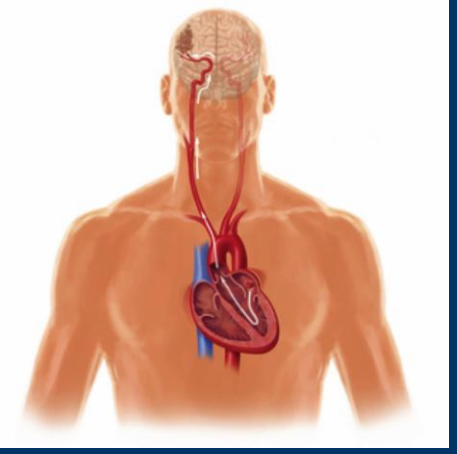

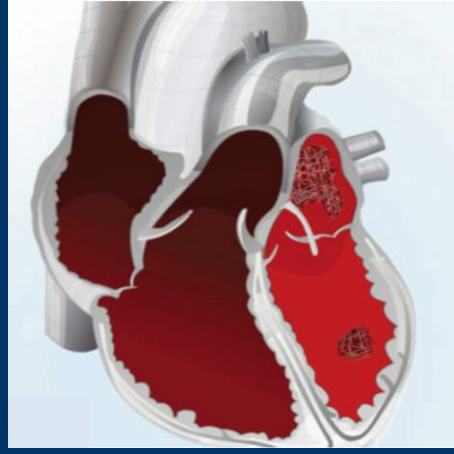

New Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation

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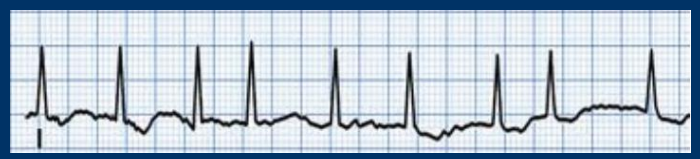


Disclosure

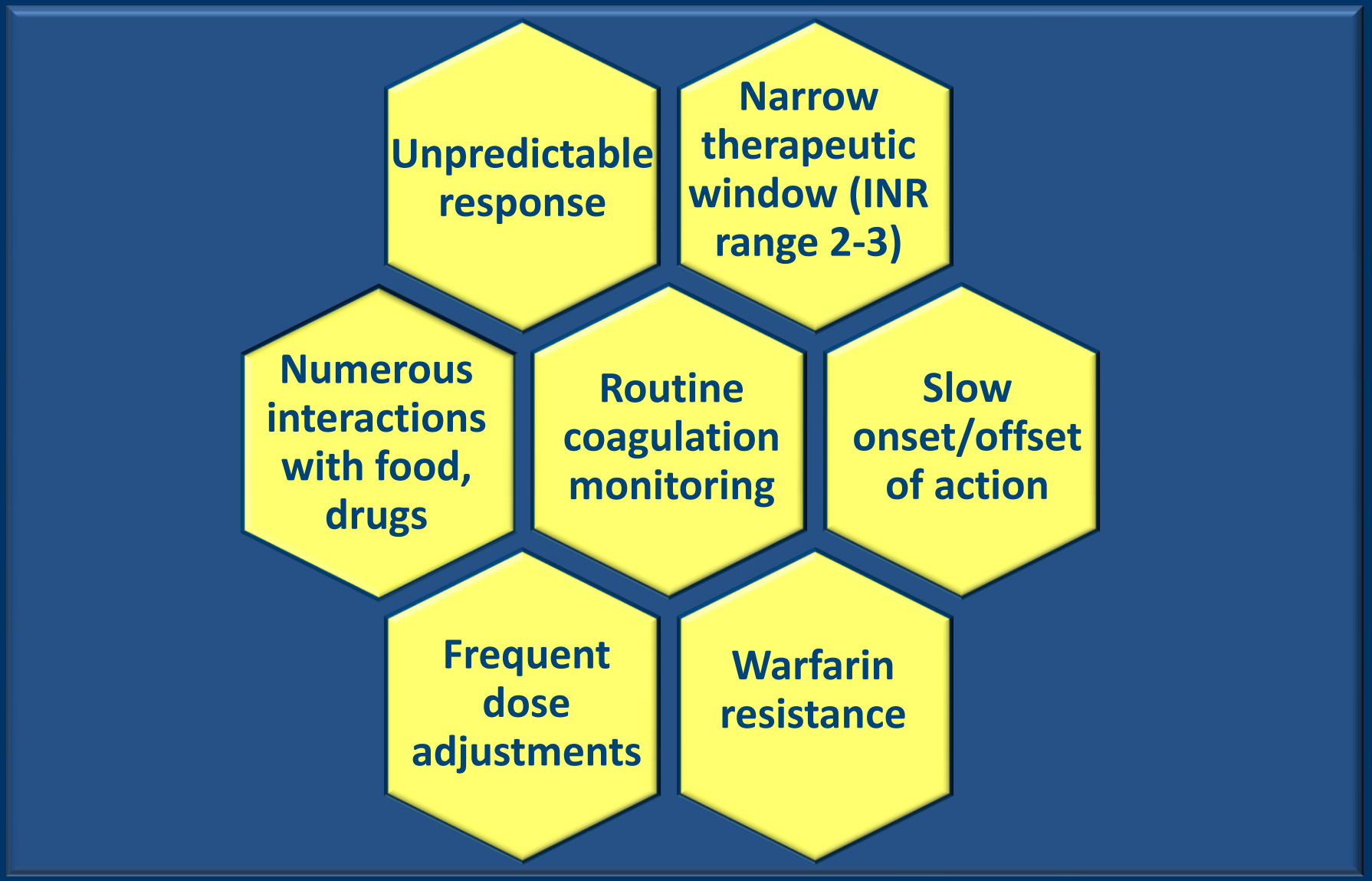
- Dr. Cox
  - Has served on advisory boards for Astra Zeneca, Bayer, Boehringer-Ingelheim, BMS, Pfizer and Sanofi-Aventis
  - Has participated in research funded by Merck, Pfizer and Sanofi-Aventis
  - Has served as/is a consultant to the Nova Scotia Department of Health, the New Brunswick Department of Health, the Public Health Agency of Canada, and the Canadian Agency for Drugs and Technologies in Health
  - Is a member of the Canadian Cardiovascular Society's Atrial Fibrillation Guidelines panel and Chair of the Atrial Fibrillation Quality Indicator Subcommitee

