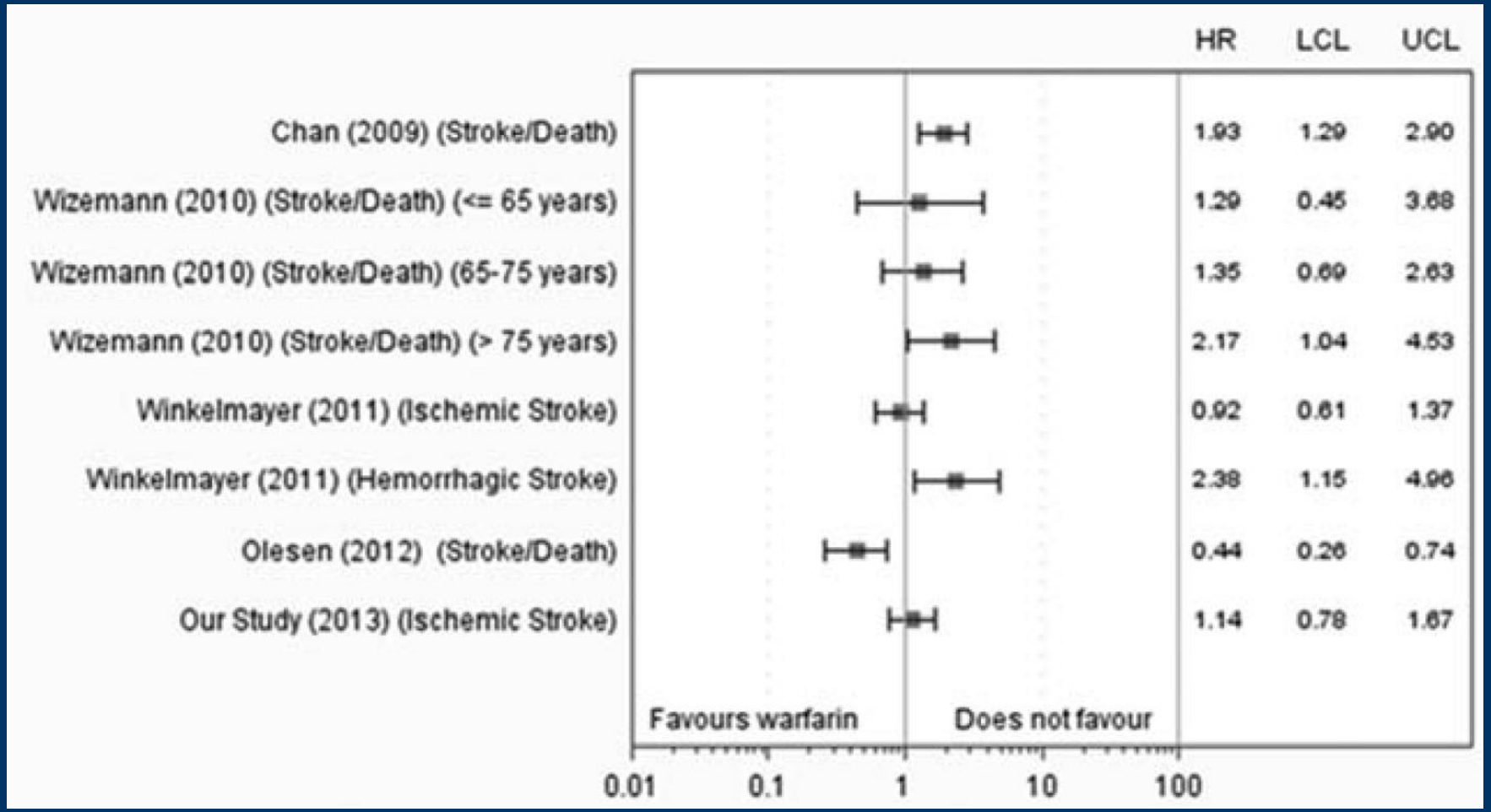
An Observational Cohort Study

Anders Nissen Bonde, MB; Gregory Y.H. Lip, MD*; Anne-Lise Kamper, MD, DMSc; Emil L. Fosbøl, MD, PhD; Laila Staerk, MD; Nicholas Carlson, MD; Christian Torp-Pedersen, MD, DMsC; Gunnar Gislason, MD, PhD; Jonas Bjerring Olesen, MD, PhD*



Stroke. 2016 Nov; 47(11):2707-2713

AF, dialysis, warfarin use in Ontario and Quebec, 1998 to 2007



Shah M et al. *Circulation* 2014.

