Séminaire
Winter Arrhythmia
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Annual Cardiac Arrhythmia Meeting
Division of Cardiology, University of Toronto

Oral Anticoagulation Update in Atrial Fibrillation

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February 11, 2017

14th Annual
Collingwood, Ontario,
February 10 -12, 2017

Disclosures

- Relationships with commercial interests:
  - Speakers Bureau/Honoraria: Servier, Boehringer Ingelheim.
  - Research support: BMS; Pfizer; Bayer.

- I will be discussing off-label use of approved products.

Learning Objectives

- To examine “real-world” NOAC outcomes and safety data

- To discuss OAC in the context of valvular heart disease and renal dysfunction

Terminology

- NOAC
  - "Novel/New" oral anticoagulant
  - "Non-vitamin K" oral anticoagulant

- DOAC
  - "Direct" oral anticoagulant

Interchangeable in clinical practice and research setting

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ELSEVIER

Canadian Journal of Cardiology ■ (2016) 1–16

Society Guidelines

2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

Laurent Macle, MD (Co-chair),[a] John Cairns, MD,[b] Kori Leblanc, PharmD,[c] Teresa Tsang, MD,[b] Allan Skanes, MD,[d] Jafna L. Cox, MD,[e] Jeff S. Healey, MD,[f] Alan Bell, MD,[g] Louise Pilote, MD,[h] Jason G. Andrade, MD,[a] L. Brent Mitchell, MD,[i] Clare Atzema, MD,[j] David Gladstone, MD,[j] Mike Sharma, MD,[f,k] Subodh Verma, MD,[l] Stuart Connolly, MD,[f] Paul Dorian, MD,[l] Ratika Parkash, MD,[e] Mario Talajic, MD,[a] Stanley Nattel, MD,[a] and Atul Verma, MD (Co-chair);[m] for the CCS Atrial Fibrillation Guidelines Committee*

14th Annual
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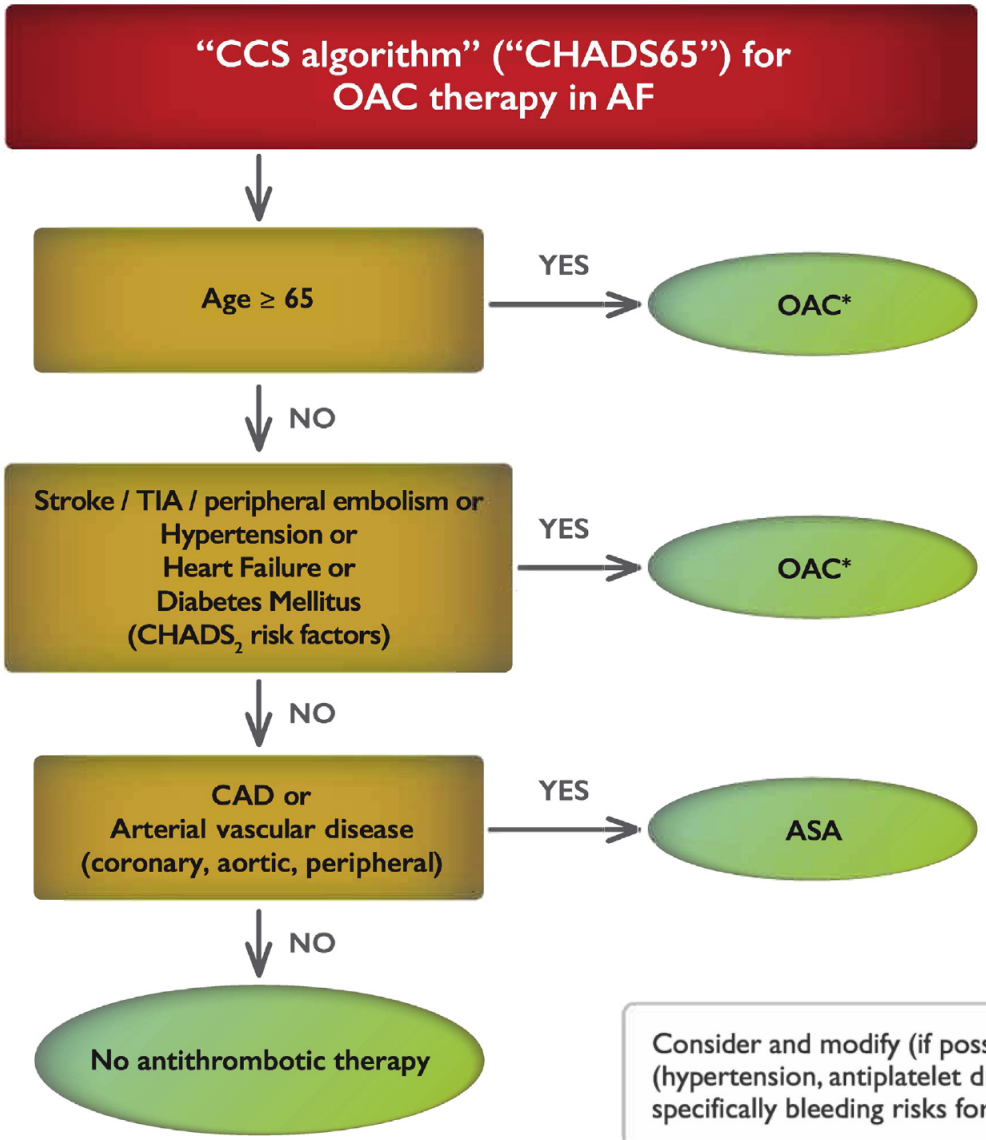
Macle et al. CJC 2016; 32: 1170-1185.



Consider and modify (if possible) all factors influencing risk of bleeding during OAC treatment (hypertension, antiplatelet drugs, NSAIDs, corticosteroids, excessive alcohol, labile INRs) and specifically bleeding risks for NOACs (low creatinine clearance, age ≥ 75, low body weight)†

*A NOAC is preferred over warfarin for non-valvular AF

Macle et al. CJC 2016; 32: 1170-1185.

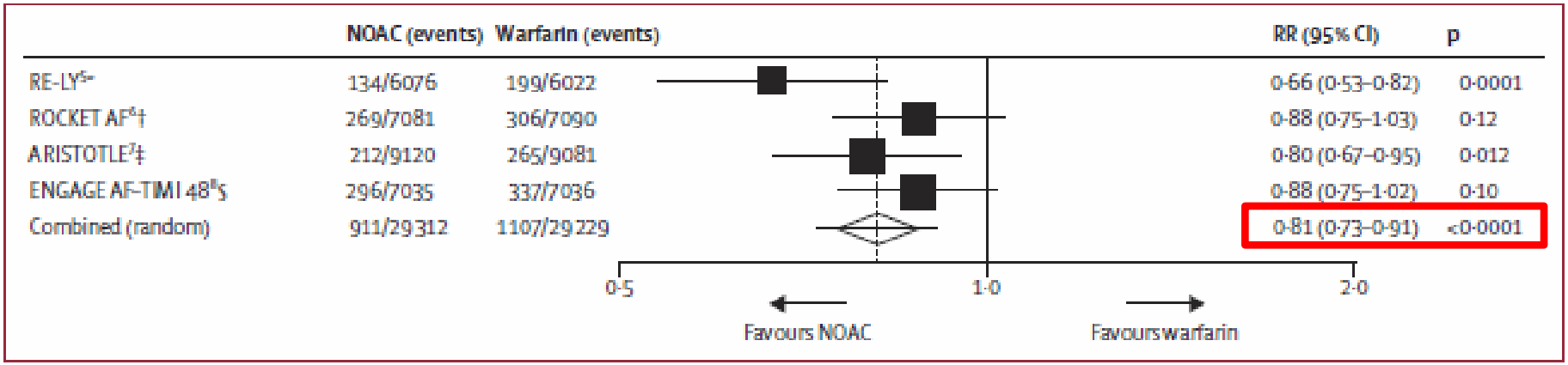
Novel OACs vs. Warfarin Summary

	DABIGATRAN 110 VS. WARFARIN[1]	DABIGATRAN 150 VS. WARFARIN[1]	RIVAROXABAN VS. WARFARIN[2]	APIXIBAN VS. WARFARIN[3]	EDOXABAN 30 VS. WARFARIN[4]	EDOXABAN 60 VS. WARFARIN[4]
Stroke/SE	9% ↓	34% ↓	12% ↓	21% ↓	13% ↑	13% ↓
Major Bleed	20% ↓	7% ↓	4% ↑	58% ↓	53% ↓	20% ↓
ICH	69% ↓	60% ↓	33% ↓	49% ↓	70% ↓	53% ↓
GI Bleeding	10% ↑	50% ↑	61% ↑	11% ↓	33% ↓	23% ↑
All Cause Death	9% ↓	12% ↓	8% ↓	11% ↓	13% ↓	8% ↓

[1]Connolly et al. NEJM 2009; 361: 1139 – 51
[2]Patel et al. NEJM 2011; 365: 883 – 91
[3]Granger et al. NEJM 2011; 365: 981 – 92
[4]Guigliano et al. NEJM 2013; 369: 2093 - 104

NOACs are better at preventing strokes…

Stroke or systemic embolic events

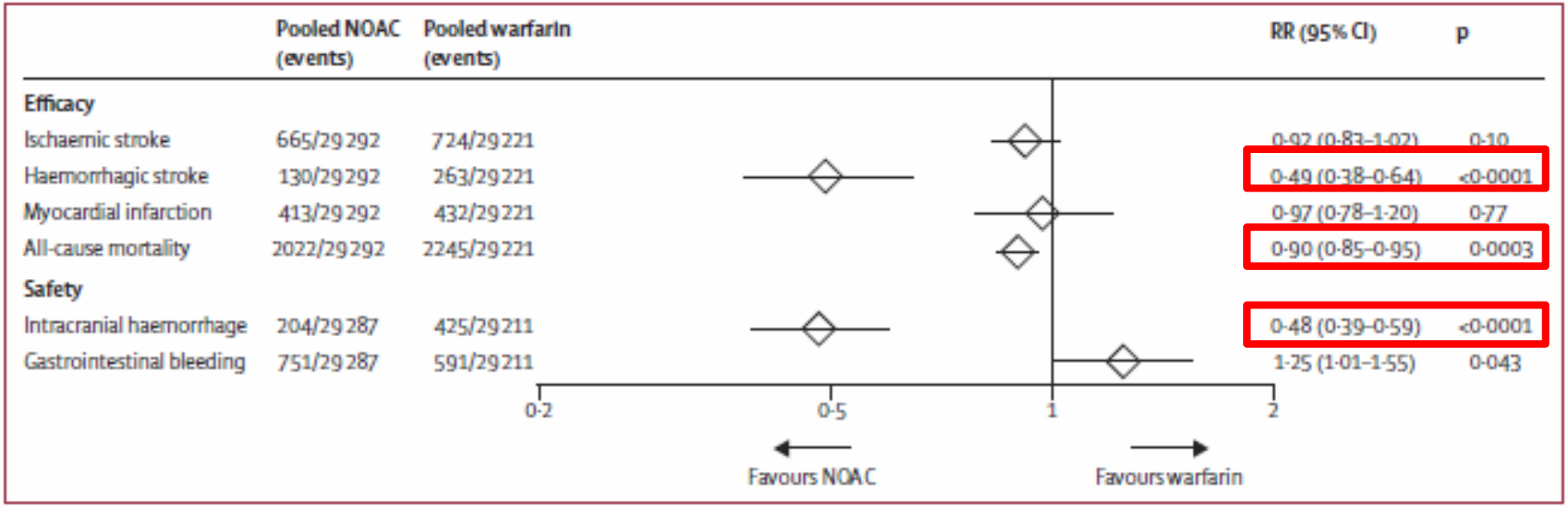


NOACs ↓ stroke and systemic embolic events by 19% compared with warfarin
ARR = 0.007 NNT = 147

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

…with lower ICH and mortality

Secondary efficacy and safety outcomes

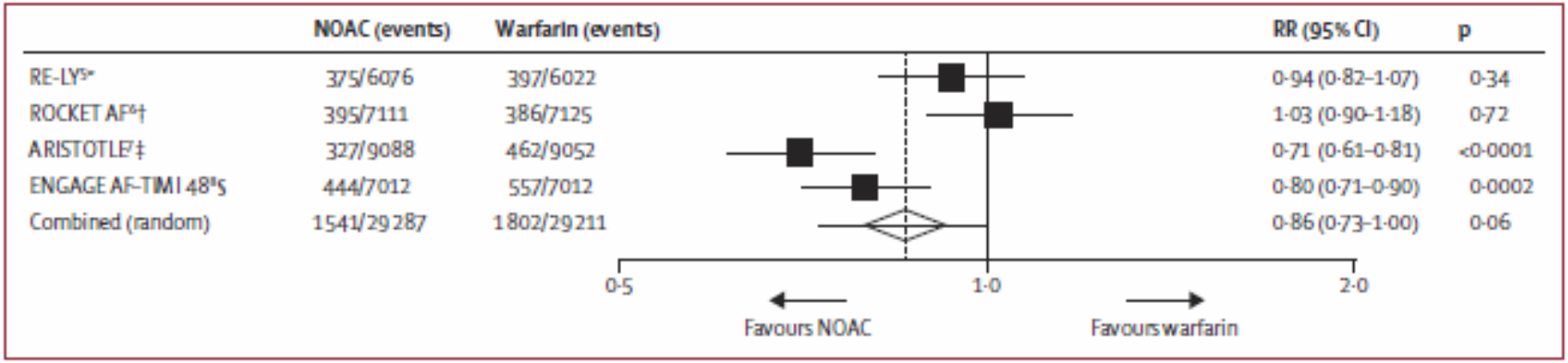


NOACs ↓ haemorrhagic stroke by 51% compared with warfarin
ARR = 0.005 NNT = 219
NOACs ↓ ICH by 52% compared with warfarin
ARR = 0.008 NNT = 132
NOACs ↓ all cause mortality by 10% compared with warfarin
ARR = 0.008 NNT = 128

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

…with a trend towards less bleeding

Major bleeding



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

"Real-Life" Data and NOACs

Clinical Trials Versus Real-World Observation

Randomized Clinical Trial Data: Interventional, Controlled		Real-World Data: Non-Interventional, Observational
The standard for assessing efficacy of safety of novel therapies	vs	Describes treatment practices/ outcomes in a real world population and may inform temporal trends and safety

Most important difference: Treatment allocations are *random* in clinical trials, and *individualized* in the real-world clinical environment

• Prospective with rigorous inclusion and exclusion criteria that promote homogeneity	• Retrospective or prospective with limited inclusion or exclusion criteria that promote inclusiveness
• Randomized and powered to evaluate key endpoints	• Potential for incomplete reporting
• Hypothesis driven	• Hypothesis generating
• Audit, training and quality control; independent endpoint adjudication	• Only some have audit, training and quality control; independent endpoint adjudication

	Efficacy study	Effectiveness study
Question	Does the intervention work under ideal circumstance?	Does the intervention work in real-world practice?
Setting	Resource-intensive 'ideal setting'	Real-world everyday clinical setting
Study population	Highly selected, homogenous population Several exclusion criteria	Heterogeneous population Few to no exclusion criteria
Providers	Highly experienced and trained	Representative usual providers
Intervention	Strictly enforced and standardized No concurrent interventions	Applied with flexibility Concurrent interventions and cross-over permitted

Explanatory trials

Pragmatic trials

Efficacy and effectiveness exist in a continuum

Singal et al. Clin and Transl Gastro 2014; 5: e45

Registries

- Potential for selection bias high
- Usually prospective
- Large sample size
- High level patient detail
- Outcomes typically pre-specified and adjudicated
- Higher cost

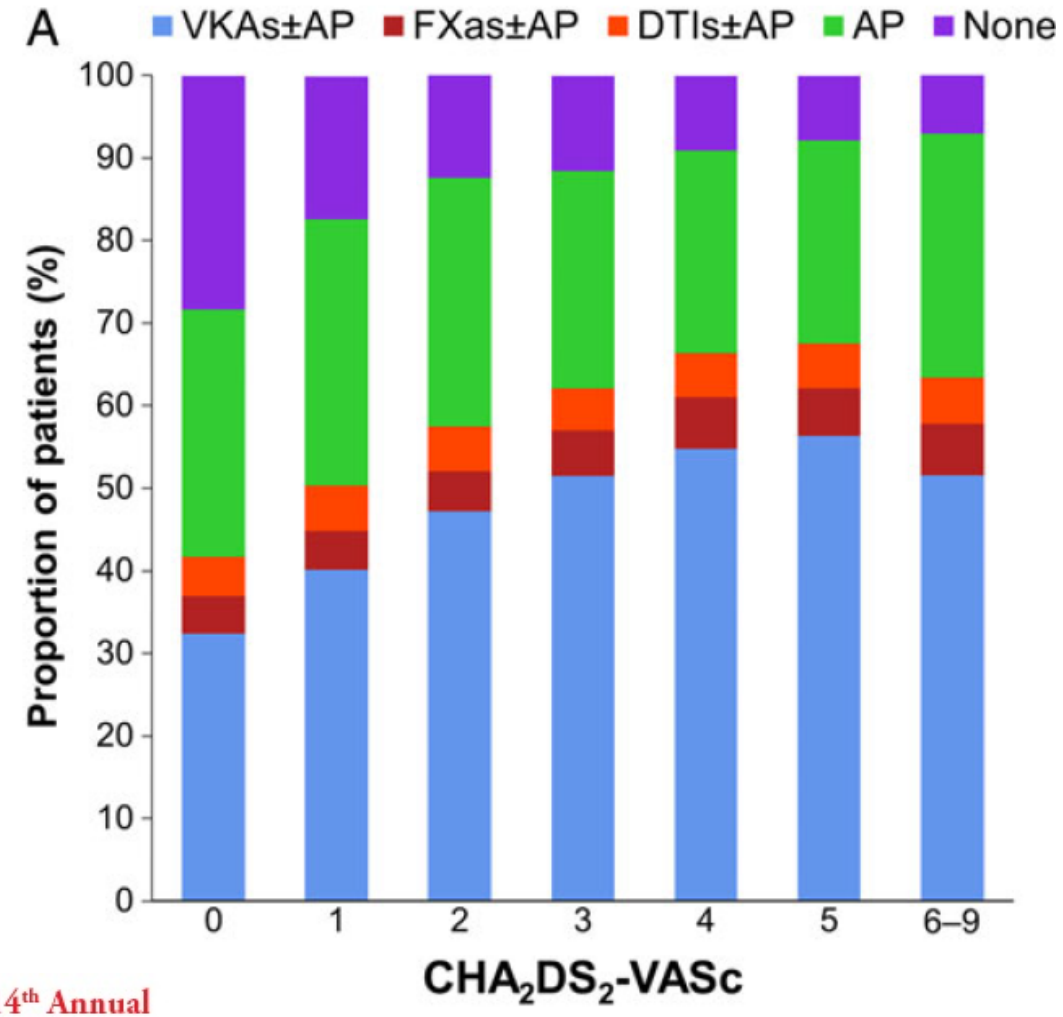
Administrative Data

- Potential for selection bias low (population-based)
- Usually retrospective
- Very large sample size
- Less patient detail
- Outcome data is not adjudicated and often lagging
- Lower cost

“Real-world” Data

Guideline-indicated OAC use must be high by now?