Warfarin is Underused and Suboptimally Used in Atrial Fibrillation

- Notwithstanding that warfarin is highly effective – reducing stroke in AF by 64% – its use is problematic
  - Associated with significant increase in intracranial and other hemorrhage
  - Registries show that only 50-60% of eligible patients receive warfarin
  - In clinical trials, time in therapeutic range (TTR) is 60-68%; in general practice, TTR is typically <50%

Hart *Ann Int Med* 2007;146:857; Hylek *Stroke* 2006;37:1075; Singer *Chest* 2008;133:546S; Gladstone *Stroke* 2009;40:235; CCS guidelines 2004; Matchar *Am J Med* 2002;113:42; Bungard *Pharmacotherapy* 2000;20:1060

Limitations of Warfarin Therapy Make it Difficult to Use in Practice

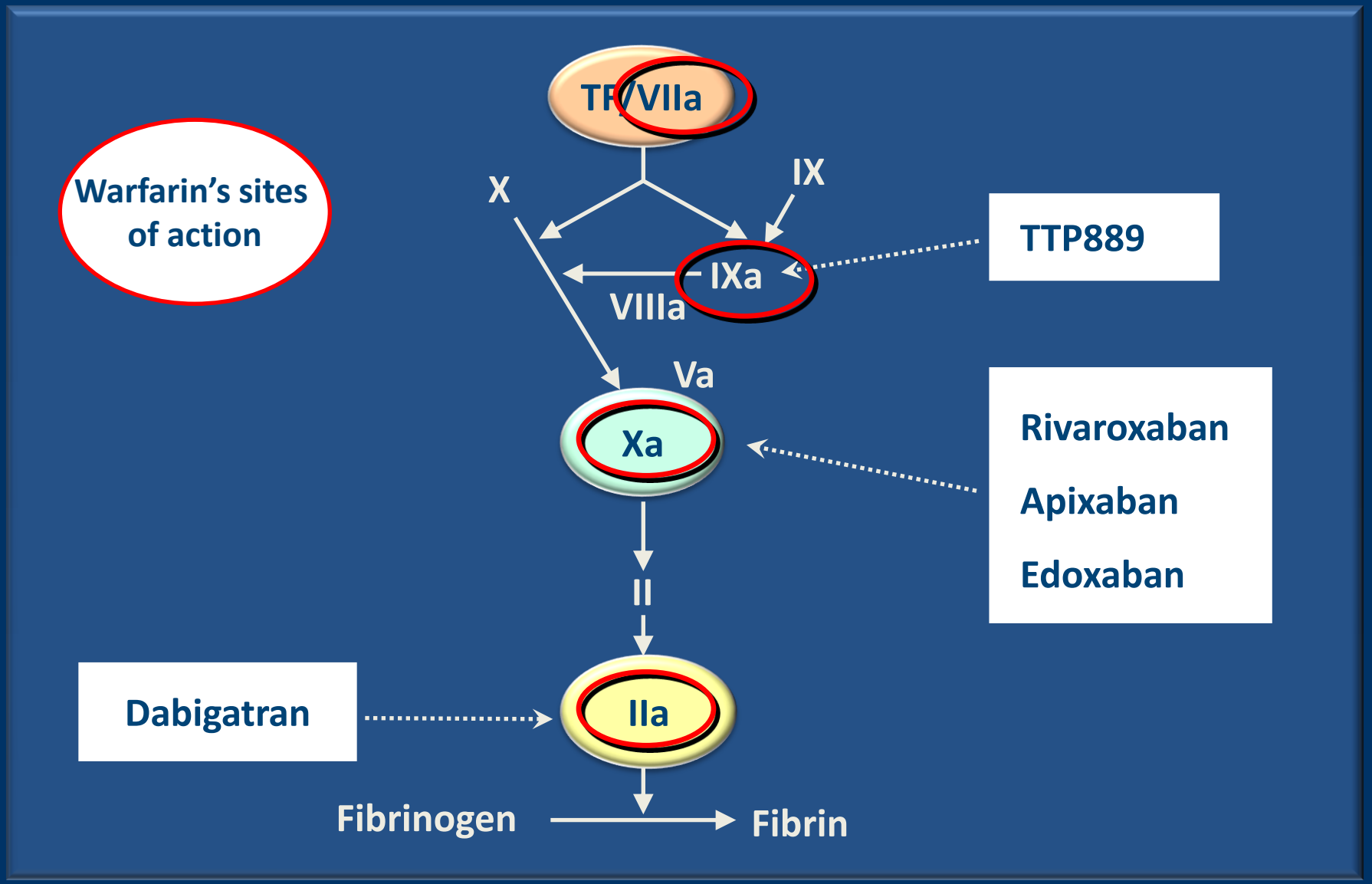


New and Emerging Anticoagulants for Stroke Prevention in AF

- **Direct Thrombin Inhibitors**
  - Dabigatran
- **Factor Xa Inhibitors**
  - Rivaroxaban
    - Phase III results published Aug. 2011
  - Apixaban
    - Phase III results published Aug. 2011
  - Edoxaban
    - Phase III trial results expected March, 2012

http://www.clinicaltrials.gov/ct2/search

New Oral Anticoagulant Agents in AF



Adapted from Turpie *Eur Heart J* 2008; 29:155

Key Features of New Oral Anticoagulants

	Dabigatran[1,2,3,7]	Rivaroxaban[3,4,7]	Apixaban[3,5,7]	Edoxaban[3,6,7]
Mechanism of action	Direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Current Indications (Canada)	• Stroke prevention in AF (Oct/2010) • VTE prophylaxis post orthopedic surgery (Mar/2009)	• VTE prophylaxis post orthopedic surgery (Sep/2008)	None	None
Prodrug	Prodrug	No	No	No
Bioavailability	6 %	> 80 %	66 %	45 %
Tmax	2 hrs	2-4 hrs	3 hrs	1.5 hs
Half-life	14-17 hours	7-11 hours	8-15 hours	9-11 hours
Dosing Frequency	QD (orthopedic) BID (AF)	QD (orthopedic & AF)	BID (orthopedic & AF)	QD (AF)
Excretion	80% renal, 20% fecal	66% renal (33% unchanged, 33% inactive metabolites); 33% fecal	70% fecal; 25% renal	65% fecal; 35% renal
Food Interactions	None	None	None	None
Drug Interactions	P-glycoprotein	CYP3A4 and P-glycoprotein	CYP3A4 and P-glycoprotein	Potentially P-glycoprotein