AF and CKD
To Anticoagulate (VKA) or Not?

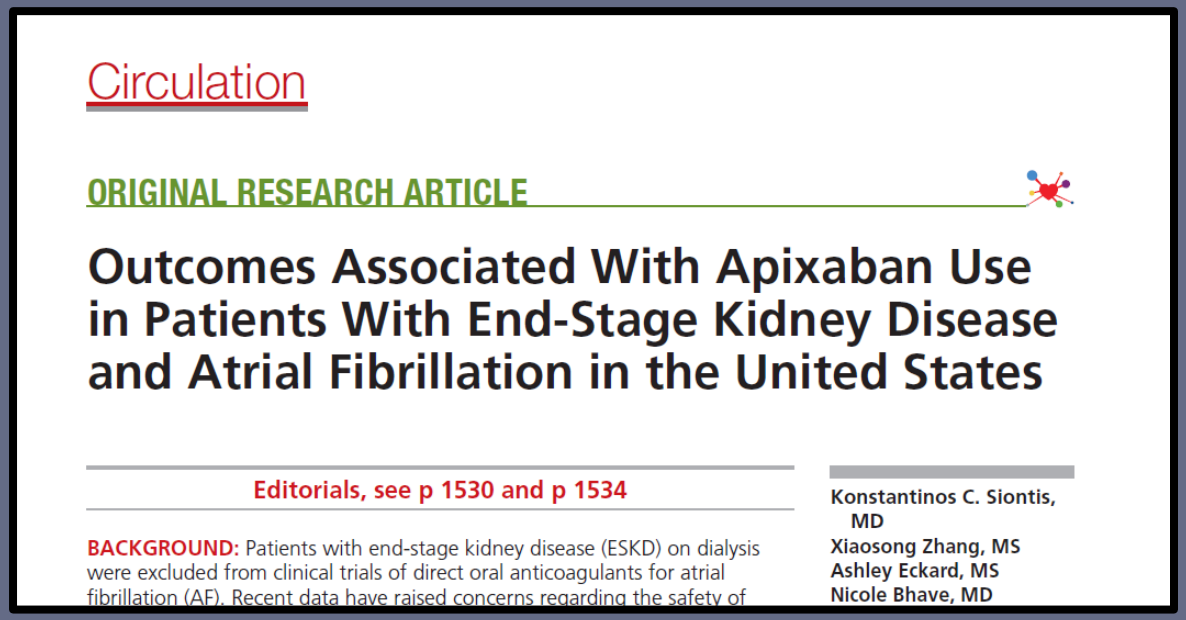
CKD not on dialysis:

- Evidence supporting efficacy of VKA / NOAC in CKD 3
- Some support for its effectiveness in CKD 4 & 5

ESRD on hemodialysis:

- No trials
- Rather conflicting evidence on effectiveness
  - Results dependent on study designs
- Low treatment persistence
- High likelihood of INR excursions/low TTR
- Increased risk of bleeding and vascular calcification
- Very low use of VKA, perhaps reflecting evidence gap