OAC is still underutilized



- GARFIELD-AF is an ongoing global registry of adults with newly dx NVAF
- 2 year outcomes in 17 162 pts
- Overall OAC use 60.8%
- **OAC not prescribed in 36.9% of patients with a CHA_2DS_2-VASc ≥ 2**

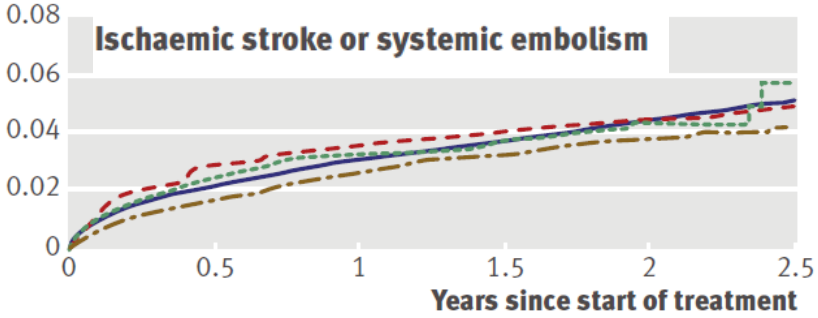
Bassand J-P et al. *EHJ* 2016;37:2882-2889

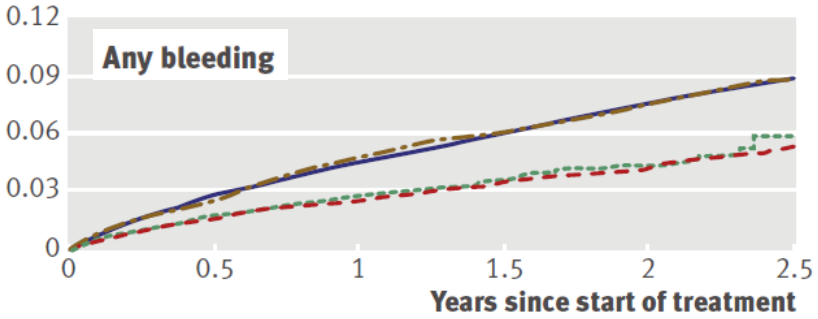
“Real-world” Data

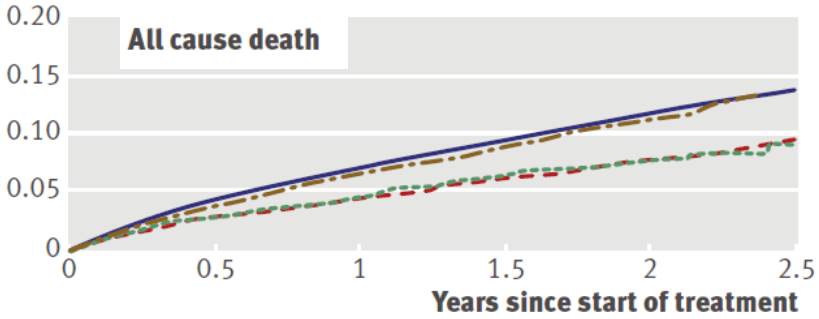
Effectiveness and Safety of
Warfarin vs. NOACs

Comparative Effectiveness and Safety – NOACs vs. Warfarin

- Danish Nationwide Databases 2011-2015
- 61 678 NVAF pts naïve to OAC and no prior indication for OAC
- Warfarin, n=35 436 (57%)
- Dabigatran 150 mg, n=12 701 (21%)
- Rivaroxaban 20 mg, n=7192 (12%)
- Apixaban 5 mg, n=6349 10%)

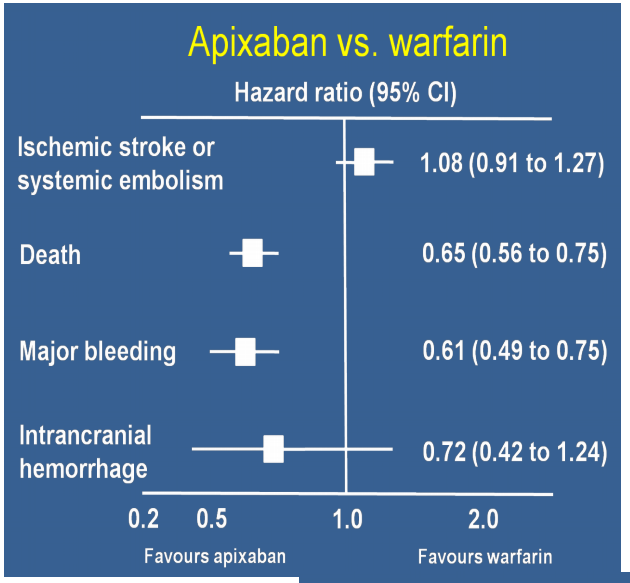


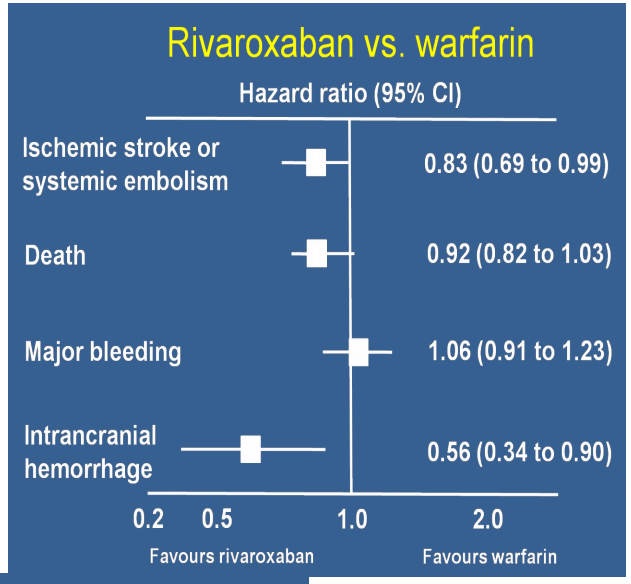


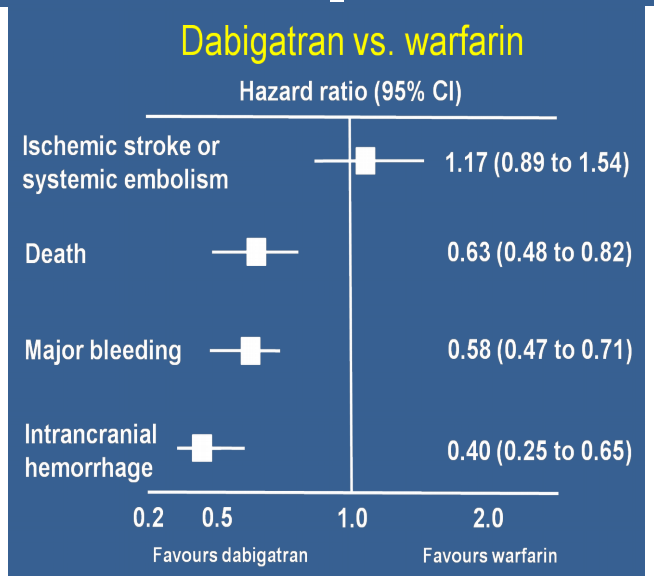


Larsen et al. BMJ 2016; 353: 1-9

Comparative Effectiveness and Safety – NOACs vs. Warfarin



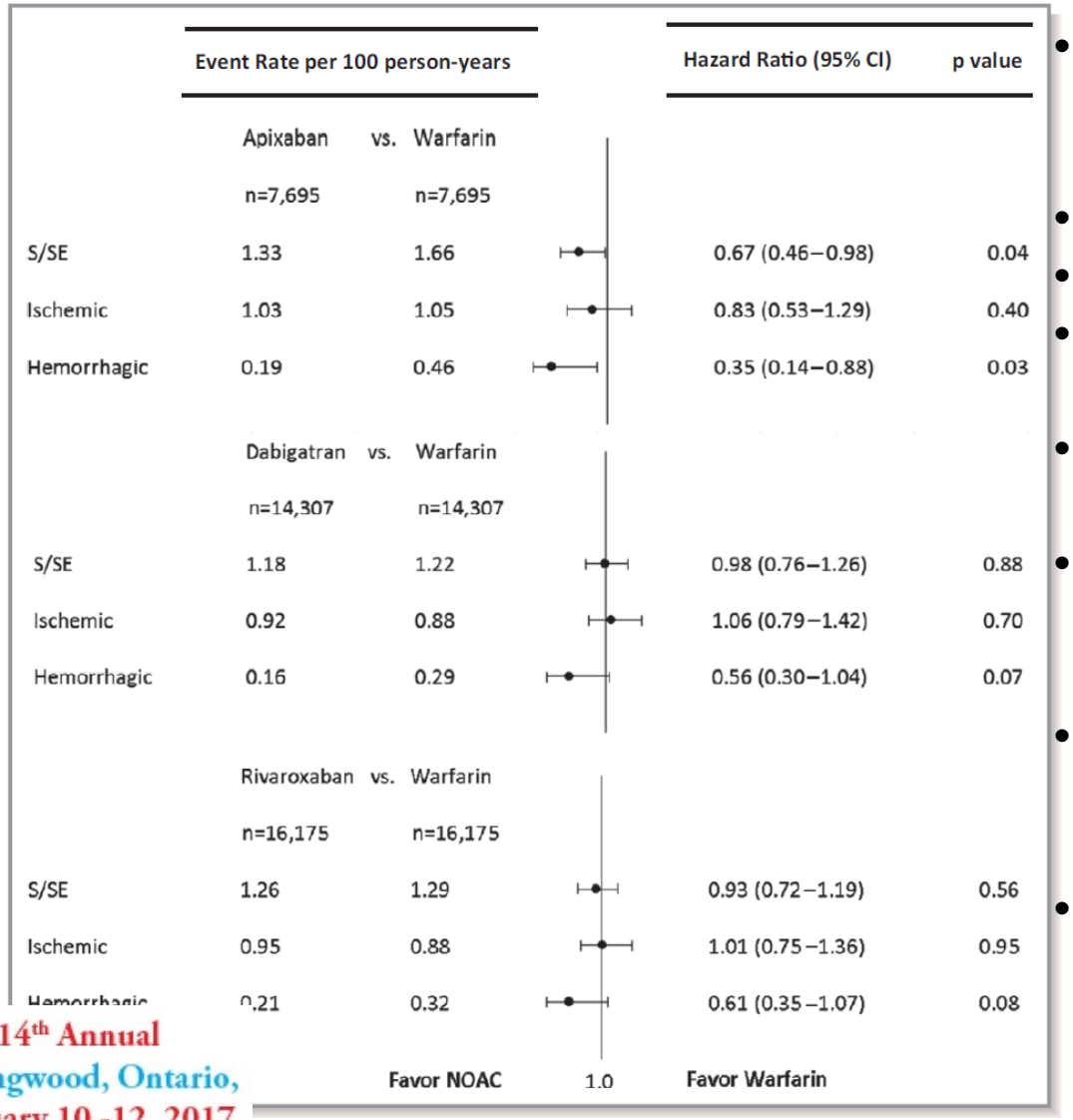




- All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting
- No significant diff was found between NOACs and warfarin for ischaemic stroke.
- The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin

Larsen et al. BMJ 2016; 353: 1-9

Effectiveness and Safety of NOACs and Warfarin



- Propensity matched study in large US claims database
- Apixaban vs warfarin (n=15 390)
- Dabigatran vs warfarin (n=28 614)
- Riva vs warfarin (n=32 350)
- Compared with warfarin:
- Apixaban was associated with lower risks of stroke
- Dabigatran was associated with similar risk of stroke
- Rivaroxaban was associated with similar risks of both stroke

Yao et al. JAHA 2016; 7-18

Effectiveness and Safety of NOACs and Warfarin

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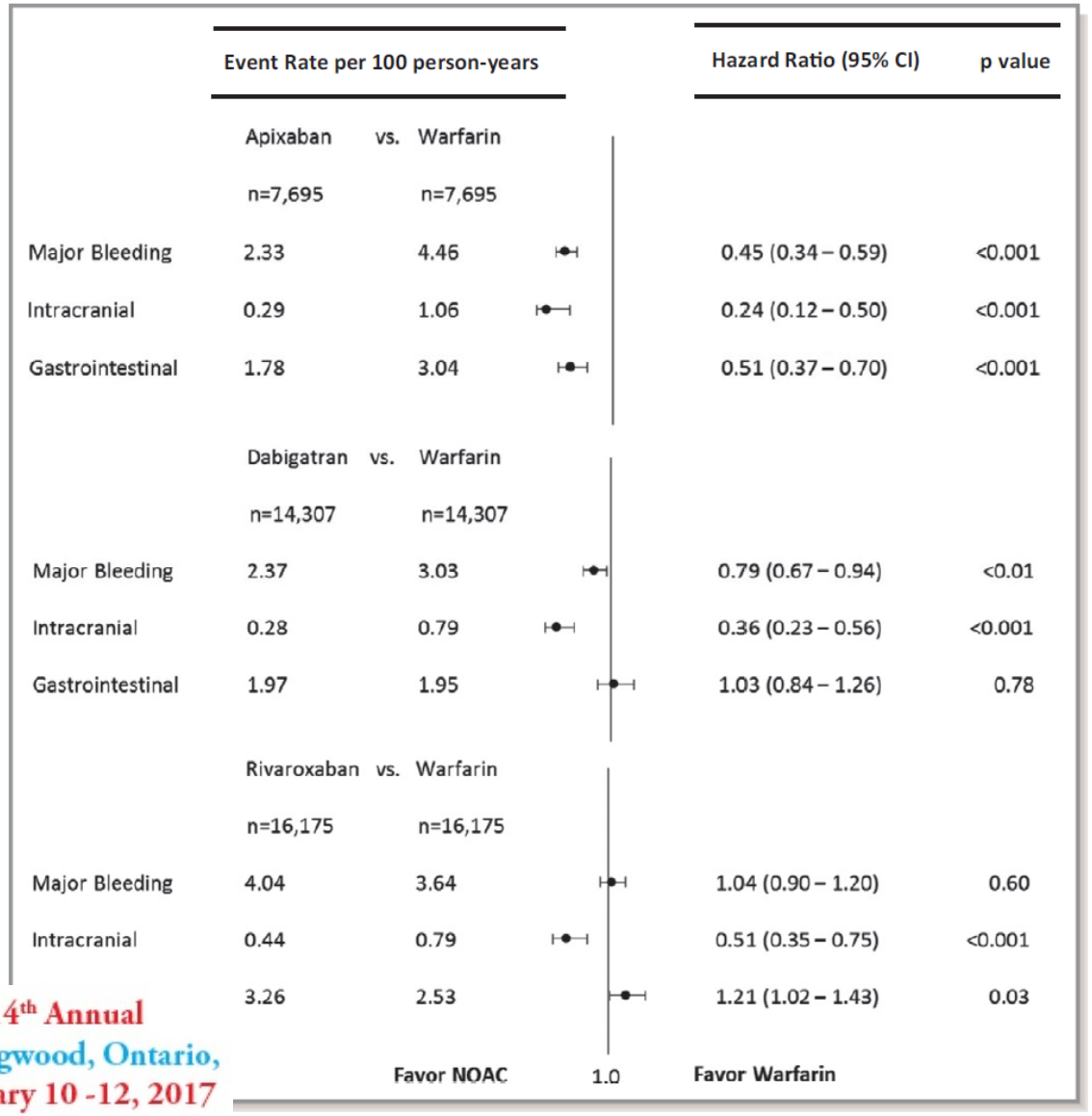


- Compared to warfarin:
- Apixaban was associated with lower risks major bleeding
- Dabigatran was associated lower risk of major bleeding
- Rivaroxaban was associated with similar risks of major bleeding

Yao et al. JAHA 2016; 7-18

Bleeding and NOACs

Table 2 **Oral anticoagulant follow-up time and number (percentage) of patients experiencing a first time bleeding episode after initiating oral anticoagulant (subsequent bleeding episodes not considered) for the different bleeding endpoints**