[1]*Pradax* Product Monograph 2010; [2]Stangier *Clin Pharmacokinet* 2008; [3]Eriksson *Clin Pharmacokinet* 2009; [4]*Xarelto* Product Monograph 2008 ; [5]Raghaven *Drug Metab Dispos* 2009; [6]Ruff *Am Heart J* 2010; [7]Nutescu *J Thromb Thrombolysis* 2011

Summary of Phase III Trials in AF

Trial	Drug	Dose	Comparator	N	Trial Design
RE-LY	Dabigatran	110 & 150 mg BID	Warfarin	18,113	Open-label
ROCKET-AF	Rivaroxaban	20 / 15 mg QD	Warfarin	14,264	Double-blind
ARISTOTLE	Apixaban	5 / 2.5 mg BID	Warfarin	18,201	Double-blind
ENGAGE AF	Edoxaban	30 & 60 mg QD	Warfarin	20,500	Double-blind

http://www.clinicaltrials.gov/ct2/search

Dabigatran Phase III: RE-LY Study

20,240 patients with NVAF assessed for eligibility:

Inclusion Criteria

≥1 of: stroke, TIA , systemic embolus, LVD, age ≥75,
age 65-75 + (diabetes mellitus, CAD, or hypertension)

18,113 patients randomized
from 967 centres in 44 countries

- **Warfarin INR 2.0-3.0**
- **Dabigatran etexilate 110 mg BID**
- **Dabigatran etexilate 150 mg BID**

- Non-inferiority with pre-specified superiority comparisons if both doses demonstrated non-inferiority
- Prospective, open-label, randomized trial with blinded evaluation of outcomes (PROBE design)
- Patients randomized to 1 of 2 blinded doses of dabigatran or open-label warfarin
- Primary outcome measures: Stroke (including haemorrhagic) or systemic embolism; ISTH major bleeding
- Balanced enrolment of warfarin naïve & experienced

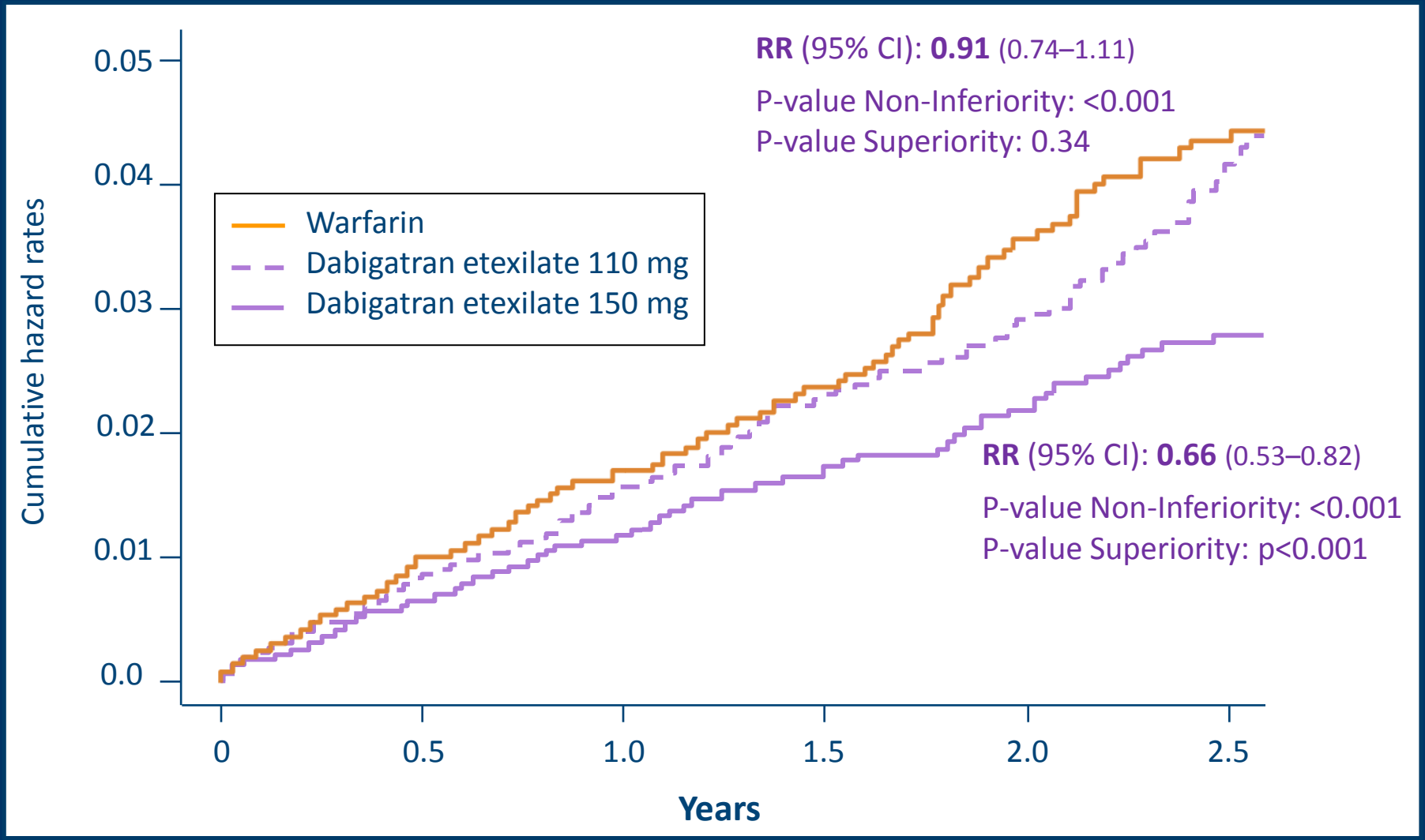
Connolly *et al. N Engl J Med* 2009

Baseline Characteristics

Characteristic	Dabigatran 110 mg N=6015	Dabigatran 150 mg N= 7076	Warfarin N=6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean) 0-1 (%) 2 (%) 3+ (%)	2.1 32.6 34.7 32.7	2.2 32.2 35.2 32.6	2.1 30.9 37.0 32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin naïve (%)	49.9	49.8	51.4
Discontinued rate (%)	20.7	21.1	16.6