Apixaban in ESRD



Circulation

ORIGINAL RESEARCH ARTICLE

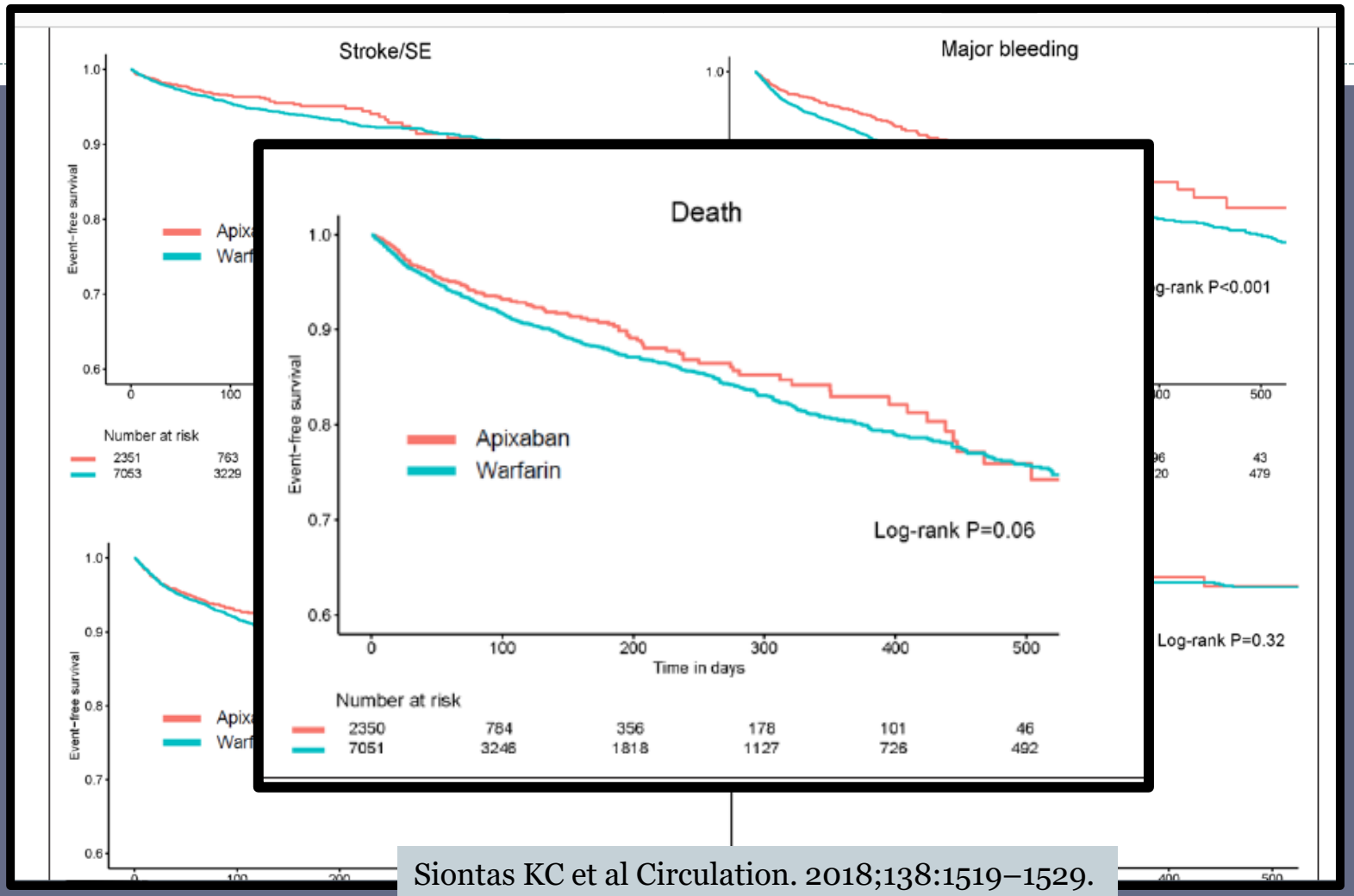
Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

Editorials, see p 1530 and p 1534

Konstantinos C. Siontis, MD
Xiaosong Zhang, MS
Ashley Eckard, MS
Nicole Bhave, MD