	Warfarin (n = 11 427)	Dabigatran (n = 7925)	Rivaroxaban (n = 6817)	Apixaban (n = 6506)	Total (n = 32 675)
Follow-up time (days), median (25th–75th percentile)	156 (84–309)	212 (97–413)	209 (105–410)	143 (73–247)	173 (84–340)
Major or CRNM bleeding:	824 (7.21)	407 (5.14)	578 (8.48)	272 (4.18)	2081 (6.37)
Severity					
Major bleeding	181 (1.58)	80 (1.01)	109 (1.60)	49 (0.75)	419 (1.28)
CRNM bleeding	643 (5.63)	327 (4.13)	469 (6.88)	223 (3.43)	1662 (5.09)
Organ system					
GI bleeding	199 (1.74)	150 (1.89)	175 (2.57)	70 (1.08)	594 (1.82)
ICH bleeding	90 (0.79)	28 (0.35)	63 (0.92)	26 (0.40)	207 (0.63)
Other bleeding	535 (4.68)	229 (2.89)	340 (4.99)	176 (2.71)	1280 (3.92)

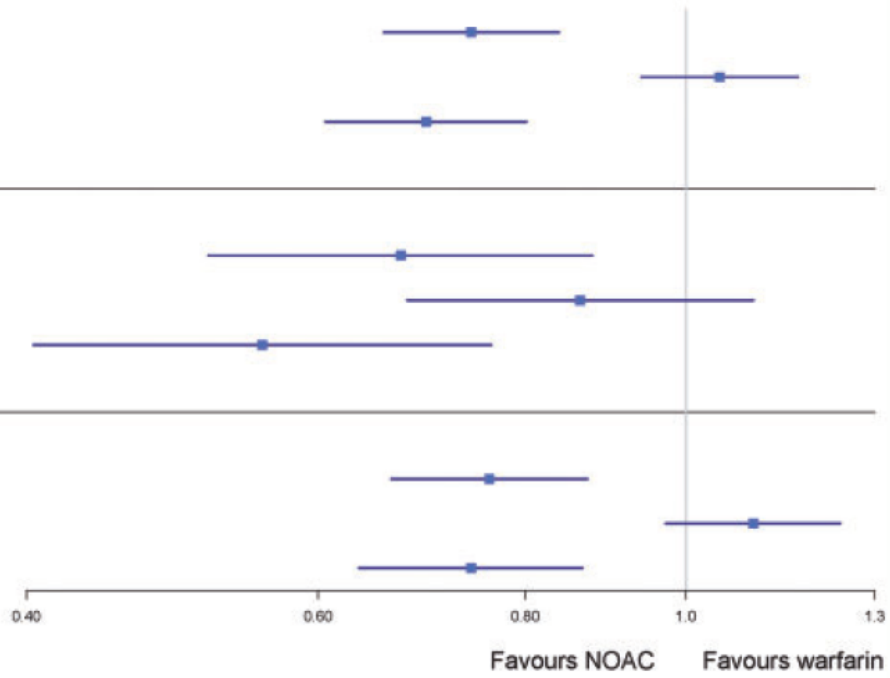
CRNM, Clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage.

- Norwegian Patient Registry and Norwegian Prescription Database
- Major bleeding – any bleeding in critical organ or bleeding requiring transfusion
- CRNM bleeding – any bleeding requiring intervention, leading to hospitalization or increased level of care that did not meet major bleeding
- 32 675 AF pts Jan 2013 – June 2015

Halvorsen et al. European Heart J CV Pharm 2017; 3: 28-36

Bleeding and NOACs

OAC	IR	HR (95%CI)	P
Major or CRNM			
Warfarin	11.44	1 (ref.)	
Dabigatran	6.74	0.74 (0.66,0.84)	<0.001
Rivaroxaban	11.43	1.05 (0.94,1.17)	0.400
Apixaban	8.58	0.70 (0.61,0.80)	<0.001
Major			
Warfarin	2.42	1 (ref.)	
Dabigatran	1.29	0.67 (0.52,0.88)	0.004
Rivaroxaban	2.07	0.86 (0.68,1.10)	0.231
Apixaban	1.51	0.56 (0.40,0.76)	0.001
CRNM			
Warfarin	8.85	1 (ref.)	
Dabigatran	5.38	0.76 (0.66,0.87)	<0.001
Rivaroxaban	9.20	1.10 (0.97,1.24)	0.133
Apixaban	7.00	0.74 (0.64,0.87)	<0.001



- Apixaban and dabigatran were associated with a lower risk of major or CRNM bleeding compared with warfarin

- The risk of GI bleeding was higher with rivaroxaban and dabigatran compared with warfarin.

Halvorsen et al. European Heart J CV Pharm 2017; 3: 28-36

“Real-world” Data

Effectiveness and Safety of
Warfarin vs. NOACs

Observational “real-world” studies seem to confirm the results of RCTs which comparing warfarin to NOACs

“Real-world” Data

Effectiveness and Safety of NOACs

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

A. John Camm[1]*, Pierre Amarenco[2], Sylvia Haas[3], Susanne Hess[4], Paulus Kirchhof[5,6], Silvia Kuhls[7], Martin van Eickels[4], and Alexander G.G. Turpie[8], on behalf of the XANTUS Investigators

- Observational cohort study (enrollment-based registry)
- NVAF patients (n=6 784) in 311 centres in Europe, Canada and Israel who start treatment with Rivaroxaban for prevention of stroke or non-CNS SE
- Rivaroxaban duration at treating MD discretion
  - 1◦ outcomes → Major bleeds, AE, SAEs, ACM
  - 2◦ outcomes → TE events, non-major bleeds, QOL, resource utilization

Camm et al. Eur Heart J 2016; 37(14): 1145-53

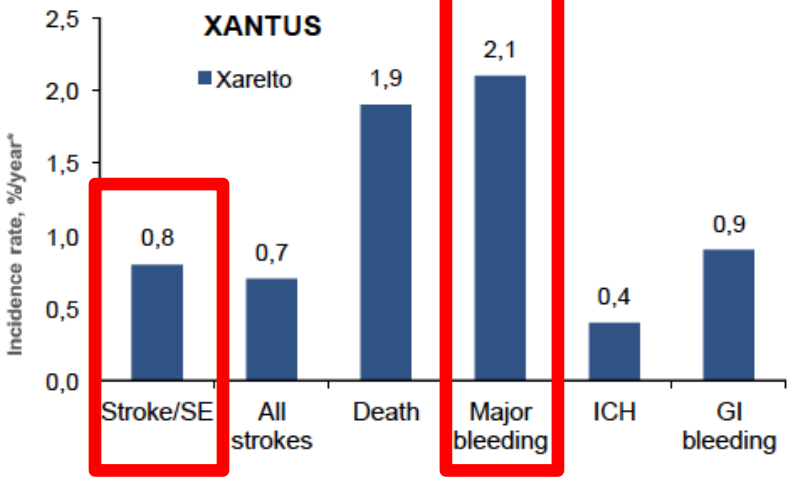
Baseline Characteristics – XANTUS vs. ROCKET-AF

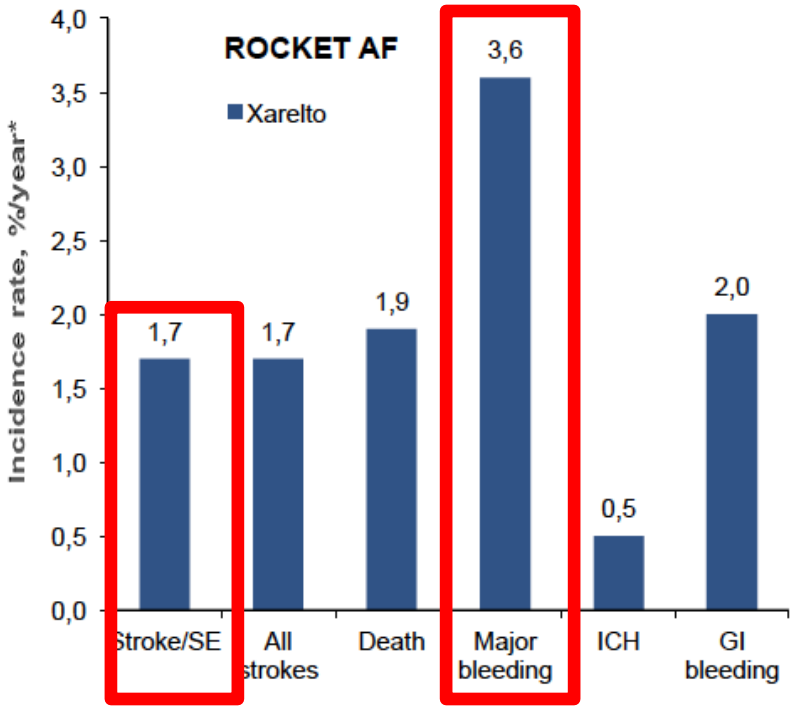
Characteristics, %	XANTUS (n=6,784)	ROCKET-AF (n=7,131)
Age (years)	71.5 ± 10.0	73 (IQR: 65,78)
Age ≥75 years	37.2%	43.8%
Male sex	59.2%	60.3%
$CHADS_2$ score ≥3	29.3%	87.0%
Hypertension	74.7%	90.3%
Prior MI	10.1%	16.6%
Diabetes	19.6%	40.4%
Heart failure	18.6%	62.6%
Prior CVA / TIA / SE	19.0%	54.9%
Creatinine clearance < 50 ml/min	9.4%	21%

Camm et al. Eur Heart J 2016; 37(14): 1145-53
Patel M et al. *NEJM* 2011;365:883-891

XANTUS vs. ROCKET AF

	$CHADS_2$	Prior stroke#
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%



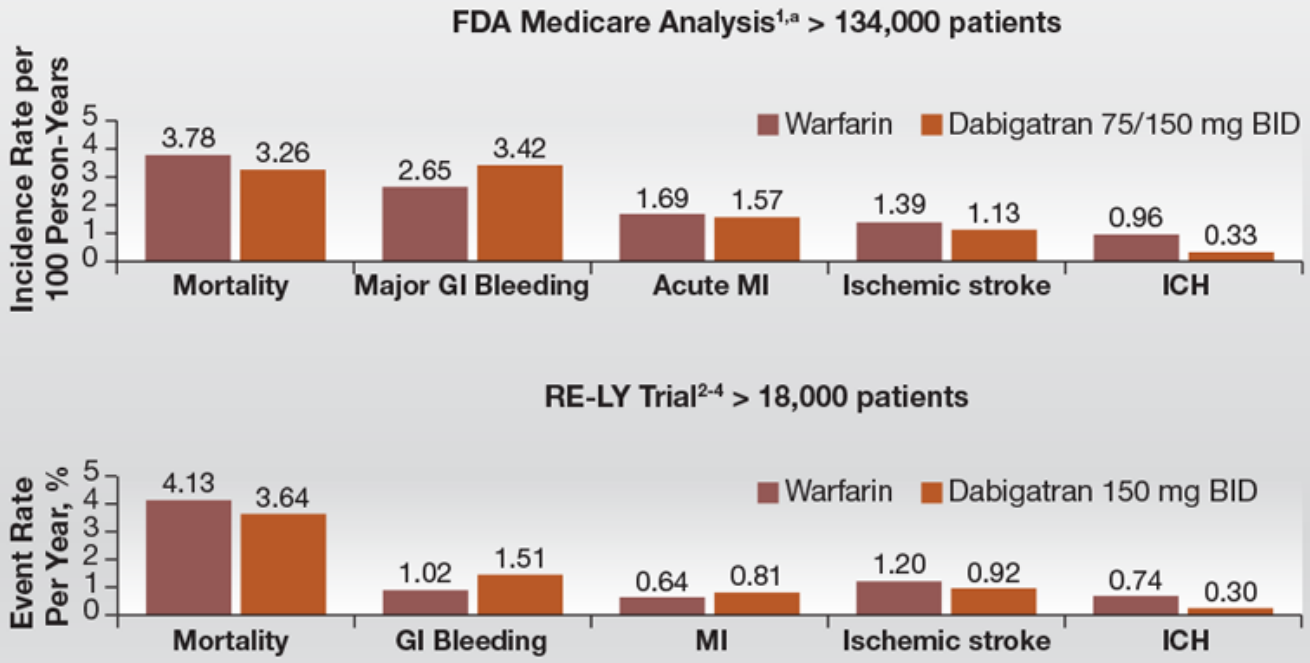


#Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al, Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

http://www.venicearrhythmias.org/wp-content/uploads/2015/05/A-J-Camm1.pdf

Incidence of Outcome: FDA Medicare Analysis and RE-LY Clinical Data



[a] **Study Design:** Observational cohort study of Medicare beneficiaries.

Data are from multiple studies and cannot be directly compared. Baseline characteristics, endpoint definitions, and methodology between RCT and RWD analyses show important differences.

“Real-world” Data

Effectiveness and Safety of
NOACs

Observational “real-world” studies seem to support the results of RCTs that NOACs are safe and effective

“Real-world” Data

Effectiveness and Safety of

NOAC vs. NOAC

Clinical Outcomes of Elderly AF Medicare Beneficiaries – Dabi vs. Riva

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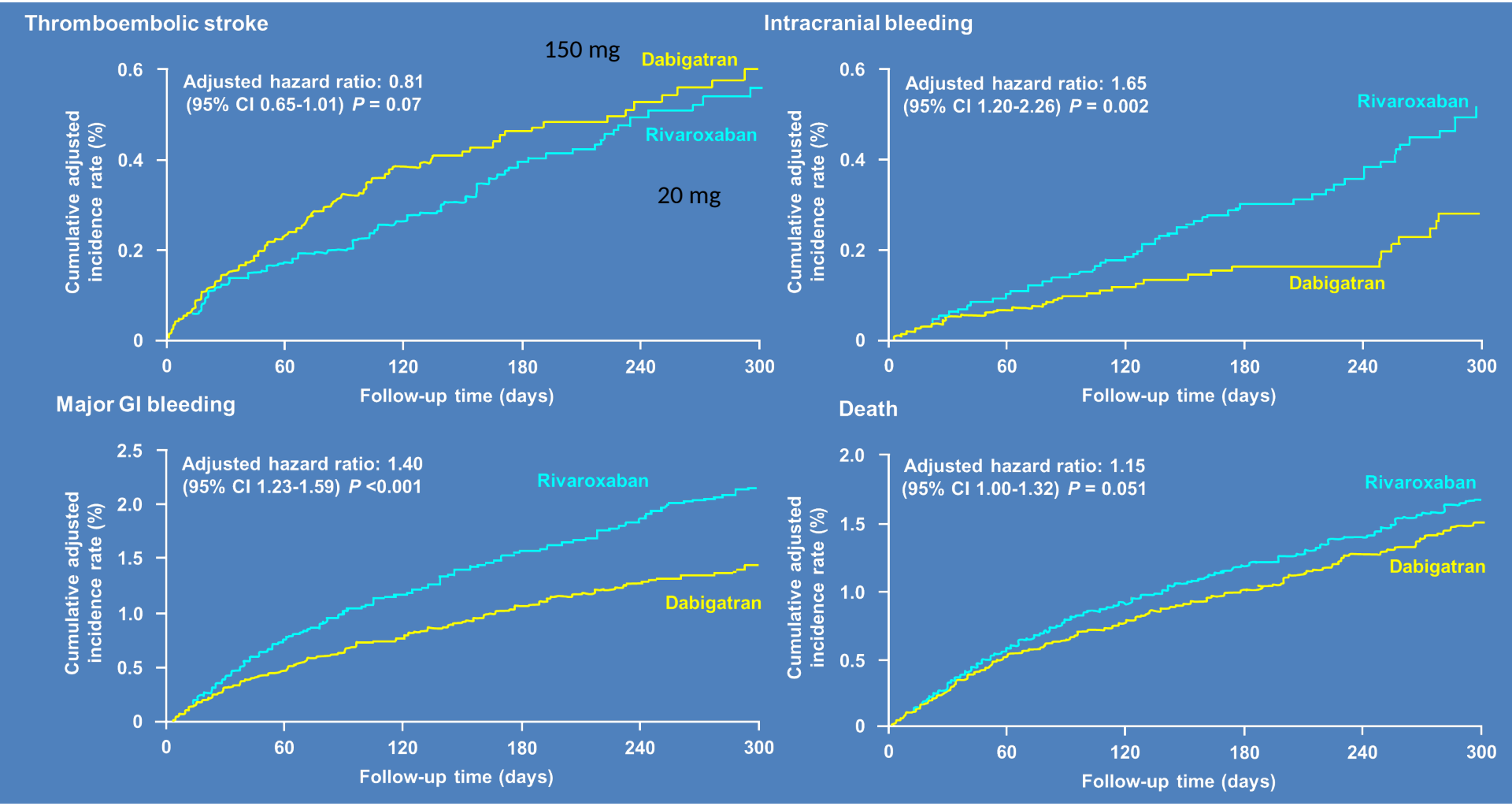


118 891 new patients with NVAF ≥ 65 years old enrolled in FFS Medicare from Nov 2011 – June 2014 – Propensity score matched

Graham et al. JAMA Int Med 2016; 176(11): 1662-1671

Clinical Outcomes of Elderly AF Medicare Beneficiaries – Dabi vs. Riva

Table 2. Outcome Event Counts, Adjusted Incidence Rate Differences, and Crude and Adjusted Hazard Ratios Comparing Inverse Probability of Treatment-Weighted New-User Cohorts of Dabigatran and Rivaroxaban for Nonvalvular Atrial Fibrillation[a]

Outcome	Crude (Unadjusted) Incidence Rate per 1000 Person-years (No. of Events)		Adjusted Incidence Rate Difference per 1000 Person-years (95% CI)[b]	Hazard Ratio (95% CI)		P Value
	Dabigatran (n = 52 240)	Rivaroxaban (n = 66 651)		Crude	Adjusted	
Primary Outcomes						
Thromboembolic stroke	9.7 (150)	7.7 (156)	−1.8 (−3.8 to 0.1)	0.80 (0.64 to 1.00)	0.81 (0.65 to 1.01)	.07
Intracranial hemorrhage	3.7 (58)	5.8 (118)	2.3 (0.9 to 3.7)	1.58 (1.15 to 2.16)	1.65 (1.20 to 2.26)	.002
Major extracranial bleeding event	26.6 (413)	39.4 (796)	13.0 (9.2 to 16.7)	1.47 (1.31 to 1.66)	1.48 (1.32 to 1.67)	<.001
Gastrointestinal	23.3 (362)	32.5 (656)	9.4 (6.0 to 12.8)	1.39 (1.22 to 1.58)	1.40 (1.23 to 1.59)	<.001
Mortality	22.2 (346)	24.7 (500)	3.1 (−0.1 to 6.3)	1.12 (0.98 to 1.29)	1.15 (1.00 to 1.32)	.051
Secondary Outcomes						
All hospitalized extracranial bleeds	39.2 (608)	54.0 (1091)	15.1 (10.7 to 19.6)	1.38 (1.25 to 1.52)	1.39 (1.25 to 1.53)	<.001
Acute myocardial infarction	12.9 (200)	11.0 (223)	−1.7 (−4.0 to 0.6)	0.86 (0.71 to 1.05)	0.88 (0.72 to 1.06)	.18

[a] Dabigatran served as the reference group.