Connolly *NEJM* 2009;361:1139

Primary Efficacy Outcome:
Stroke or Non-CNS Embolism



Connolly *NEJM* 2009;361:1139

Primary Outcome:
Superiority Analysis

	D 110mg Annual rate	D 150mg Annual rate	W Annual rate	D 110 mg vs. W RR 95% CI	P	D 150 mg vs. W RR 95% CI	P
Stroke or Systemic Embolism	1.5 %	1.1 %	1.7 %	0.90 0.74-1.10	0.30	0.65 0.52-0.81	<0.001
Stroke	1.4 %	1.0 %	1.6 %	0.91 0.74-1.12	0.38	0.64 0.51-0.81	<0.001
Ischemic or Unspecified	1.3 %	0.9 %	1.2 %	1.11 0.88-1.39	0.35	0.76 0.59-0.97	0.03
Hemorrhagic	0.12 %	0.10 %	0.38 %	0.31 0.17-0.56	<0.001	0.26 0.14-0.49	<0.001
Non-disabling	0.50 %	0.37 %	0.58 %	0.86 0.61-1.22	0.40	0.62 0.43-0.91	0.01
Disabling or fatal	0.94%	0.66%	1.0 %	0.93 0.72-1.21	0.61	0.66 0.50-0.87	0.004

Connolly *NEJM* 2010;363:1876

Safety Outcome:
Bleeding

	D 110mg Annual rate	D 150mg Annual rate	W Annual rate	D 110 mg vs. W RR 95% CI	D 110 mg vs. W P	D 150 mg vs. W RR 95% CI	D 150 mg vs. W P
Total Bleeding	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Intracranial Bleeding	0.23 %	0.30 %	0.74 %	0.31 0.20-0.47	<0.001	0.40 0.27-0.60	<0.001
Major Bleeding	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life-Threatening Major Bleed	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Fatal Bleed	0.19 %	0.23 %	0.32 %	0.60 0.36-1.00	0.05	0.72 0.44-1.17	0.19
GI Major Bleed	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001

Connolly *NEJM* 2009;361:1139

Additional Clinical Outcomes

	D 110mg Annual rate	D 150mg Annual rate	W Annual rate	D 110 mg vs. W RR 95% CI	P	D 150 mg vs. W RR 95% CI	P
Myocardial Infarction*	0.82% *(0.72%)*	0.81% *(0.74%)*	0.64% *(0.53%)*	1.29 0.96-1.75	0.09 *(0.07)*	1.27 0.94-1.71	0.12 *(0.048)*
Death*	3.8 %	3.6 %	4.1 %	0.91 0.80-1.03	0.13	0.88 0.77-1.00	0.05
Vascular Death*	2.4 %	2.3 %	2.7 %	0.90 0.77-1.07	0.21	0.85 0.72-0.99	0.04
Dyspepsia	11.8%	11.3%	5.8%	Either dose vs. warfarin p<0.001			
Net Clinical Benefit*	7.34	7.11	7.92	0.92 0.84-1.01	0.09	0.90 0.82-0.99	0.02

Net Clinical Benefit: Stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage

Connolly *NEJM* 2009;361:1139
*Connolly *NEJM* 2010;363:1876

Summary of Key Findings for Dabigatran

In a population of low-moderate to high risk patients:

Efficacy:

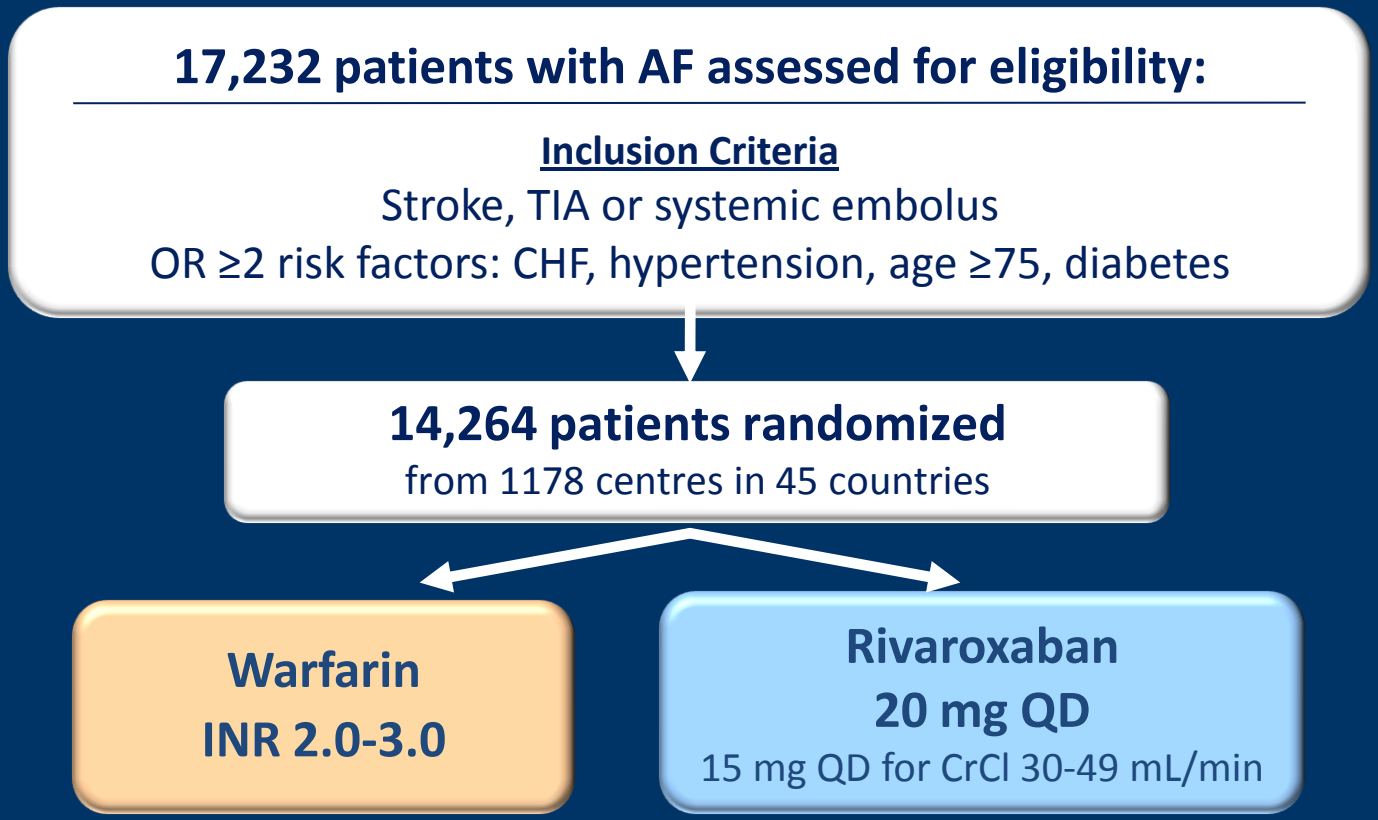
- Dabigatran 150 mg was superior to warfarin for stroke prevention, reducing the risk of both ischemic and hemorrhagic stroke
- Dabigatran 110 mg was similar to warfarin for stroke prevention
- Dabigatran 150 mg reduced the risk of cardiovascular mortality

Safety:

- Major bleeding was reduced with dabigatran 110 mg vs. warfarin
- The risk of major bleeding with dabigatran 150 mg was similar to warfarin
- Both doses of dabigatran reduced the risk of ICH

Connolly *NEJM* 2009;361:1139

Rivaroxaban Phase III: ROCKET-AF Study



- Non-inferiority with pre-specified superiority comparisons if non-inferiority demonstrated
- Prospective, double-blind, double-dummy
- Primary outcome measures: Stroke (including haemorrhagic) or non-CNS systemic embolism; Major and non-major clinically relevant bleeding

Patel *N Engl J Med* 2011;365:883

Baseline Characteristics

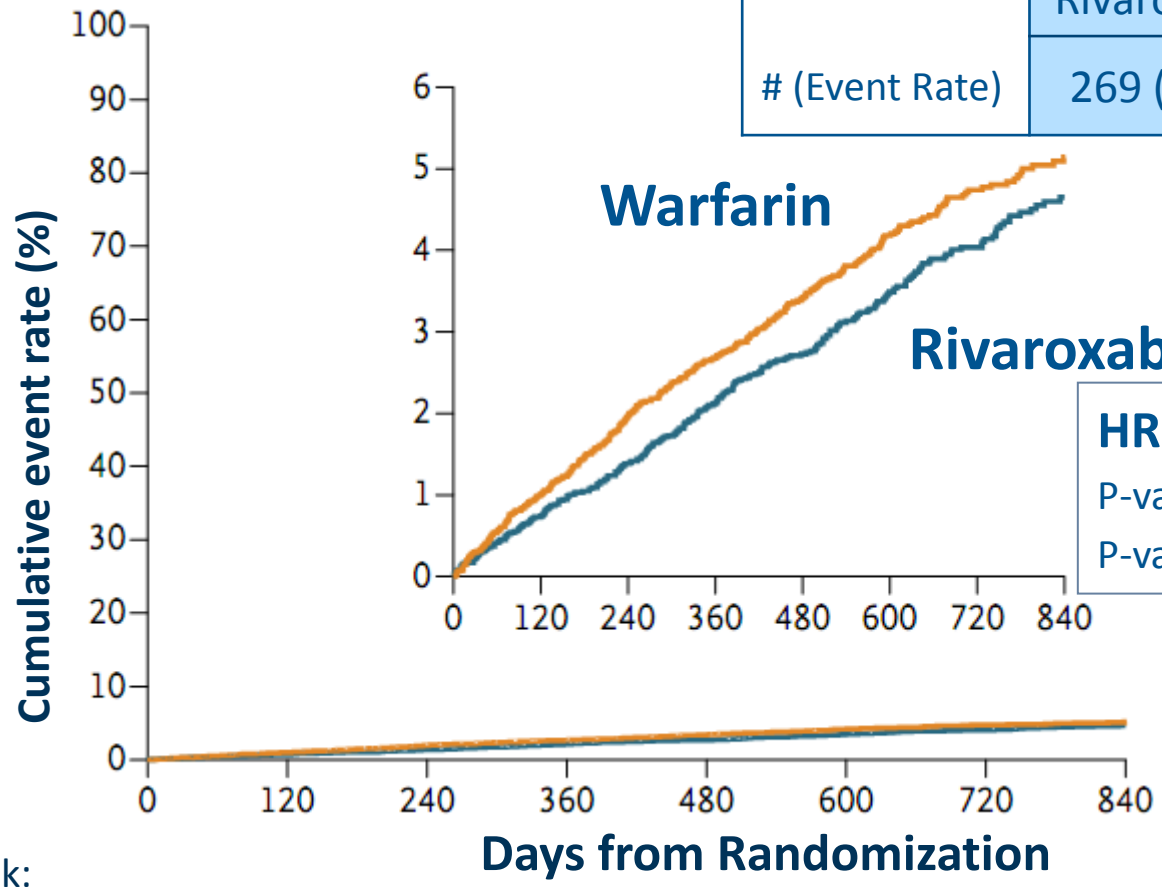
	Rivaroxaban (N=7081)	Warfarin (N=7090)
Age (years) (median (IQR))	73 (65, 78)	73 (65, 78)
Female (%)	39.7	39.7
$CHADS_2$ Score (mean) **2 (%)** **3 (%)** **≥4 (%)**	3.48 13.0 42.9 44.1	3.46 13.1 44.3 42.6
Prior VKA Use (%)	62.3	63.5
Congestive Heart Failure (%)	62.6	62.3
Hypertension (%)	90.3	90.8
Diabetes Mellitus (%)	40.4	39.5
Prior Stroke / TIA / Embolism (%)	54.9	54.6
Prior Myocardial Infarction (%)	16.6	18.0