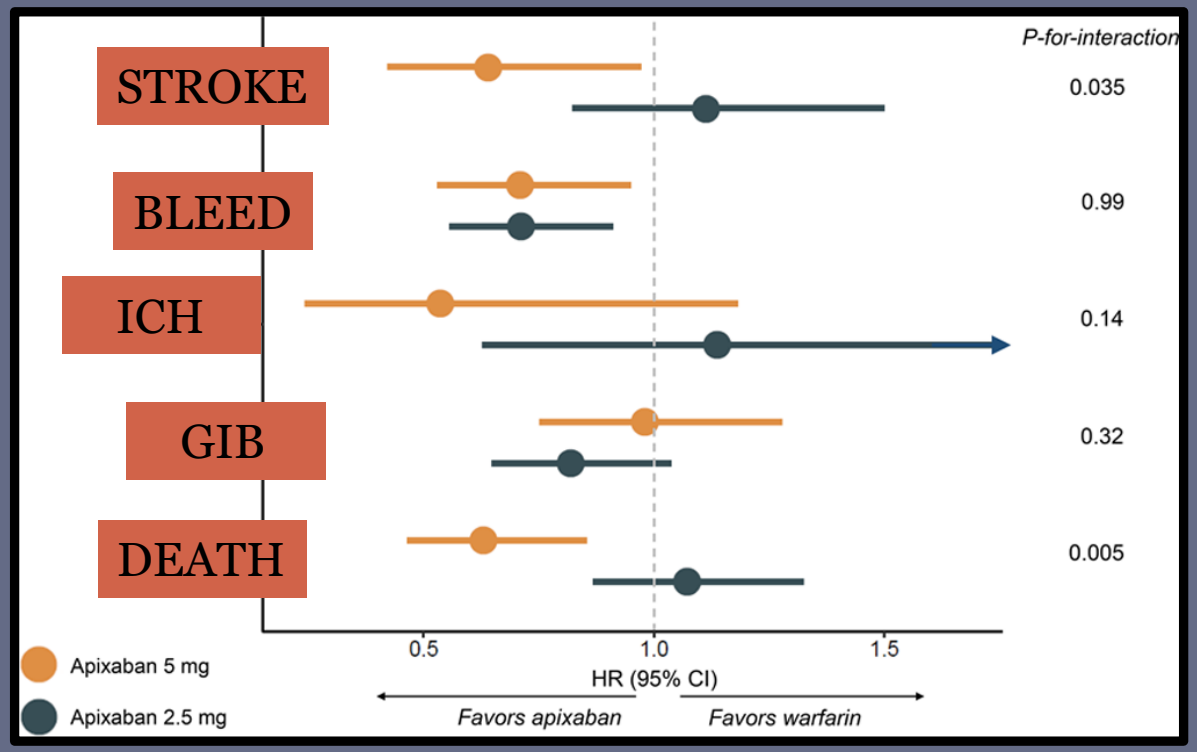
BACKGROUND: Patients with end-stage kidney disease (ESKD) on dialysis were excluded from clinical trials of direct oral anticoagulants for atrial fibrillation (AF). Recent data have raised concerns regarding the safety of

Siontas KC et al Circulation. 2018;138:1519–1529.