[b] Adjusted incidence rate difference = (rivaroxaban rate) – (dabigatran rate).

Graham et al. JAMA Int Med 2016; 176(11): 1662-1671

Major bleeding in patients initiating NOACs and Warfarin

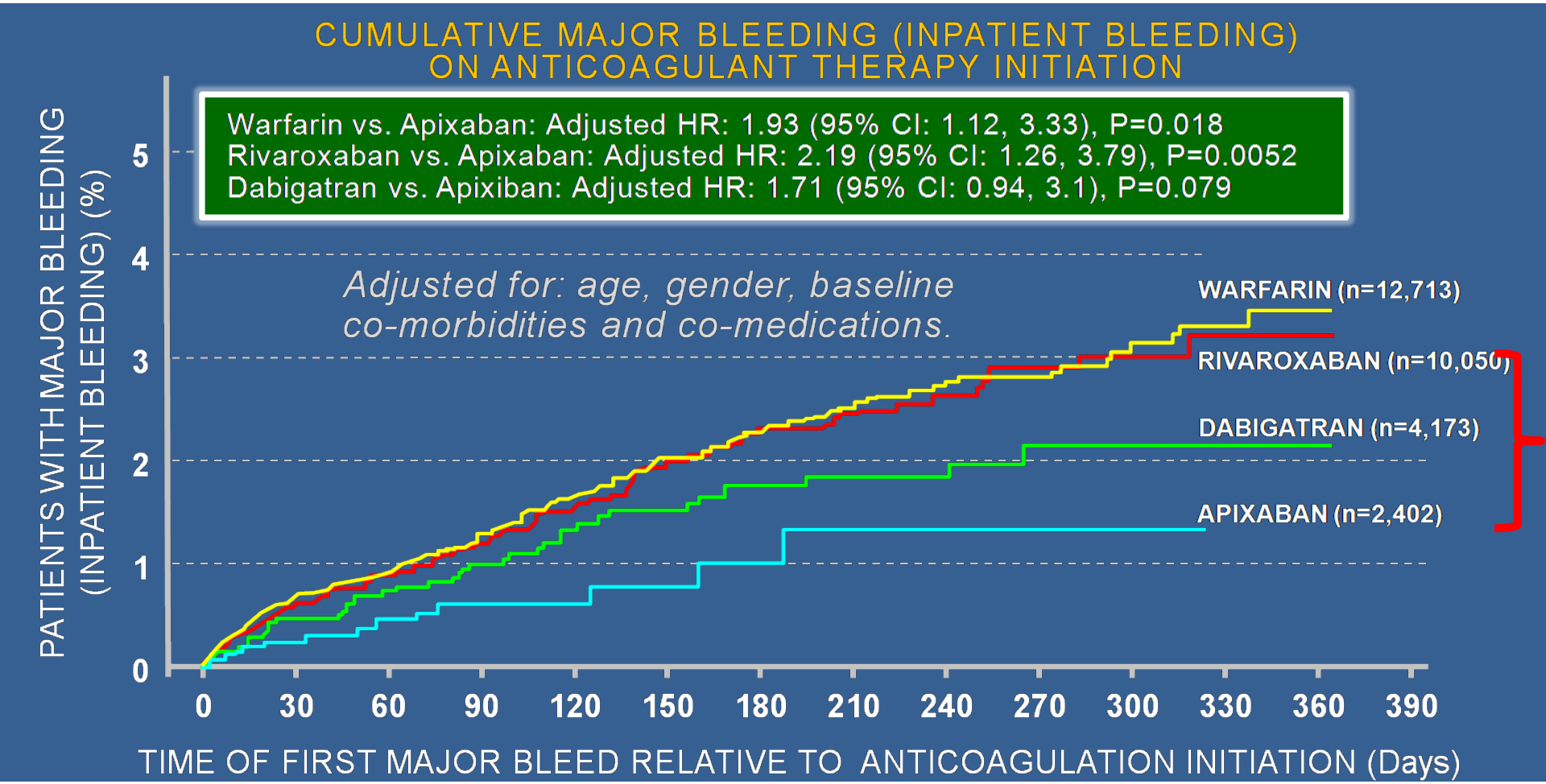
- Retrospective analysis of Truven Marketscan database® - US claims database
- Enrolment period: Jan – Dec 2013
- >18 years old with at least 1 claim with diagnosis of AF in the baseline period
- No prior anticoagulation in the baseline period (treatment naïve)
- No valvular heart disease, transient AF, cardiac surgery or VTE history
- **Objective → To compare the major bleeding risk of among newly anticoagulated NVAF patients initiation apixaban, warfarin, dabigatran or rivaroxaban**

Lip et al. Int J Clin Prac; 2016; 752-763

Major Bleeding in patients initiating NOACs and Warfarin

Characteristics	Apixaban (n=2 402)	Dabigatran (n=4 173)	Rivaroxaban (n=10 050)	Warfarin (n=12 713)
Mean Age	69.3	66.8	67.3	72.5
CHF	20.2	20.3	19.5	27.3
DM	26.8	27.6	26.7	31.8
HTN	72.7	70.5	70.8	73.1
Renal disease	7.6	7.3	8.1	14.6
MI	6.1	5.1	5.3	6.3
Stroke/TIA	10.6	9.2	9.0	12.2
CAD	34.6	28.8	29.7	34.1
Prior bleeding	11.5	11.0	12.8	16.1
CHADS2	1.78 ± 1.21	1.66 ± 1.19	1.66 ± 1.20	2.05 ± 1.26
CHA2DS2-VASc	2.83 ± 1.64	2.58 ± 1.65	2.62 ± 1.65	3.22 ± 1.65

Major Bleeding in patients initiating NOACs and Warfarin



Lip et al. Int J Clin Prac; 2016; 752-763

[Original Research **Antithrombotic Therapy**]

CHEST

Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation

Peter A. Noseworthy, MD; Xiaoxi Yao, PhD; Neena S. Abraham, MD; Lindsey R. Sangaralingham, MPH; Robert D. McBane, MD; and Nilay D. Shah, PhD

- Large US administrative claims database – Optum Labs Data Warehouse (>100M)
- ≥ 18 years users of dabigatran, rivaroxaban and apixaban for NVAF (≥ inpatient or outpatient AF diagnosis)
- Oct 1 2010 – Feb 28 2015
- Excluded valvular heart disease, dialysis, renal transplantation
- Propensity-score matched cohorts (3 cohorts – riva-dabi, apix-riva, apix-dabi)
- Cox Proportional Hazards model

Noseworthy et al. Chest 2016; 150(6): 1302-1312

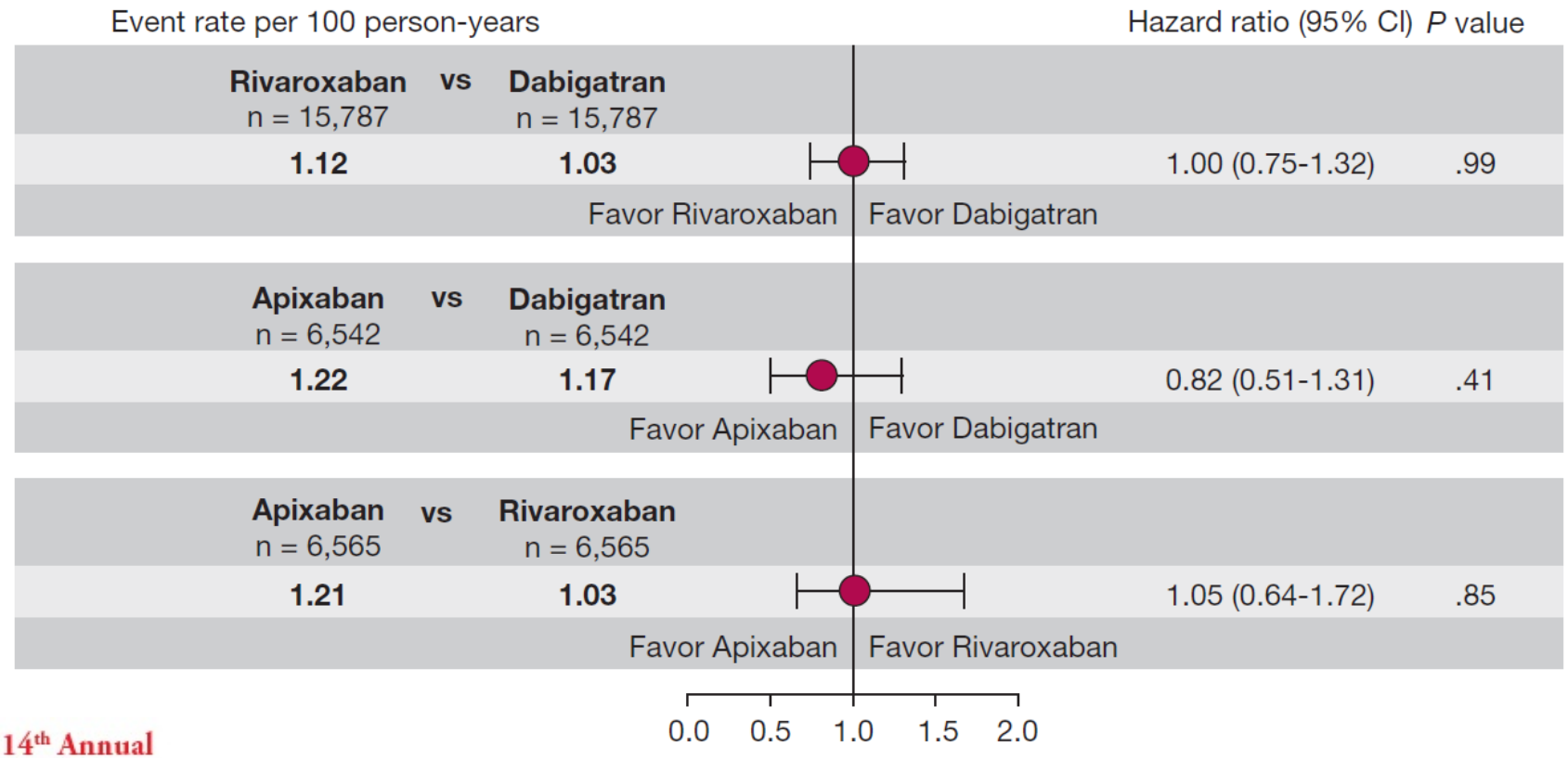
TABLE 1] Baseline Characteristics in Propensity-Score-Matched NOAC Users

Variable	Rivaroxaban (n = 15,787)	Dabigatran (n = 15,787)	Apixaban (n = 6,542)	Dabigatran (n = 6,542)	Apixaban (n = 6,565)	Rivaroxaban (n = 6,565)
Age, y						
Median (IQR)	70 (62-78)	71 (62-78)	73 (65-81)	73 (65-81)	73 (65-81)	73 (65-81)
18-64, %	33.6	31.9	24.1	24.5	24.0	24.8
65-74, %	31.2	31.0	30.4	30.0	30.3	29.7
≥ 75, %	35.2	37.0	45.5	45.4	45.7	45.5
Male sex, %	59.7	58.9	54.1	53.9	54.0	54.4
Race, %						
Asian	2.6	2.6	2.5	2.8	2.5	2.3
Black	9.1	9.1	9.0	8.5	9.1	8.8
Hispanic	4.7	4.7	5.1	5.2	5.1	5.0
Unknown	4.6	4.6	4.8	4.5	4.8	4.5
White	78.9	78.9	78.6	79.0	78.6	79.3
Region of residence, %						
Midwest	24.8	25.3	27.7	27.9	27.9	27.6
Northeast	19.6	19.6	18.4	18.4	18.4	17.5
South	45.0	44.4	41.9	41.2	41.8	42.5
West	10.6	10.7	12.0	12.5	12.0	12.4
CHA_2DS_2-VASc						
Median (IQR)	4 (2-5)	4 (2-5)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)
0-1, %	14.5	14.0	9.2	9.4	9.1	9.7
2-3, %	33.5	32.8	30.0	30.7	29.9	30.1
≥ 4, %	52.1	53.2	60.9	59.9	61.0	60.2
HAS-BLED						
Median (IQR)	2 (1-3)	2 (1-3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)
≥ 3, %	38.3	39.5	44.7	43.9	44.9	43.7

Noseworthy et al. Chest 2016; 150(6): 1302-1312

Direct Comparison of NOACs for Effectiveness and Safety in NVAF

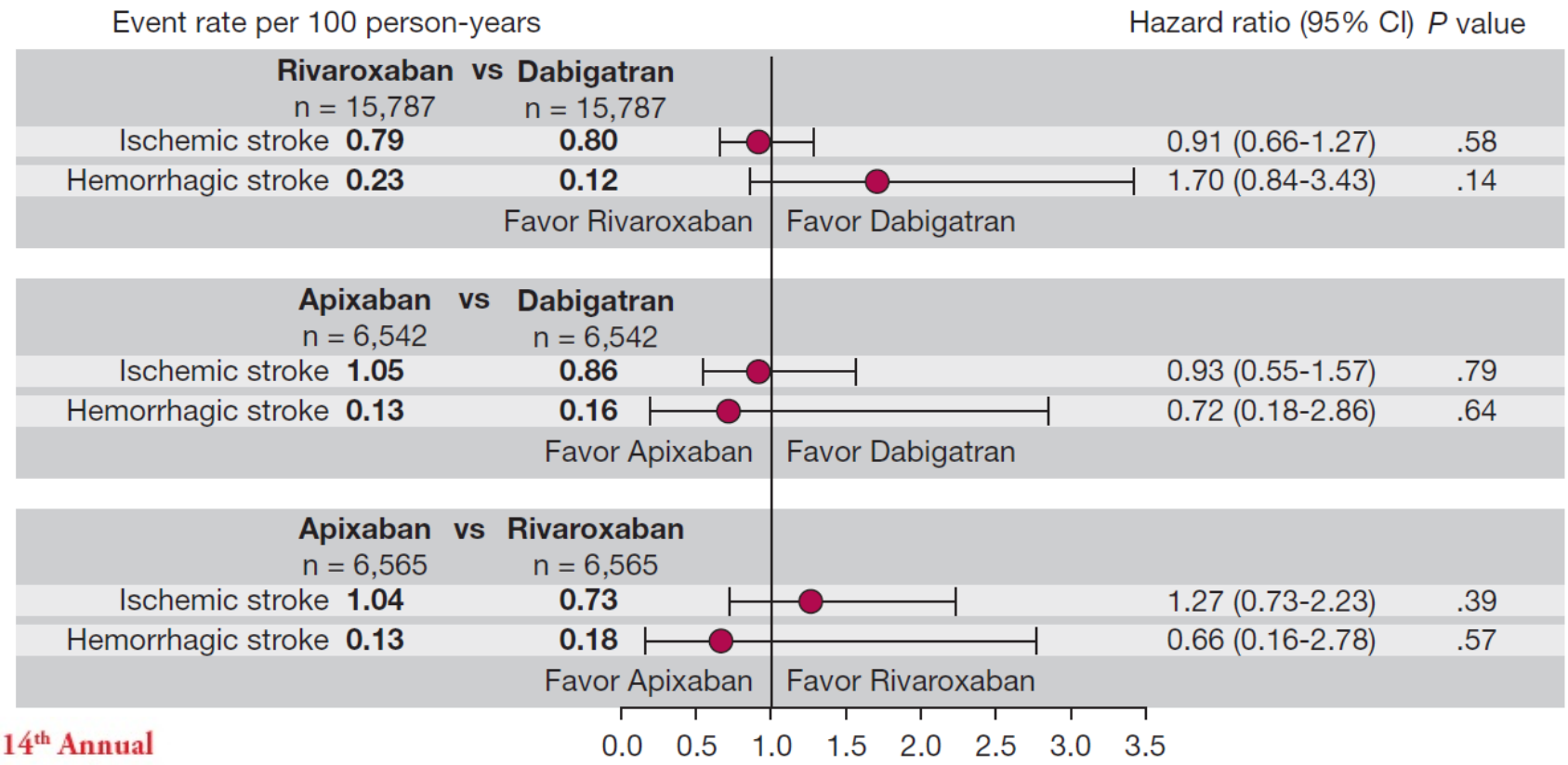
Effectiveness: Primary outcome (stroke or systemic embolism)