Based on Intention-to-Treat Population

Patel *N Engl J Med* 2011;365:883

Primary Efficacy Outcome*:
Stroke or Non-CNS Embolism

	Rivaroxaban	Warfarin
# (Event Rate)	269 (2.1%)	306 (2.4%)



HR (95% CI): **0.88** (0.74, 1.03)
P-value Non-Inferiority: <0.001
P-value Superiority: 0.12

No. at risk:

Rivaroxaban	7081	6879	6683	6470	5264	4105	2951	1785
Warfarin	7090	6871	6656	6440	5225	4087	2944	1783

Event Rates are per 100 patient-years
*** Based on Intention-to-Treat Population**

Patel *N Engl J Med* 2011;365:883

Key Secondary Efficacy Outcomes*

	Rivaroxaban Event Rate (per 100 patient/years)	Warfarin Event Rate (per 100 patient/years)	HR (95% CI)	P-value
Vascular Death, Stroke, Embolism	4.51	4.81	0.94 (0.84, 1.05)	0.27
Stroke				
Hemorrhagic	0.26	0.44	0.58 (0.38, 0.89)	0.01
Ischemic	1.62	1.64	0.99 (0.82, 1.20)	0.92
Unknown Type	0.15	0.14	1.05 (0.55, 2.01)	0.87
Non-CNS Embolism	0.16	0.21	0.74 (0.42, 1.32)	0.31
Myocardial Infarction	1.02	1.11	0.91 (0.72, 1.16)	0.46
All Cause Mortality	4.52	4.91	0.92 (0.82, 1.03)	0.15
Vascular	2.91	3.11	0.94 (0.81, 1.08)	0.35
Non-vascular	1.15	1.22	0.94 (0.75, 1.18)	0.61
Unknown Cause	0.46	0.57	0.80 (0.57, 1.12)	0.20

*Based on Intention-to-Treat Population

Patel *N Engl J Med* 2011;365:883

Safety Outcomes*

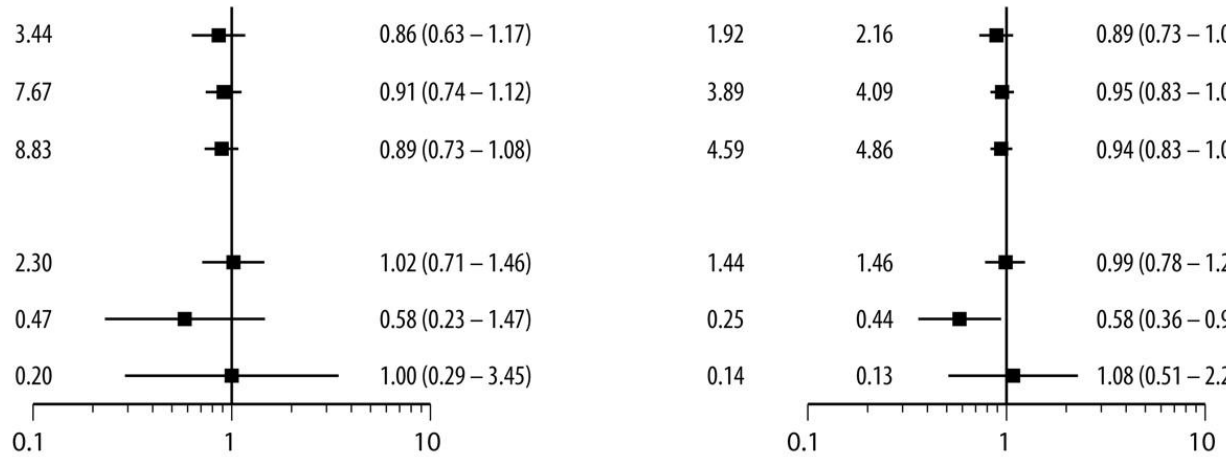
	Rivaroxaban Event Rate (per 100 patient/years)	Warfarin Event Rate (per 100 patient/years)	HR (95% CI)	P-value
Primary: Major and Non-Major Clinically Relevant Bleeding	14.9	14.5	1.03 (0.96, 1.11)	0.44
Major:	3.6	3.4	1.04 (0.90, 1.20)	0.58
≥2 g/dL Hgb drop	2.8	2.3	1.22 (1.03, 1.44)	0.02
Transfusion (> 2 units)	1.6	1.3	1.25 (1.01, 1.55)	0.04
Critical Bleeding	0.8	1.2	0.69 (0.53, 0.91)	0.007
Fatal Bleeding	0.2	0.5	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	0.5	0.7	0.67 (0.47, 0.93)	0.02
Major GI Bleeding	3.2 % of pts	2.2% of pts	Not reported	<0.001
Non-Major Clinically Relevant Bleeding	11.8	11.4	1.04 (0.96, 1.13)	0.35