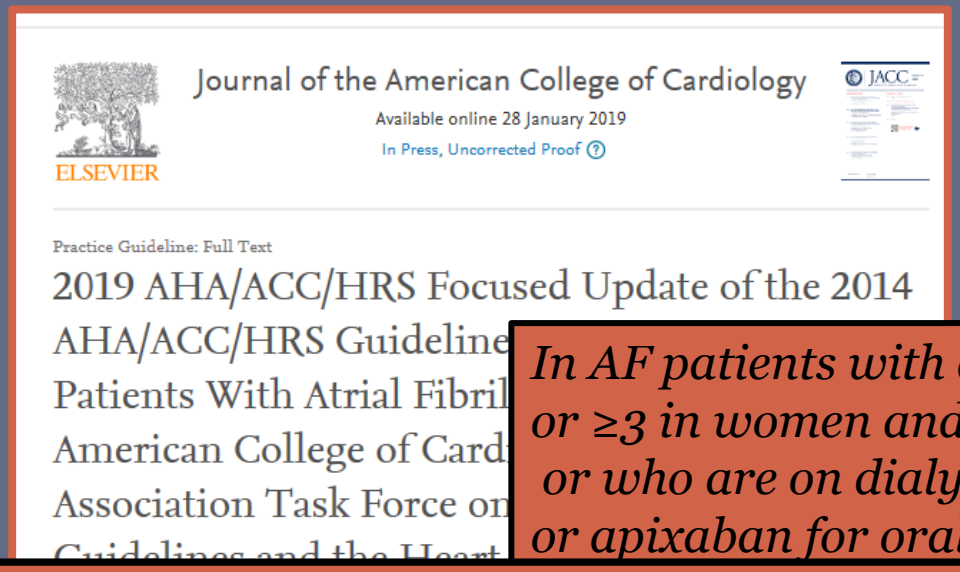
Siontas KC et al Circulation. 2018;138:1519–1529.

Apixaban in ESRD



Siontas KC et al Circulation. 2018;138:1519–1529.

2019 AHA/ACC/HRS AFIB Guidelines



Journal of the American College of Cardiology

Available online 28 January 2019

In Press, Uncorrected Proof

ELSEVIER

Practice Guideline: Full Text

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline

Patients With Atrial Fibril

American College of Card

Association Task Force on

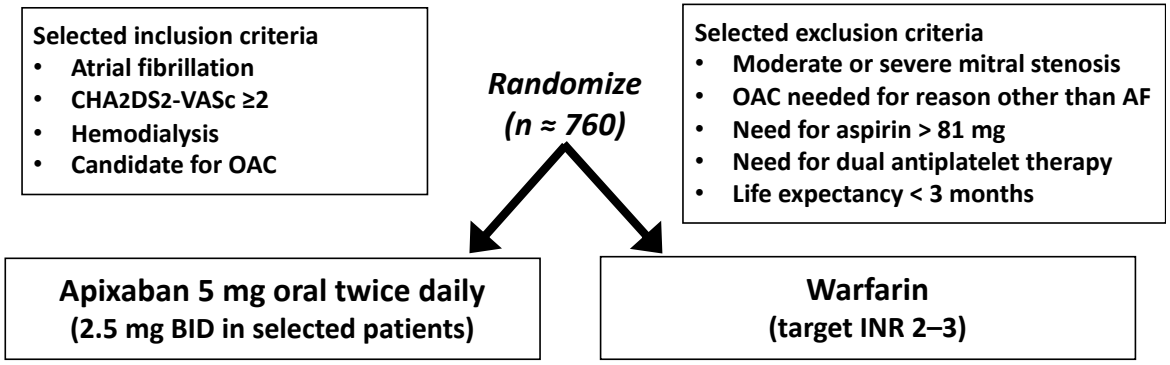
In AF patients with a CHA2DS2-VASc score ≥2 in men or ≥3 in women and a creatinine clearance <15 ml/min or who are on dialysis, it is reasonable to use warfarin or apixaban for oral anticoagulation

EHRA-routine use of NOACs best avoided in CrCl < 15 ml/min & HD; given lack of strong evidence for VKA decision to anticoagulate remains an individualized one

Wanns J et al. J Amer Coll Cardiol 2019 Jan 28

There is equipoise regarding warfarin use in AF and HD, and lack of any meaningful randomized data to guide care