Noseworthy et al. Chest 2016; 150(6): 1302-1312

Direct Comparison of NOACs for Effectiveness and Safety in NVAF

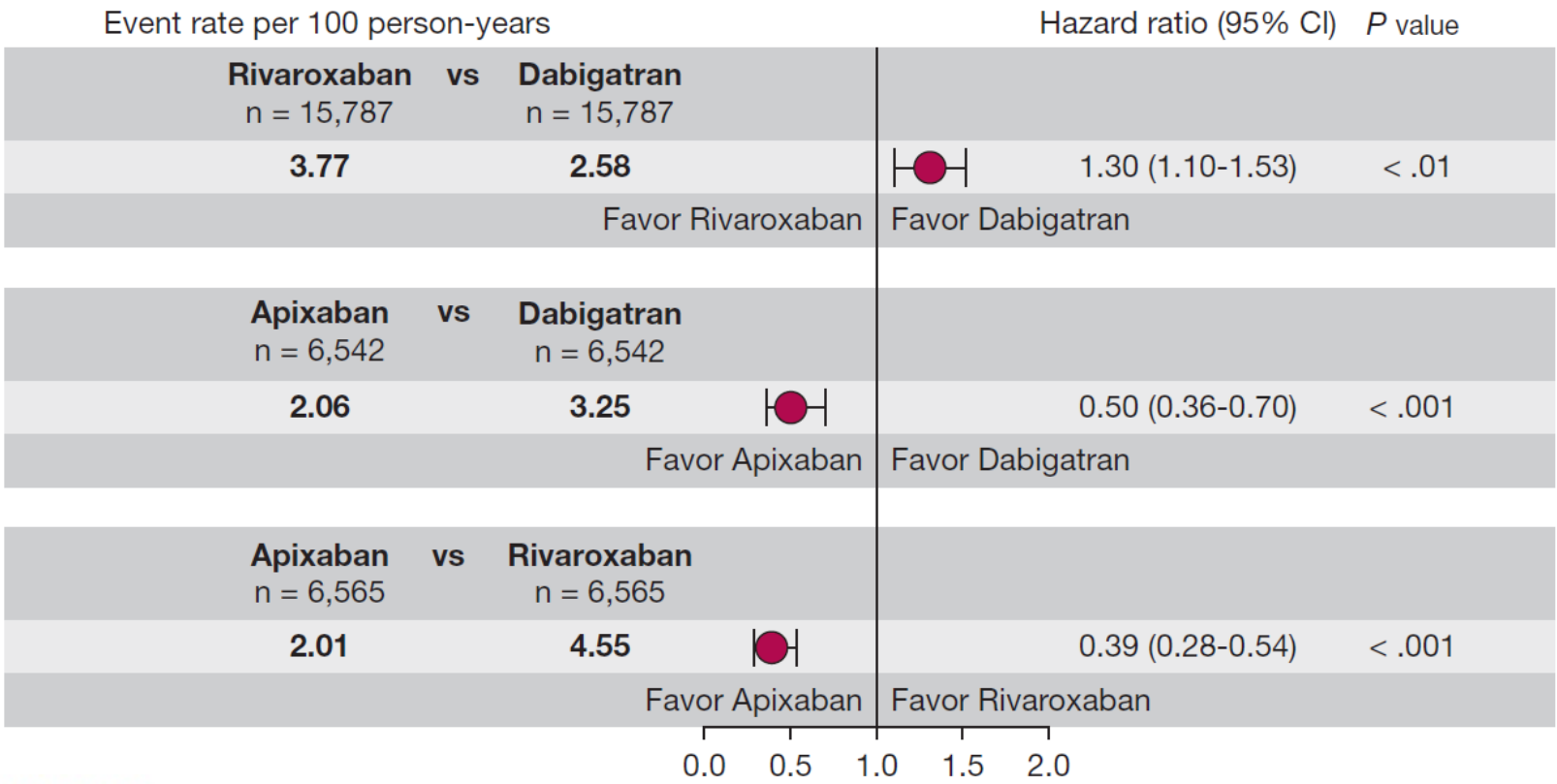
Effectiveness: Secondary outcomes



Noseworthy et al. Chest 2016; 150(6): 1302-1312

Direct Comparison of NOACs for Effectiveness and Safety in NVAF

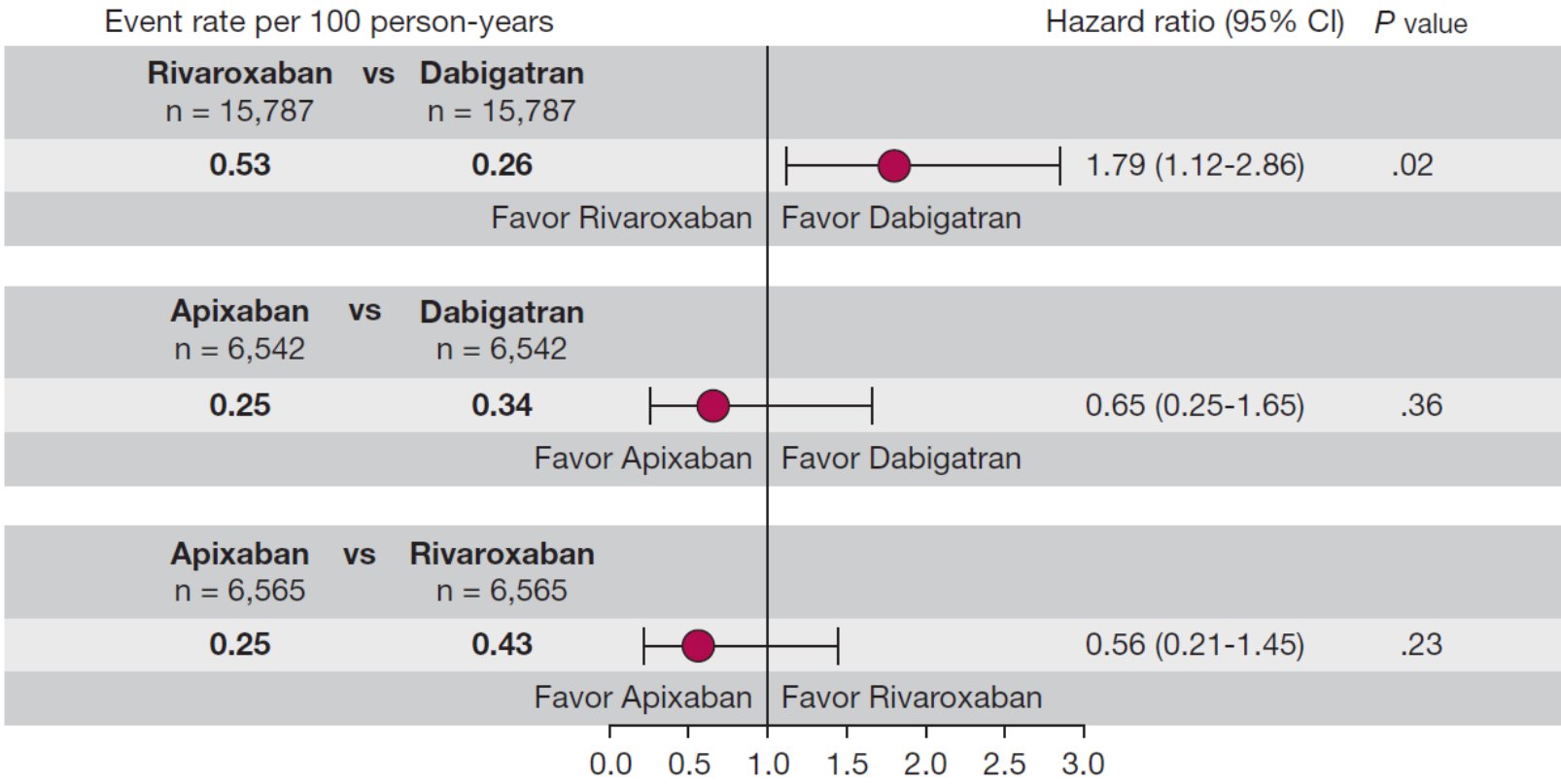
Safety: Primary outcome (major bleeding)



Noseworthy et al. Chest 2016; 150(6): 1302-1312

Direct Comparison of NOACs for Effectiveness and Safety in NVAF

Safety: Secondary outcome (intracranial bleeding)



Noseworthy et al. Chest 2016; 150(6): 1302-1312

Direct Comparison of NOACs for Effectiveness and Safety in NVAF

- Dabigatran, rivaroxaban and apixaban have similar effectiveness in the reduction of stroke of systemic embolism
- Apixaban was associated with the lower risk of bleeding, rivaroxaban is associated with a higher risk of major bleeding
- Limitations of confounding, particularly with selection of a particular NOAC, pharmacy claims

Noseworthy et al. Chest 2016; 150(6): 1302-1312

“Real-world” Data

Effectiveness and Safety of

NOAC vs. NOAC

Observational “real-world” studies seem to support that there <u>may</u> be differences between NOACs

“Real-world” Data

Are patients taking NOACs being dosed properly?

Does it matter?

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes

The ORBIT-AF II Registry

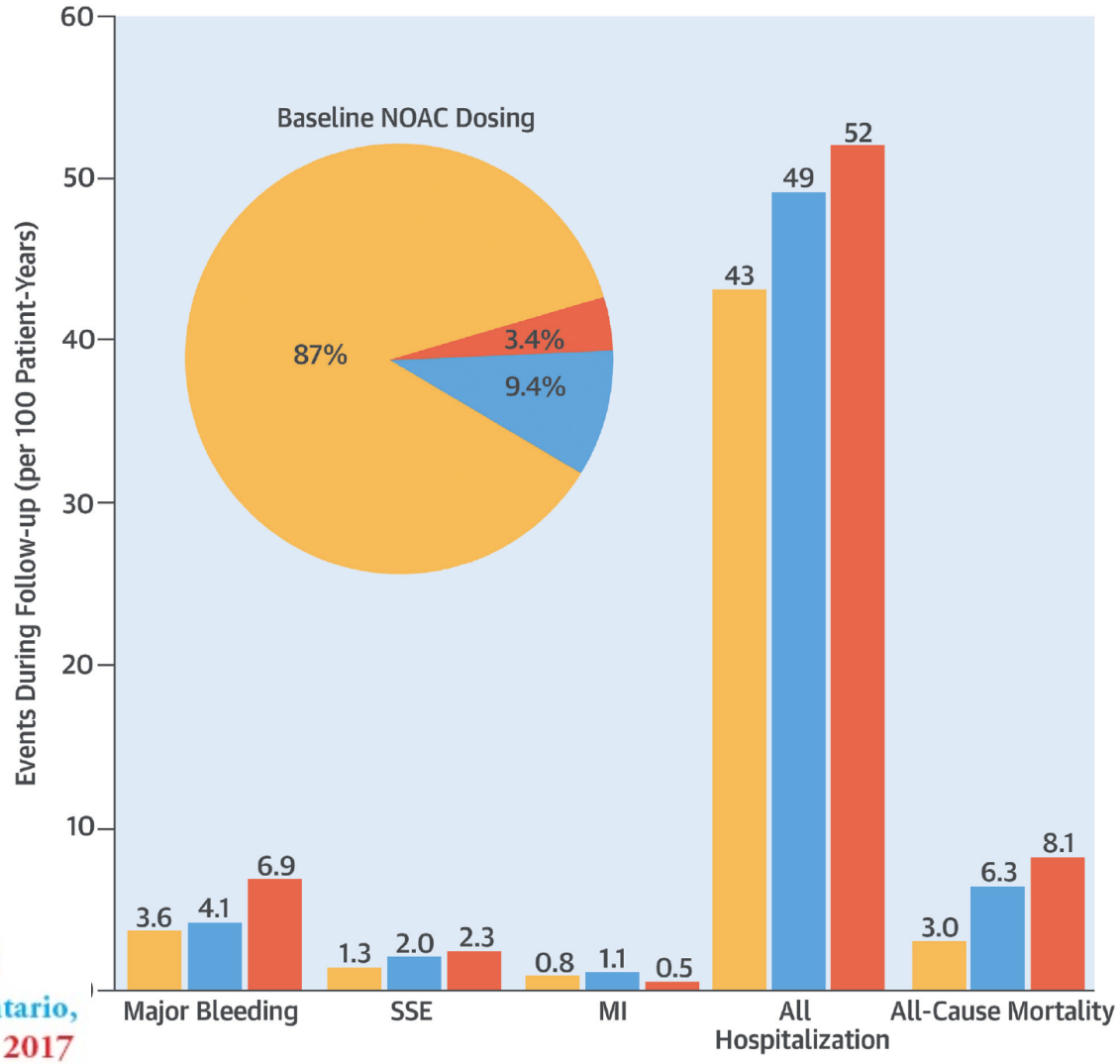
Benjamin A. Steinberg, MD, MHS,[a,b,c] Peter Shrader, MA,[c] Laine Thomas, PhD,[c] Jack Ansell, MD,[d] Gregg C. Fonarow, MD,[e] Bernard J. Gersh, MB, ChB, DPhil,[f] Peter R. Kowey, MD,[g] Kenneth W. Mahaffey, MD,[h] Gerald Naccarelli, MD,[i] James Reiffel, MD,[j] Daniel E. Singer, MD,[k] Eric D. Peterson, MD, MPH,[b,c] Jonathan P. Piccini, MD, MHS,[b,c] for the ORBIT-AF Investigators and Patients

- ORBIT-AF II - 5738 patients treated with a NOAC
- Underdosed (9.4%), Overdosed (3.4%), Recommended dose (87%)
- Patients receiving "off-label doses" were more likely:
  - Older
  - Female
  - Less likely treated by an EP
  - Higher CHADS-VASc scores
  - Higher ORBIT bleeding scores

Steinberg et al. JACC 2016; 68 (24): 2597-604

Off-Label Dosing

CENTRAL ILLUSTRATION Off-Label Dosing of Nonvitamin K Antagonist Oral Anticoagulant Agents: Prevalence and Outcomes by Dosing



Steinberg et al. JACC 2016; 68 (24): 2597-604

Worse Outcomes with Off-Label Dosing

TABLE 2 Unadjusted and Adjusted Association Between Appropriateness of NOAC Dosing and Clinical Outcomes

		Unadjusted			Adjusted		
	Number of Events	HR (95% CI)	p Value	Global p Value	HR (95% CI)	p Value	Global p Value
All-cause death				**<0.0001**			0.0674
Appropriately dosed	158 (2.95)	Reference			Reference		
Underdosed	36 (6.30)	2.18 (1.57–3.02)	<0.0001		1.25 (0.89–1.76)	0.1975	
Overdosed	18 (8.05)	1.43 (0.76–2.67)	0.2650		1.91 (1.02–3.60)	**0.0438**	
First CV hospitalization				**0.0481**			**0.0050**
Appropriately dosed	1,093 (24.16)	Reference			Reference		
Underdosed	129 (26.11)	1.12 (0.92–1.35)	0.2609		1.26 (1.07–1.50)	**0.0065**	
Overdosed	45 (23.82)	0.70 (0.51–0.97)	0.0316		0.73 (0.53–1.02)	0.0625	

- Overdosing with significantly associated with ↑ risk of all-cause mortality
- Underdosing with significantly associated with a ↑ risk of CV hospitalization

Steinberg et al. JACC 2016; 68 (24): 2597-604

“Real-world” Data

Are patients taking NOACs staying on them?

Higher Persistence with NOAC vs. Warfarin

Table 3. Persistence of Propensity Score–Matched Patients

	30-Day Medication Gap		60-Day Medication Gap	
Time Period	Dabigatran	Warfarin	Dabigatran	Warfarin
n	1745	1745	1745	1745
6-mo persistence rate, %	63.9	41.3	71.8	53.3
9-mo persistence rate, %	56.3	30.7	66.9	44.0
1-y persistence rate, %	50.3	24.1	63.3	38.8
P value*	<0.001		<0.001	

*The persistence rates were compared using a log-rank test.