*Based on Safety On-Treatment Population

Patel *N Engl J Med* 2011;365:883

Efficacy According to Renal Function:
Intention to Treat Analysis

Clinical Endpoint	CrCl 30 – 49 ml/min			CrCl ≥50 ml/min			P Value
	Rivaroxaban 15 mg (N=1462)*	Warfarin N=1459	HR (95% CI) Rivaroxaban vs Warfarin	Rivaroxaban 20 mg (N=5619)*	Warfarin N=5622	HR (95% CI) Rivaroxaban vs Warfarin	Interaction
Principal Efficacy Endpoint (Stroke and Systemic Embolism)	2.95	3.44	0.86 (0.63 – 1.17)	1.92	2.16	0.89 (0.73 – 1.08)	0.85
PE + Vascular Death	7.00	7.67	0.91 (0.74 – 1.12)	3.89	4.09	0.95 (0.83 – 1.09)	0.74
PE + MI, Vascular Death	7.86	8.83	0.89 (0.73 – 1.08)	4.59	4.86	0.94 (0.83 – 1.07)	0.61
Stroke							
Ischemic	2.34	2.30	1.02 (0.71 – 1.46)	1.44	1.46	0.99 (0.78 – 1.24)	0.89
Hemorrhagic	0.27	0.47	0.58 (0.23 – 1.47)	0.25	0.44	0.58 (0.36 – 0.94)	0.99
Undetermined	0.20	0.20	1.00 (0.29 – 3.45)	0.14	0.13	1.08 (0.51 – 2.29)	0.92



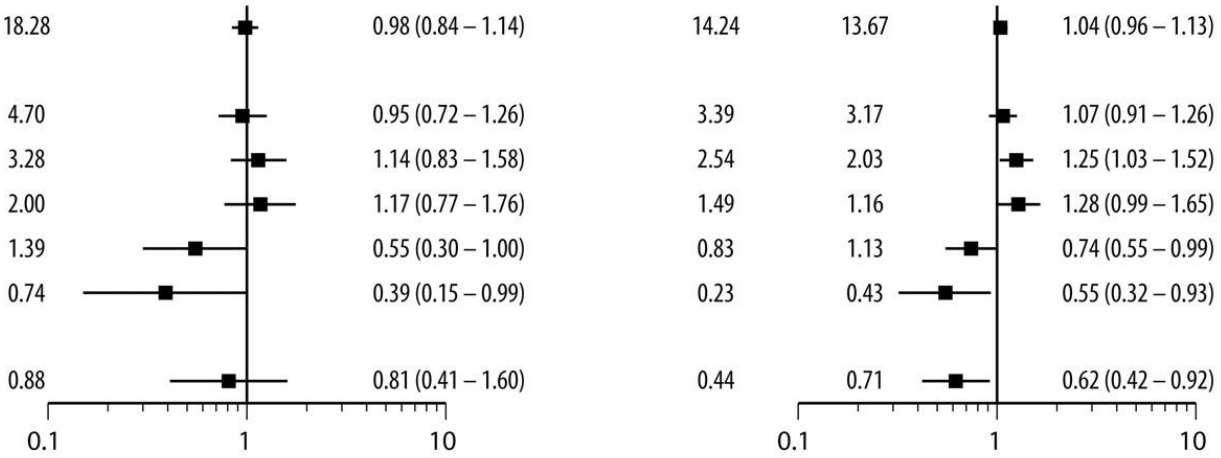
* Event rates per 100 pt/yrs of follow-up

Fox K A et al. Eur Heart J 2011;eurheartj.ehr342

European Heart Journal

Safety According 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

Fox K A et al. Eur Heart J 2011;eurheartj.ehr342

European Heart Journal

Summary of Key Findings for Rivaroxaban

In a population of moderate to high risk patients:

Efficacy:

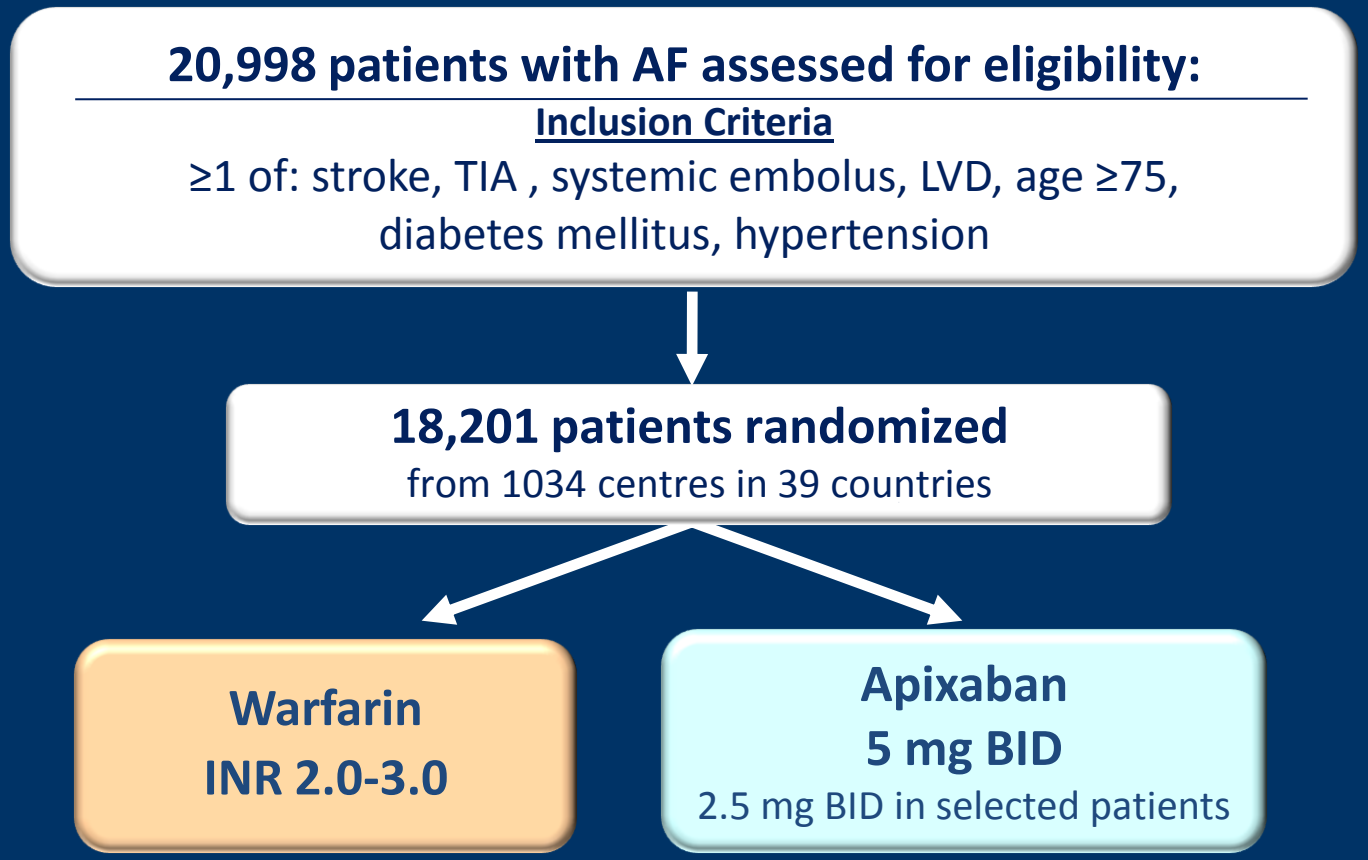
- Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism
- Rivaroxaban reduced the risk of hemorrhagic but not ischemic stroke