Original Study Design



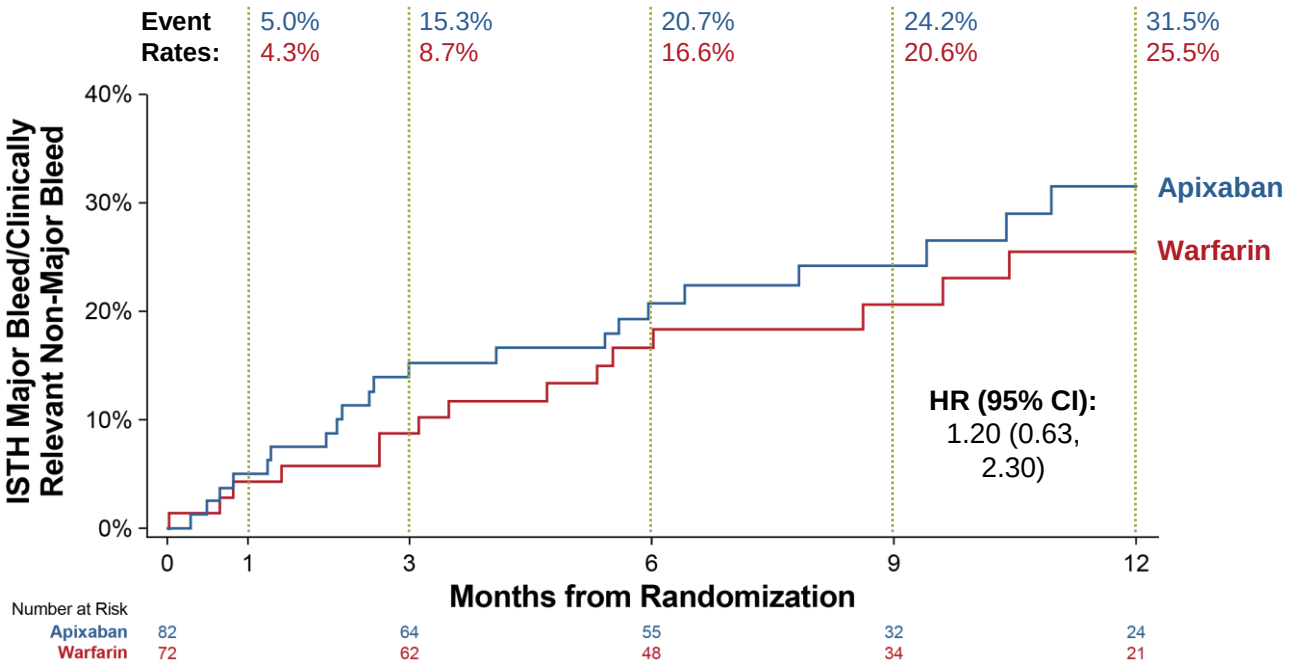
Open label with blinded event adjudication

Primary outcome: ISTH major and clinically relevant non-major bleeding

Secondary outcomes:

- ***PK in patients randomized to apixaban***
- ***Stroke and systemic embolism***
- ***Death***
- ***Tolerability/persistence/adherence parameters***

Time to Major or Clinically Relevant Non-Major Bleed for Intention to Treat



Conclusions

- We are in a new era of anticoagulation for atrial fibrillation
- We need to embrace this era
- Patients with AF are still at risk even when treated with traditional therapies. Thus, ensuring that all eligible AF patients receive an appropriate anticoagulant according to assessment of stroke and bleeding risk and patient preferences is critically important
- The new oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) are all safe and effective and all have important advantages over warfarin
- Compared to warfarin, the risk of fatal bleeding was lower with NOACs in large RCTs

Conclusions

- In patients with AF, CKD and especially ESRD on HD, is a strong predictor of both thrombosis and bleeding
- In patients with AF and CKD (not on HD)
  - OAC is beneficial
  - NOACs are better than VKAs
  - The issue is getting dosing and monitoring (Cr) right
  - Standard dose should be used. Remember - we can adjust the dose, but should not lower the dose!!!
- In patients with AF and ESRD on HD
  - Outcomes are terrible
  - The benefits of OAC is not established
  - Increased bleeding and risk of vascular calcification are well established
  - We desperately need RCTs to guide practice in these patients

Thank you!

Duke Clinical Research Institute

From Thought Leadership to Clinical Practice

Duke Clinical Research Institute

From Thought Leadership to Clinical Practice

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