- Dabigatran – median persistence 389 days vs. warfarin 135 days (p<0.001) – 30 day gap

- US DOD administrative claims
- Warfarin & Dabigatran
- Oct 2010 – June 2012
- PS matching 1745 matched pairs

- Patients on dabigatran with higher likelihood of non-persistence:
  - CHADS<2
    - HR 1.37 CI 1.17-1.60, p<0.001
  - HEMORR2HAGES>3
    - HR 1.24, CI 1.04-1.47, p=0.016

Zalesak et al. Circ Cardiovasc Qual Outcomes 2013; 6: 567-574

OAC Persistence

RESEARCH ARTICLE

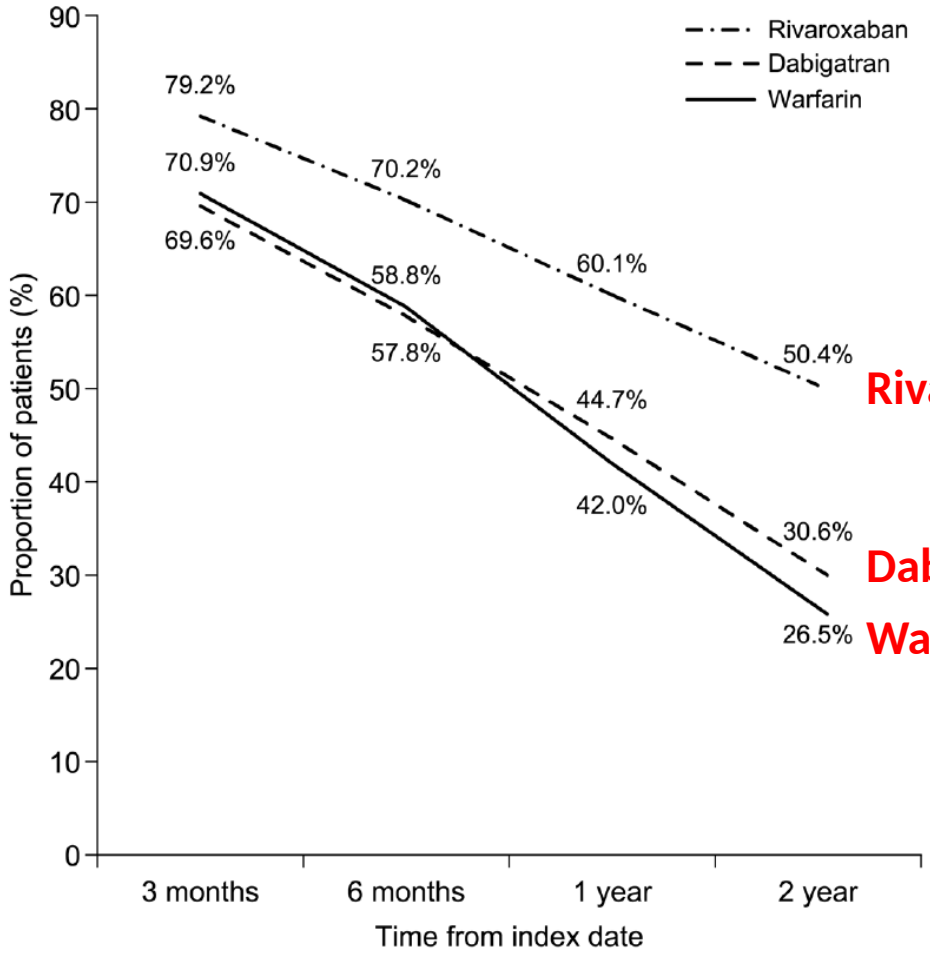
Treatment Persistence and Discontinuation with Rivaroxaban, Dabigatran, and Warfarin for Stroke Prevention in Patients with Non-Valvular Atrial Fibrillation in the United States

Craig I. Coleman[1]*, Muralikrishna Tangirala[2], Thomas Evers[3]

- US MarketScan claims
- NVAF (> 2 codes) + CHADS-VASc ≥ 2 + ≥ 6 mos pharmacy benefit prior to enrollment
- Nov 2011 – Dec 2013
- PS matching
- Persistence defined as absence of a refill gap > 60 days
- Discontinuation defined as no additional refill for > 90 days and through to end of F/U
- 32 634 pts included

Coleman et al. PLOS One 2016; June 1-9

OAC Persistence



Rivaroxaban

Dabigatran

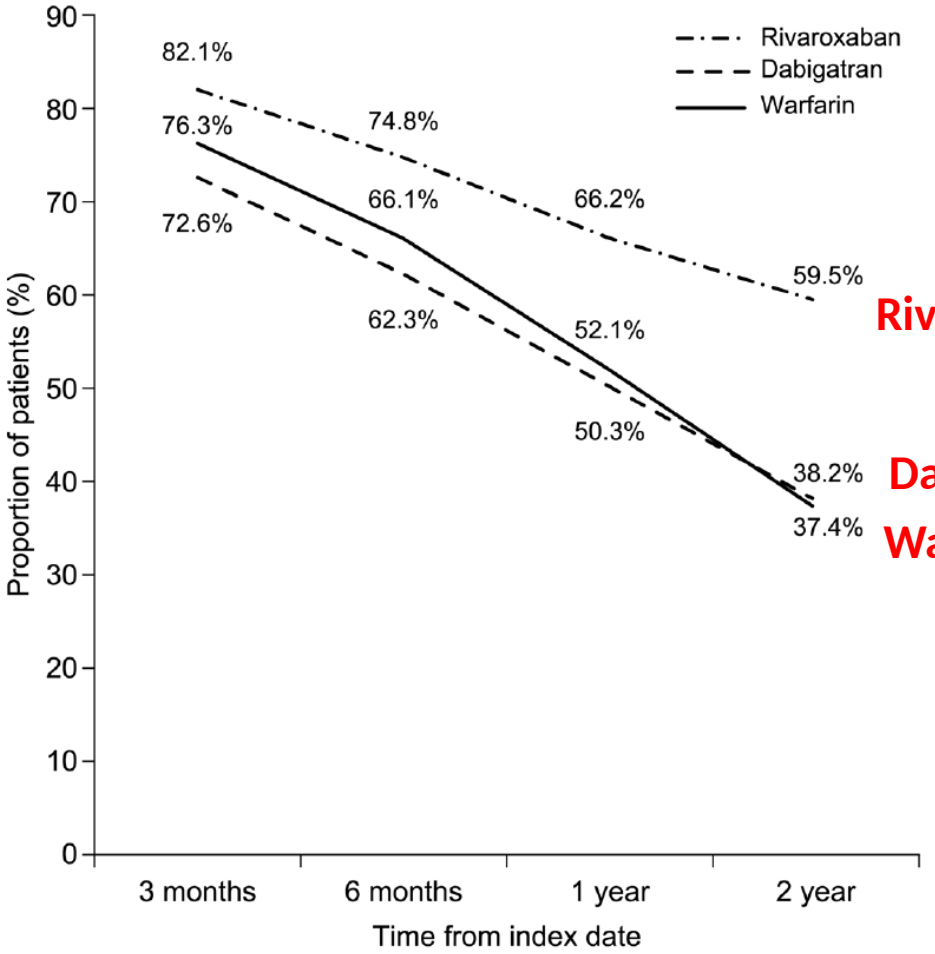
Warfarin

Rivaroxaban associated with better persistence than both dabigatran and warfarin

Fig 2. Treatment persistence according to oral anticoagulant therapy.

Coleman et al. PLOS One 2016; June 1-9

OAC Persistence



Rivaroxaban

Dabigatran

Warfarin

Rivaroxaban associated with lower discontinuation than both dabigatran and warfarin

Fig 3. Treatment discontinuation according to oral anticoagulant therapy.

Coleman et al. PLOS One 2016; June 1-9

“Real-world” Data

What about well-controlled warfarin?
(does that exist?)

Original Investigation

Outcomes in a Warfarin-Treated Population With Atrial Fibrillation

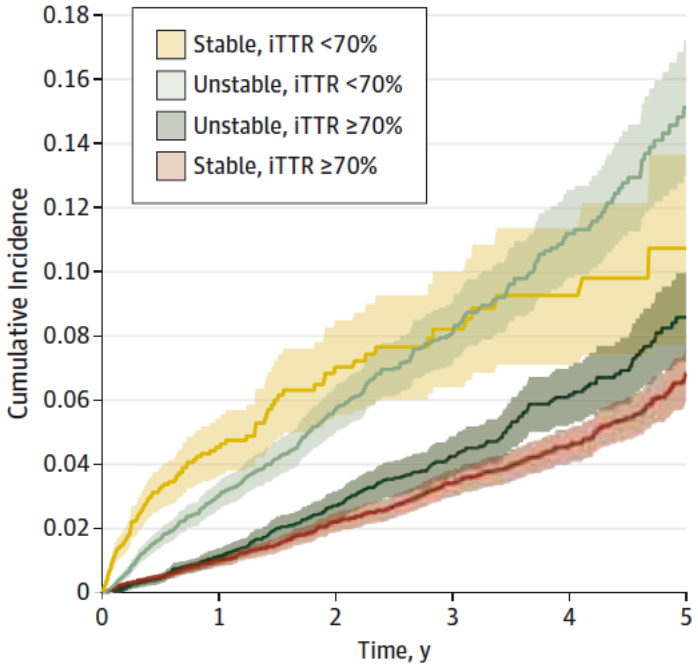
Fredrik Björck, MD; Henrik Renlund, PhD; Gregory Y. H. Lip, MD, PhD; Per Wester, MD, PhD; Peter J. Svensson, MD, PhD; Anders Själander, MD, PhD

- Retrospective, multicenter cohort study based in Sweden between Jan 2006 – Dec 2011
- n = 40 449
- Stable INR = INR st dev < 0.83

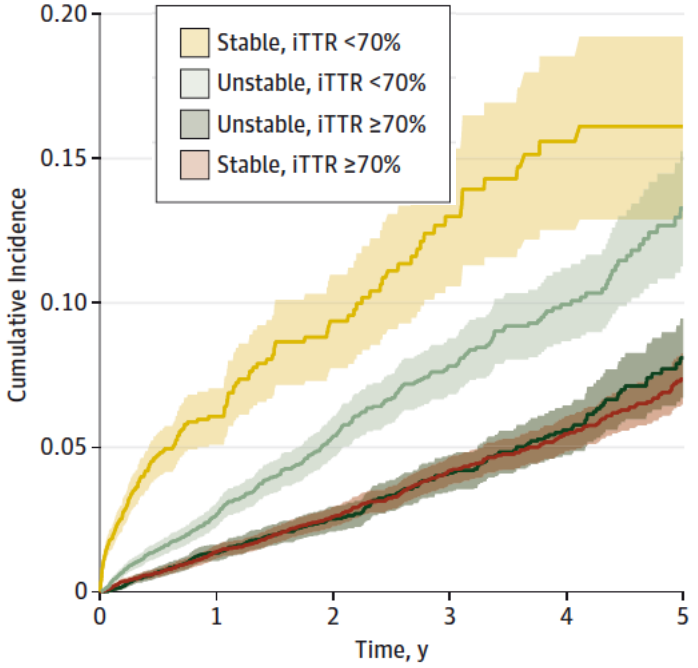
Björck F et al. JAMA Cardiology. 2016;1(2):172-180

What about well-controlled warfarin? (if that exists..)

Bleeding



Thromboembolism



Patients with TTR of ≥70% had relatively low annual rates of adverse outcomes:

Major bleeding: 1.61/yr (95% CI: 1.49-1.73)

Arterial thromboembolism: 1.41/yr (95% CI: 1.30-1.53)

Intracranial bleeding: 0.34/yr (95% CI: 0.28-0.39

Björck F et al. JAMA Cardiology. 2016;1(2):172-180

“Real-world” Data

NOACs in renal dysfunction

(this doesn’t sound like a good idea…)

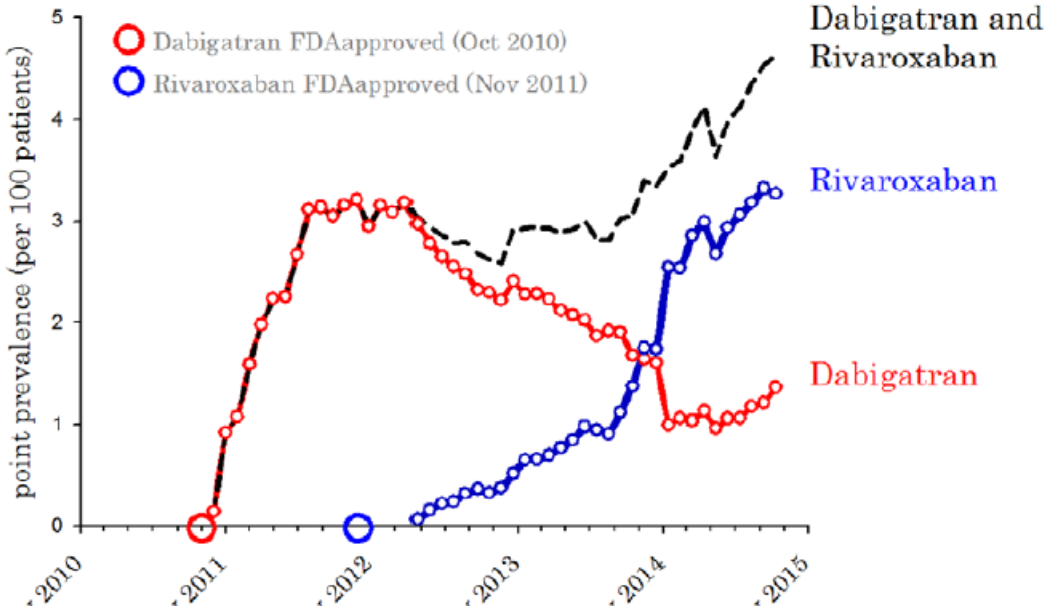
Table 3: Suggested Use of NOACs According to Patient Renal Function†

NOAC	CrCl (mL/min)	Drug Dose	Comment
Dabigatran	> 50	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding or in the elderly (e.g. age ≥ 80 years) Measure CrCl every 12 months
	30-50	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding (e.g. age ≥ 80 years) Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid dabigatran	Consider warfarin as alternative anticoagulant
Rivaroxaban	≥ 50	20 mg daily	Measure CrCl every 12 months
	30-49	15 mg daily	Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid rivaroxaban	Consider warfarin as alternative anticoagulant
Apixaban	> 50	5 mg twice daily	Measure CrCl every 12 months
	25-50	5 mg twice daily	2.5 mg twice daily in patients with 2 of following: (1) creatinine ≥ 133 µmol/L; (2) age ≥ 80 years; (3) body weight ≤ 60 kg Measure CrCl every 6 months *and* with acute illness
	15-24	No dose recommendations can be made	Very limited clinical data with apixaban Consider warfarin as alternative anticoagulant
	< 15	Avoid apixaban	Consider warfarin as alternative anticoagulant

- Edoxaban - (30 or 15 mg od): if any of – CrCl 30-50 mL/min, wt ≤ 60 kg, verapamil or quinidine use

http://thrombosiscanada.ca/guides/pdfs/NOACs_Comparison_and_FAQs.pdf. Accessed Feb 10 2017.

NOACs in Hemodialysis



- Fresenius Medical Care North America ESRD database
- 29 977 hemodialysis pts with AF
- 5.9% of anticoagulated dialysis pts are started on Dabigatran or Rivaroxaban
- Poisson regression model, both were associated with a higher risk of hospitalization or death from bleeding c/w warfarin
  - Dabigatran RR 1.48
    CI 1.21-1.81, p=0.0002
  - Rivaroxaban RR 1.38
    CI .18-2.68, p=0.0006

Chan et al. Circulation 2015; 131: 972-979

“Real-world” Data

What about valvular heart disease?
Bioprosthetic valves?
Mechanical valves?

What is the current definition of NVAF?

- The precise distinction between “valvular” and “nonvalvular” AF varies among the trials of oral anticoagulation therapy and among the AF guidelines of major societies.

- The present CCS Atrial Fibrillation Guidelines define valvular AF as that occurring in a patient with “rheumatic mitral stenosis, mitral valve repair, mechanical or bioprosthetic heart valve.”

Verma A, Cairns JA, Mitchell LB, et al. Can J Cardiol 2014;30:1114-30.

Which types of valvular AF presently exclude the use of a NOAC?

- VKA remains the treatment of choice for AF patients with mechanical heart valves
  - The RE-ALIGN trial was terminated early because of an excess of thromboembolic and bleeding events in the dabigatran treatment group. It was postulated that thrombin generation triggered by exposure of blood to the artificial surface of the valve might have overwhelmed the local effects of dabigatran.

Eikelboom JW, Connolly SJ, Brueckmann M, et al. N Engl J Med 2013;369:1206-14.

Mitral Stenosis

- Mitral stenosis remains a clear indication for anticoagulation. Because such patients were excluded from the pivotal randomized trials of NOACs for stroke prevention, VKAs remain the standard of care in this patient population until further evidence emerges.

Olesen KH. Br Heart J 1962;24:349-57.
Szekely P. BMJ 1964;1:1209-12.
Wood P. BMJ 1954;1:1051-63. contd.
Benjamin EJ, Plehn JF, D'Agostino RB, et al. N Engl J Med 1992;327:374-9.
Adams GF, Merrett JD, Hutchinson WM, Pollock AM. J Neurol Neurosurg Psychiatry 974;37:378-83.

Do other types of valvular AF confer an increased risk of AF?

- Beyond rheumatic mitral stenosis and of mechanical heart valves, there is substantial uncertainty regarding the risk of AF-related thromboembolism with other forms of VHD. For example:
  - Native VHD
  - Bioprosthetic heart valves

Boon A, Lodder J, Cheriex E, Kessels F. Stroke 1996;27:847-51.
Philippart R, Brunet-Bernard A, Clementy N, et al. Eur Heart J 2015;36:1822-30.
Nakagami H, Yamamoto K, Ikeda U, et al. Am Heart J 1998;136:528-32.
Gonzalez-Lavin L, Tandon AP, Chi S, et al. J Thorac Cardiovasc Surg 1984;87:340-51.

NVAF

TRIAL	EXCLUSION CRITERIA
RELY (DABIGATRAN)	History of heart valve disorder (i.e. prosthetic valve or hemodynamically relevant valve disease) Severe MR, AR, AS
ROCKET-AF (RIVAROXABAN)	Hemodynamically significant MS, prosthetic valve, (annuloplasty with or without ring allowed) 106 cases
ARISTOTLE (APIXABAN)	Moderate or severe MS, presence of a prosthetic heart valve
ENGAGE-AF (EDOXABAN)	Moderate or severe MS, mechanical heart valve, (bioprosthetic and valve repair included)

Can NOACs be used for patients with some types of valvular AF?

- The definition of NVAF in the pivotal trials of NOAC therapy (Dabigatran, Rivaroxaban, Apixaban) for thromboembolic event prevention varied

- Post hoc analyses evaluating these agents in VHD were performed (Table 4).
  - RELY (dabigatran, 21.8% VHD)
  - ARISTOTLE (apixaban, 26.4% VHD)
  - ROCKET-AF (rivaroxaban, 14.1% VHD)

Ezekowitz MD, Parise H, Nagarakanti R, et al. J Am Coll Cardiol 2014;63:A325.
Avezum A, Lopes RD, Schulte PJ, et al. Eur Heart J 2013;34:809.
Breithardt G, Baumgartner H, Berkowitz SD, et al. Eur Heart J 2014;35:3377-85.

Table 4. Efficacy and safety of NOACs vs warfarin in patients with and without significant VHD

	VHD	No VHD	Interaction *P*
roke or systemic embolism			
Dabigatran 150 mg vs warfarin	HR, 0.59; 95% CI, 0.37-0.93	HR, 0.67; 95% CI, 0.52-0.86	0.63
Dabigatran 110 mg vs warfarin	HR, 0.97; 95% CI, 0.65-1.45	HR, 0.88; 95% CI, 0.70-1.10	0.65
Apixaban vs warfarin	HR, 0.70; 95% CI, 0.51-0.97	HR, 0.84; 95% CI, 0.67-1.04	0.38
Rivaroxaban vs warfarin	HR, 0.83; 95% CI, 0.55-1.27	HR, 0.89; 95% CI, 0.75-1.07	0.76
ajor bleeding			
Dabigatran 150 mg vs warfarin	HR, 0.89; 95% CI, 0.68-1.16	HR, 0.99; 95% CI, 0.83-1.17	0.24
Dabigatran 110 mg vs warfarin	HR, 0.72; 95% CI, 0.54-0.96	HR, 0.85; 95% CI, 0.71-1.02	0.38
Apixaban vs warfarin	HR, 0.79; 95% CI, 0.61-1.04	HR, 0.65; 95% CI, 0.55-0.77	0.23
Rivaroxaban vs warfarin	HR, 1.25; 95% CI, 1.05-1.49	HR, 1.01; 95% CI, 0.94-1.10	0.034

Verma A, Cairns JA, Mitchell LB, et al. Can J Cardiol 2014;30:1114-30.

Prosthetic Valves

Table 5. Expert opinion survey regarding the clinical use of a NOAC in relation to the following commonly encountered scenarios: Would you consider NOAC use to be
1) contraindicated or
2) not contraindicated (i.e. reasonable to use) with the following valvular disorders?

NOAC use is contraindicated	NOAC use is reasonable
Mechanical heart valves • In any position (100% agreement)	Bioprosthetic heart valve • aortic position (82% agreement) • mitral position (73% agreement)
Rheumatic mitral stenosis • mild (47% agreement) • moderate-severe (88% agreement) • post commissurotomy (42% agreement)	Mitral annuloplasty • with or without prosthetic ring (88% agreement) Non-Rheumatic mitral stenosis • mild (97% agreement) Mitral regurgitation • mild (97% agreement) • moderate-severe (>90% agreement) Tricuspid regurgitation • Any severity (98% agreement)
Non-rheumatic mitral stenosis • moderate or severe (69% agreement)	Aortic Stenosis or Regurgitation • Mild (98% agreement) • Moderate-Severe (80% agreement)

http://www.ccs.ca/images/Guidelines/Companion_Resources/AFCompanion_Pamphlet_Final.pdf

Summary

- Real world data suggest that NOACs reduce adverse clinical outcomes compared with warfarin
- Real world data suggest that there maybe differences in effectiveness and safety between NOACs
- Although difficult, well-managed warfarin is still effective and should be used in patients in certain patient populations

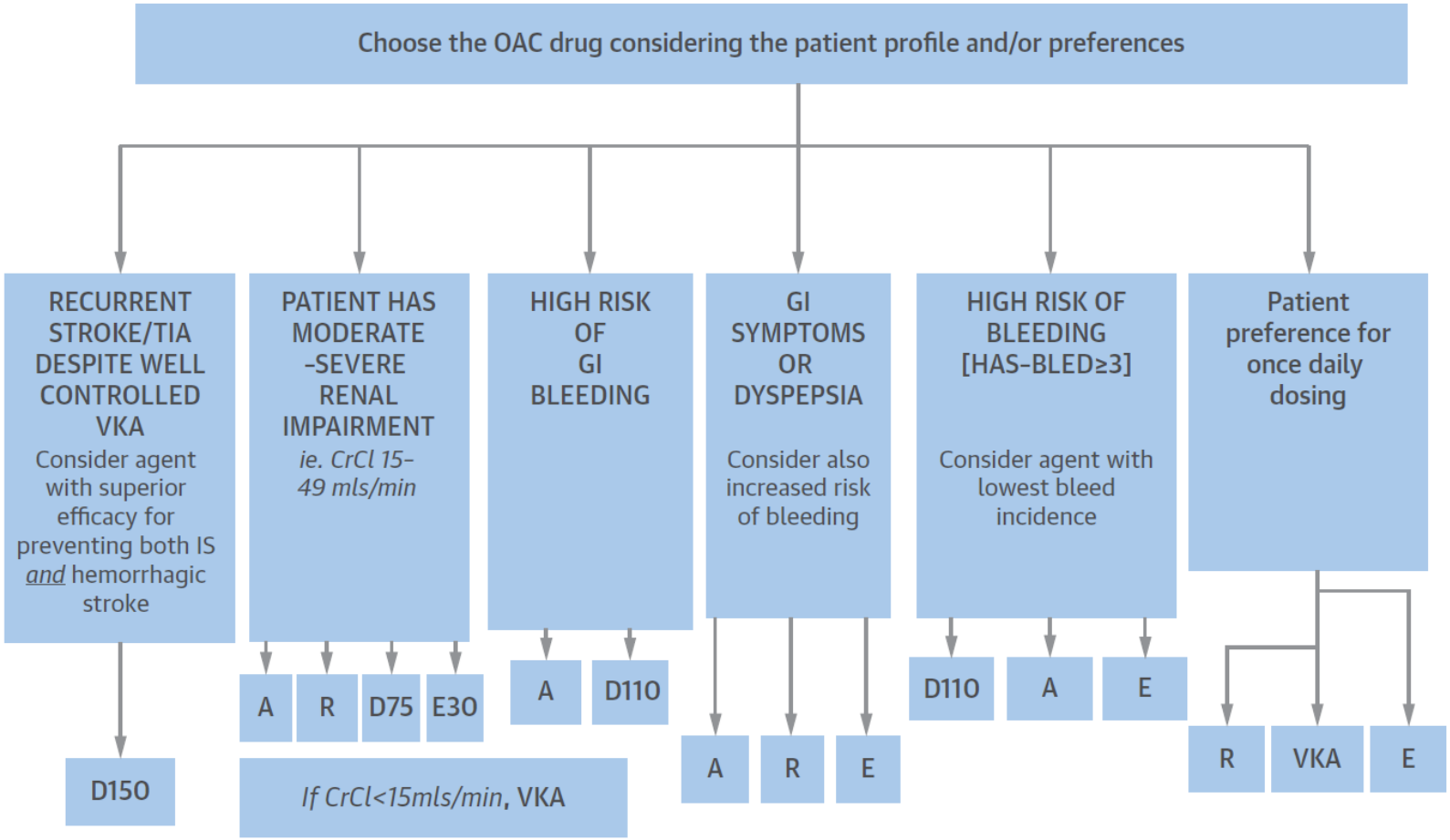
Thank You!

angaranp@smh.ca

Séminaire Winter Arrhythmia School

Annual Cardiac Arrhythmia Meeting
Division of Cardiology, University of Toronto

14th Annual
Collingwood, Ontario,
February 10 -12, 2017



Lip and Lane. JACC 2015; 66(21): 2282-2284

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Division of Cardiology, University of Toronto

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Collingwood, Ontario,
February 10 -12, 2017

Management of Antithrombotic Therapy in Patients With Concomitant AF and CAD

Séminaire Winter Arrhythmia School
Annual Cardiac Arrhythmia Meeting
Division of Cardiology, University of Toronto

CAD: Asymptomatic, stable CAD [defined by the absence of ACS for the preceding 12 months], elective PCI, NSTEACS or STEMI

- **Recommendation #1:** Patients with concomitant AF and CAD receive a regimen of antithrombotic therapy that is on the basis of a **balanced assessment** of risks of stroke, of a coronary event, and of hemorrhage associated with use of antithrombotic agents

- **Recommendation #2:** When OAC is indicated in the presence of CAD, NOAC is preferred over warfarin for NVAF

CAD - Coronary Artery Disease; ACS: Acute Coronary Syndrome;
PCI - Percutaneous Coronary Intervention;
NSTEACS - Non ST Elevation Acute Coronary Syndrome;
STEMI - ST Elevation Myocardial Infraction

Macle et al. Canadian Journal of Cardiology 2016; 32(10):117--1185

Concomitant AF and stable CAD

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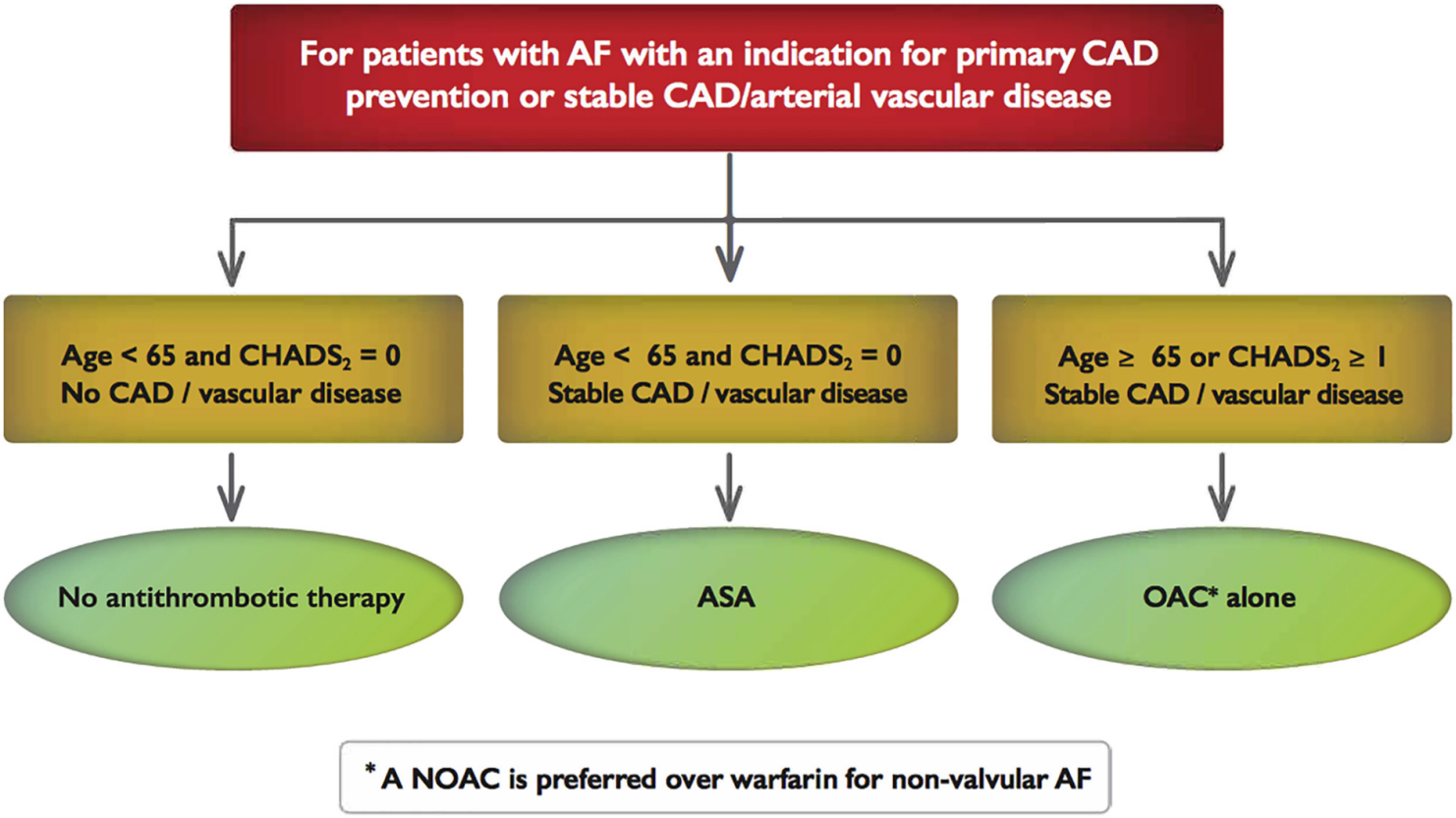

Figure 2. A summary of our recommendations for the management of antithrombotic therapy in patients with concomitant atrial fibrillation (AF) and an indication for primary coronary artery disease (CAD) prevention or stable CAD/arterial vascular disease. ASA, acetylsalicylic acid (aspirin); $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

Macle et al. Canadian Journal of Cardiology 2016; 32(10):117--1185

Concomitant AF and stable CAD

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- **Recommendation #3:** No antithrombotic therapy for patient with no evidence of CAD/vascular disease and <65 years old with no $CHADS_2$ risk factors

- **Recommendation #4:** ASA 81mg/d for patient with stable CAD/vascular disease and <65 years old with no $CHADS_2$ risk factors

- **Recommendation #5:** OAC therapy alone for patient with stable CAD/vascular disease and $\geq$65 years old or the $CHADS_2$ score $\geq$ 1

Macle et al. Canadian Journal of Cardiology 2016; 32(10):117--1185

Concomitant AF and NSTEACS or STEMI or PCI

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- Will be discussed by Dr. Racco

Macle et al. Canadian Journal of Cardiology 2016; 32(10):117--1185

Relevant clinical characteristics and dose adjustment in the four phase III NOAC trials in patients with atrial fibrillation

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 ml/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	Rivaroxaban 15 mg once daily if CrCl 30–49 mL/min	Apixaban 2.5 mg twice daily if at least two of age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 µmol/L)	Edoxaban 30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30-49 mL/min	21% with CrCl 30-49 mL/min	15% with CrCl 30-50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

European Heart Journal - doi:10.1093/eurheartj/ehw210

Measuring if there is an effect

- *Dabigatran*
  - If aPTT is normal, there is little effect
  - Dabigatran-standard thrombin time (Hemoclot test)
- *Rivaroxaban*
  - If PT is normal, there is little effect
  - Chromogenic Xa with rivaroxaban standard
- *Apixaban*
  - Less effect on PT
  - Chromogenic Xa with rivaroxaban standard
- **Time since last dose provides a good estimate!**

Reversal Agents for NOACs

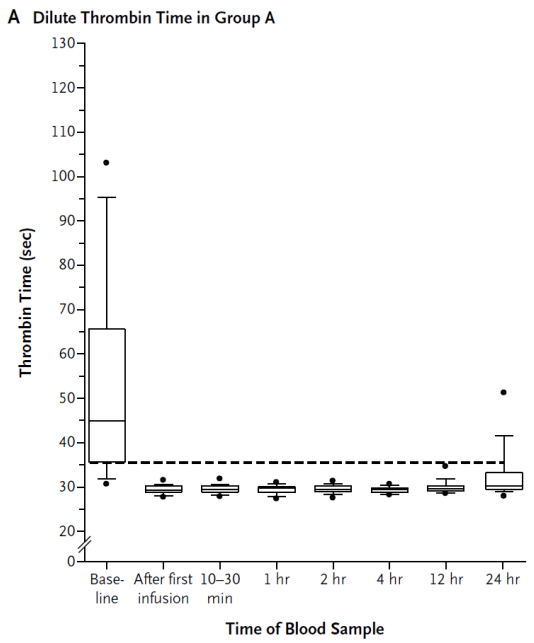
Macle et al. Canadian Journal of Cardiology 2016; 32(10):117--1185

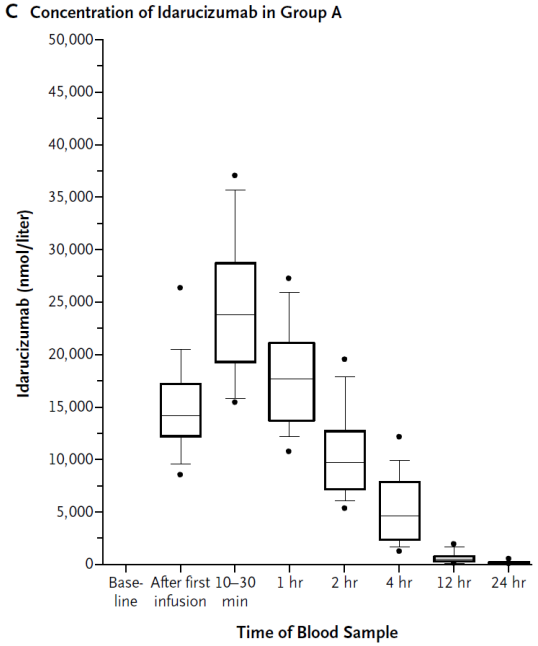
Reversal Agents for NOACs

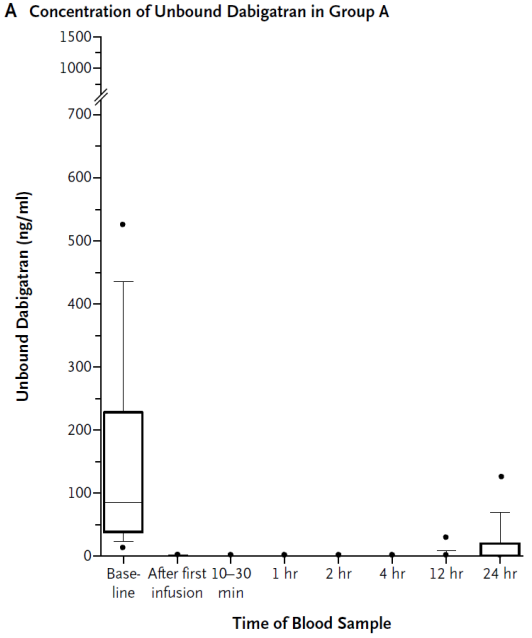
- **Recommendation #11:** Administer idarucizumab for emergency reversal of dabigatran's anticoagulant effect in patients with uncontrollable or potentially life-threatening bleeding and/or in patients who require urgent surgery for which normal hemostasis is necessary

Macle et al. Canadian Journal of Cardiology 2016; 32(10):117—1185
Pollack et al. N Eng J Med 2015:373:511-20

Idarucizumab for Dabigatran Reversal



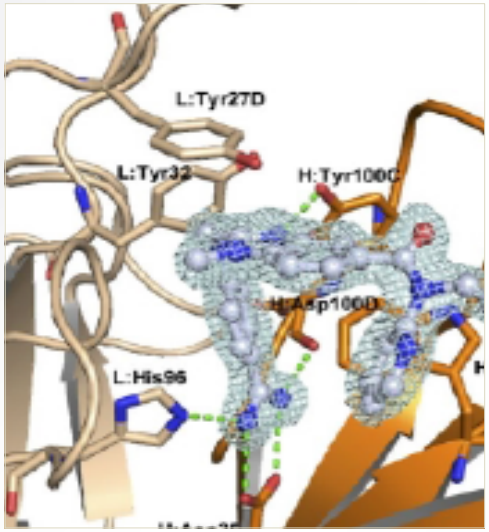




- Patients received 5 g of intravenous idarucizumab
  - Administered as two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 minutes apart

Pollack et al. NEJM 2015; 373:511-20

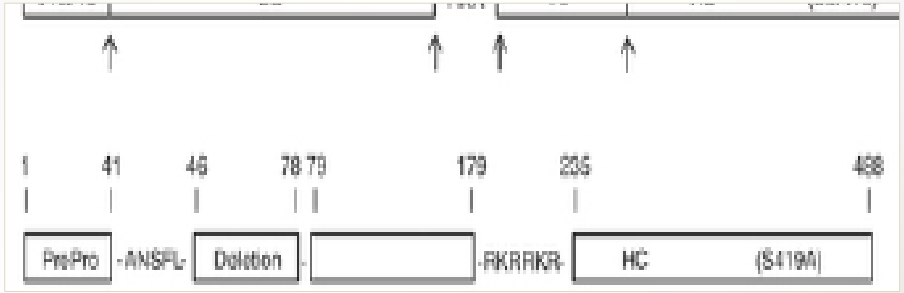
NOAC Antidotes



Idarucizumab (BI 655075)

Target: Dabigatran

Structure: Humanized antibody fragmen (Fab) to dabigatran



Andexanet alpha (PRT064445)

Target: FXa inhibitors

Structure: FXa lacking catalytic & binding activity

Aripazine (PER977; Ciraparantag)

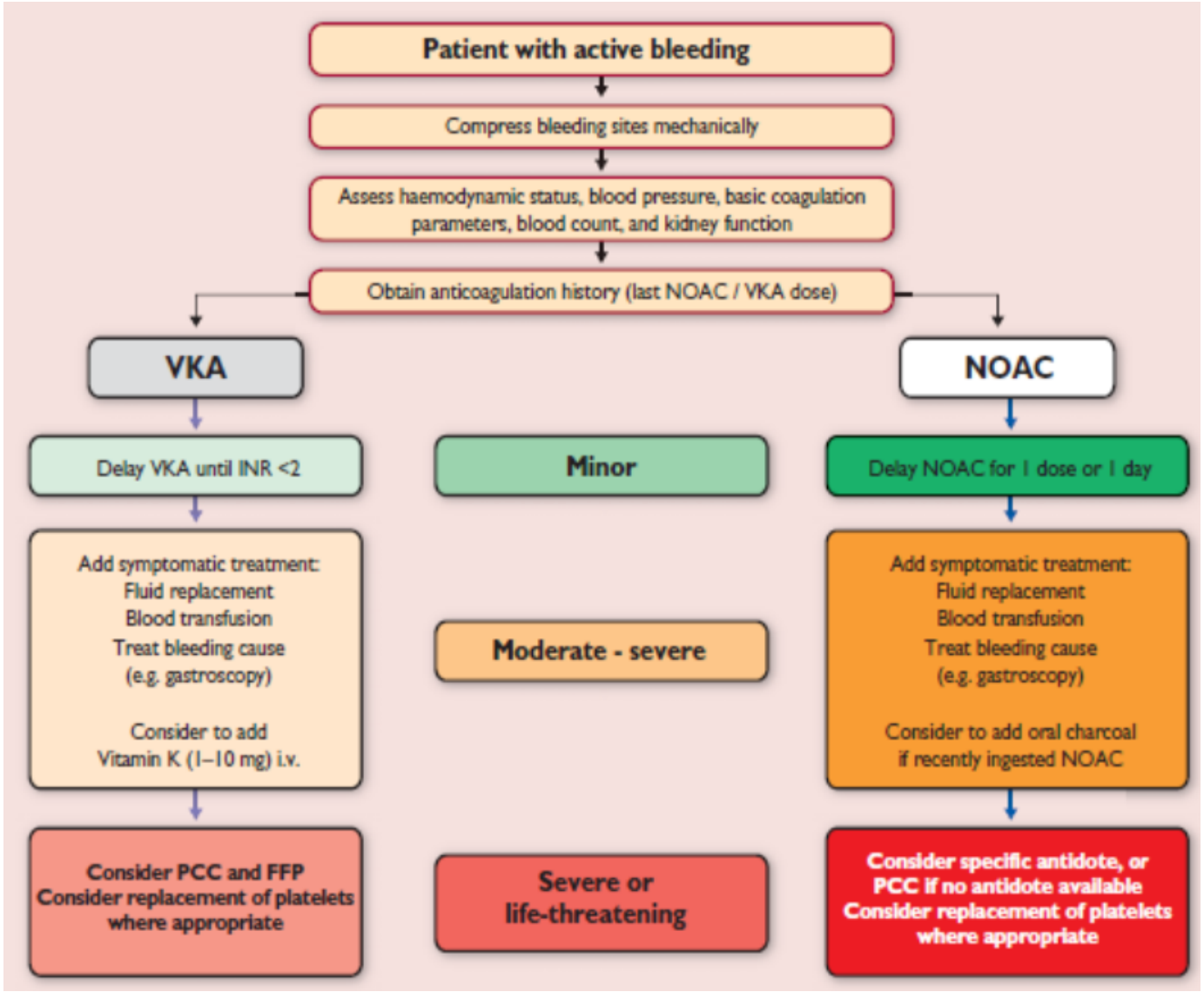
Target: Universal- all NOACs, heparin, LMWH

Structure: Synthetic small molecule (D-arginine)

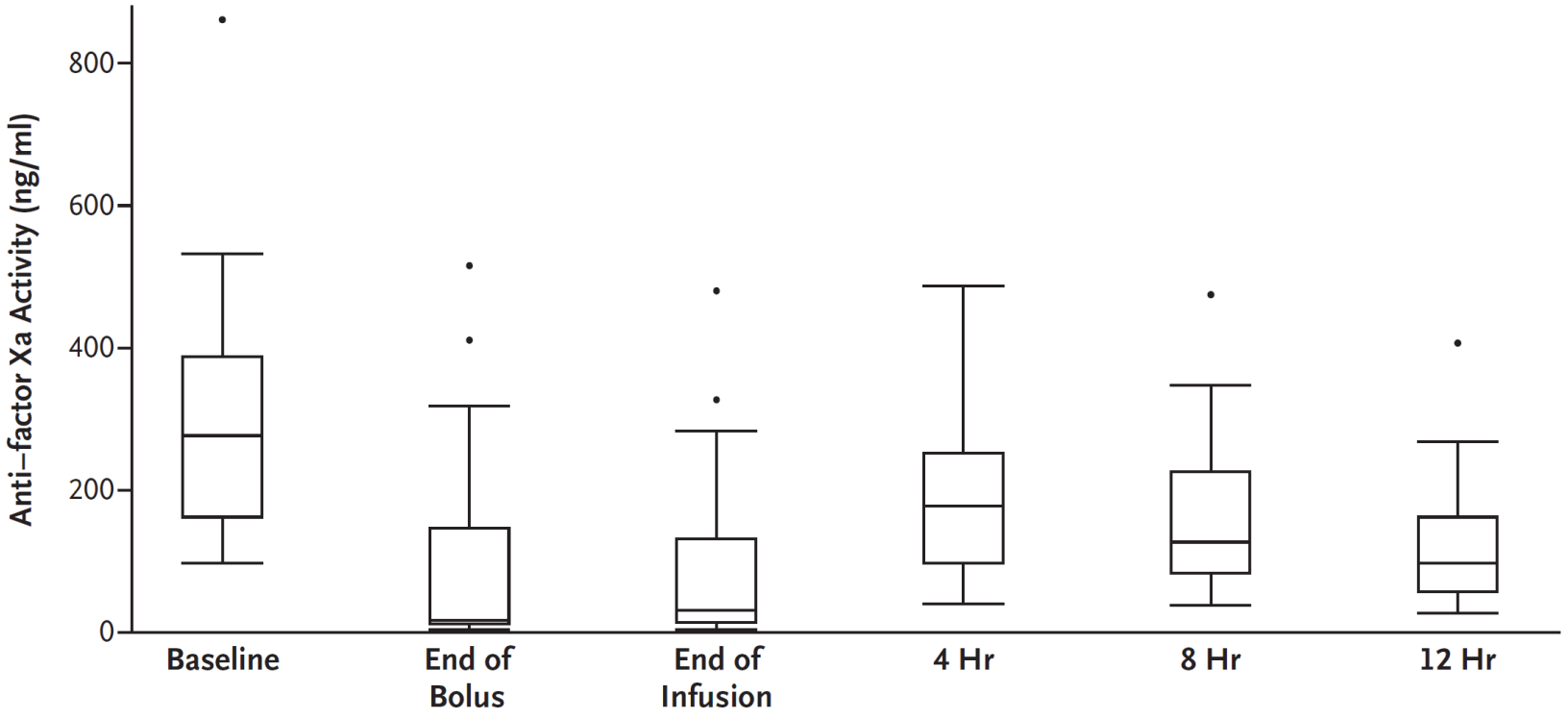
What about the Antidote?

- This has been a barrier to some physician and patient acceptance to switching from VKA to NOAC
- Utility of antidote is limited in severe bleeds, particularly intracranial hemorrhage
- In the REVERSE AD trial assessing idarucizimab (specific antidote for dabigatran), the mean time to cessation of bleeding was still over 11 hours
- However, for those who are insistent on antidotes, idarucizimab is now approved and andexanet alpha will likely be available in next year (antidote for all Xa inhibitors)
- In meantime, PCC is a great partial antidote for Xa inhibitors

ESC 2016 Bleeding management

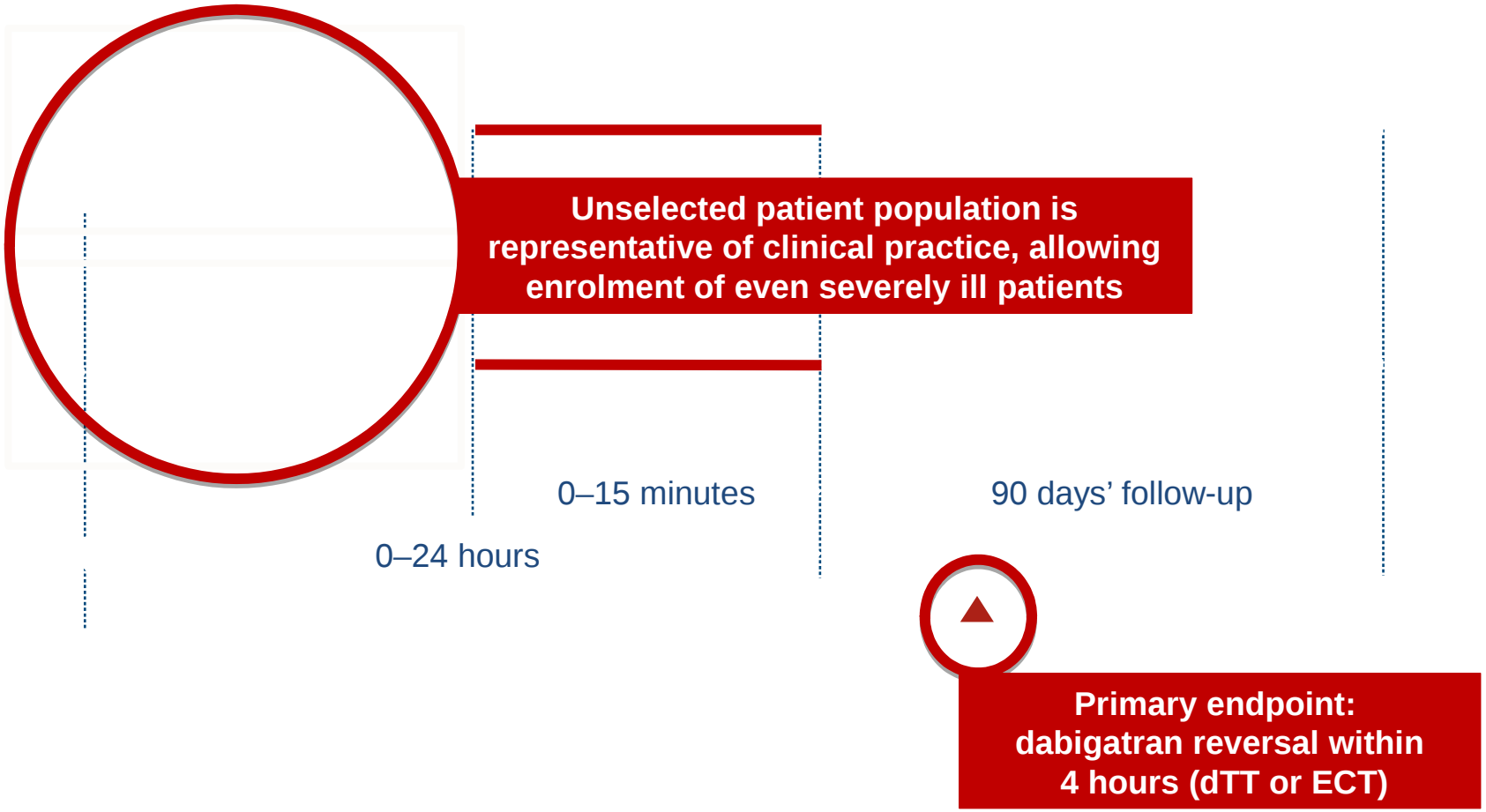


Andexanet alfa
Rivaroxaban reversal



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	277.0	16.8	30.6	177.7	127.1	97.9
Percent Change (95% CI)		–89 (–58 to –94)	–86 (–55 to –93)	–39 (–27 to –45)	–49 (–43 to –57)	–64 (–51 to –70)

REVERSE-AD
Study design



REVERSE-AD
Bleeding and thromboembolism

- Bleeding
  - Group A: cessation of bleeding
    - GI bleeding: median time to bleeding cessation 3.5 hours
    - Non GI, non ICH bleeding: median time to bleeding cessation 4.5 hours
  - Group B: peri-procedural haemostasis
    - 93% normal, 5% mildly abnormal, 2% moderately abnormal
- Thromboembolism
  - Overall rate 4.4% at 30 days; 6.3% at 90 days

REVERSE-AD
Re-initiation of anticoagulation

Summary

- Fear of bleeding remains a major barrier to the appropriate use of anticoagulants in AF
- The best way to reduce the burden of bleeding is prevention
- Most anticoagulant related bleeding can be managed with general supportive measures
- The availability of idarucizumab and future availability of andexanet alfa will help streamline bleeding management

Digoxin as rate-control agent

Macle et al. Canadian Journal of Cardiology 2016; 32(10):117--1185

Digoxin as rate-control agent

- **Recommendation #15:** Digoxin can be considered as a therapeutic option to achieve rate control in patients with AF and symptoms caused by rapid ventricular rates whose response to β-blockers and/or calcium channel blockers is inadequate, or in whom such rate controlling drugs are contraindicated or not tolerated

Macle et al. Canadian Journal of Cardiology 2016; 32(10):117--1185

Surgical Therapy for AF

Macle et al. Canadian Journal of Cardiology 2016; 32(10):117--1185

What are the definitions of stroke risk factors in the CCS AF guidelines update?

- The 2014 CCS Atrial Fibrillation Guidelines update used the $CHADS_2$ index with the evolved definitions of its component risk factors for stroke (Table 1).
- Female sex was not considered to be an independent risk factor, in agreement with the ESC 2012 guidelines.
- The 2014 CCS panel concluded that oral anticoagulant therapy was justified when the annual risk of the outcome of “stroke” exceeded 1.5%.
- CCS Algorithm recommended oral anticoagulation for patients aged 65 (even without any other criteria) and for younger patients with any of CHF, hypertension, diabetes, or stroke as defined in Table 1.

Camm AJ, Lip GY, De Caterina R, et al. Eur Heart J 2012;33:2719-47.

Canadian Journal of Cardiology 31 (2015) 24–28

Clinical Research

Atrial Fibrillation Patients Categorized as "Not for Anticoagulation" According to the 2014 Canadian Cardiovascular Society Algorithm Are Not "Low Risk"

Gregory Y.H. Lip, MD,[a,b] Peter Brønnum Nielsen, PhD,[a] Flemming Skjøth, PhD,[a,c] Lars Hvilsted Rasmussen, MD, PhD,[a,c] and Torben Bjerregaard Larsen, MD, PhD[a,c]

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See editorial by Cairns et al., pages 20-23 of this issue.

"

"Patient cohort drawn from the Danish registries who were < 65 years of age and had a $CHADS_2$ index score of 0, **included,** according to the definitions used by Lip et al., **many patients with previous systemic embolus or CHF**, the presence of either of which would lead to a recommendation for OAC treatment using the 2014 CCS algorithm."

Lip et al. Canadian Journal of Cardiology 31 (2015) 24-28
Cairns et al. Canadian Journal of Cardiology 31 (2015) 20-23

Controversy in “Low Risk Population”

- Data from epidemiological studies indicate the patients with CHA_2DS_2-VASC of 1 have an annual stroke rates of:
  - Denmark: 2.01% (Men) and 0.85% (Women)[1]
  - Sweden: 0.5% (Men) and 0.9% (Women)[2]
  - Taiwan: 2.75% (Men) ad 2.55% (Women)[3]

1 Olesen JB et al. BMJ 2011; 342:d124
2 Friberg L. et al. J Am Coll Cardiol. 2015;65(3):225-232
3 Chao TF et al. J Am Coll Cardiol. 2015;65(7):635-642

Management of Antithrombotic Therapy in Patients With Concomitant AF and CAD