Safety:

- The risk of major or non-major clinically relevant bleeding with rivaroxaban was similar to warfarin
- Rivaroxaban reduced the risk of ICH

Patel *N Engl J Med* 2011;365:883

Apixaban Phase III: ARISTOTLE Study



- Non-inferiority with pre-specified superiority comparisons if non-inferiority demonstrated
- Prospective, double-blind, double-dummy
- Primary outcome measures: Stroke (including haemorrhagic) or systemic embolism; ISTH major bleeding

Granger *N Engl J Med* 2011;365:981

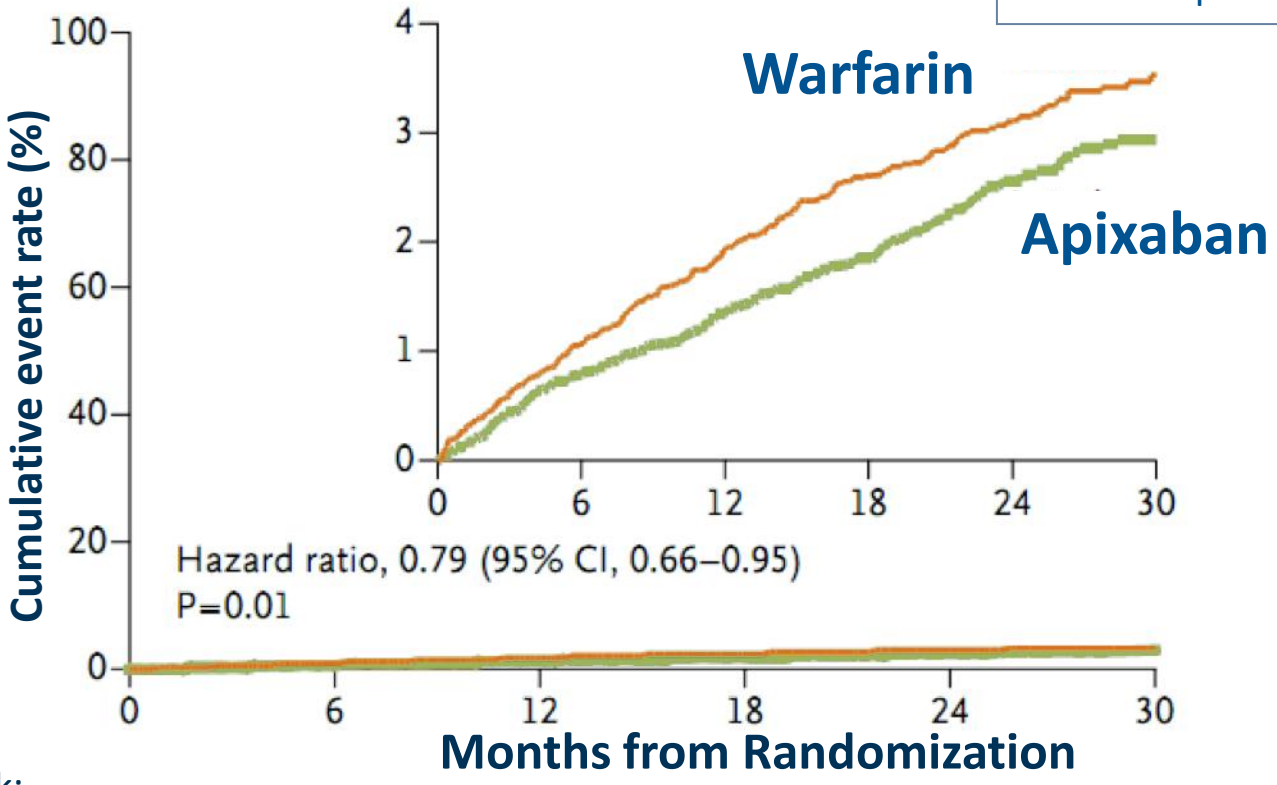
Baseline Characteristics

	Apixaban (N=9120)	Warfarin (N=9081)
Age (years) (median (IQR))	70 (63, 76)	70 (63, 76)
Female (%)	35.5	35.0
$CHADS_2$ Score (mean) ≤1 (%) 2 (%) ≥3 (%)	2.1 34.0 35.8 30.2	2.1 34.0 35.8 30.2
Prior VKA Use (%)	57.1	57.2
Congestive Heart Failure (%)	35.5	35.4
Hypertension (%)	87.3	87.6
Diabetes Mellitus (%)	25.0	24.9
Prior Stroke / TIA / Embolism (%)	19.2	19.7
Prior Myocardial Infarction (%)	14.5	13.9

Granger *N Engl J Med* 2011;365:981

Primary Efficacy Outcome:
Stroke or Systemic Embolism

HR (95% CI): **0.79** (0.66, 0.95)
P-value Non-Inferiority: <0.001
P-value Superiority: 0.01



No. at risk:

Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Granger *N Engl J Med* 2011;365:981

Efficacy Outcomes

	Apixaban Event Rate (per 100 patient/years)	Warfarin Event Rate (per 100 patient/years)	HR (95% CI)	P-value†
Primary Outcome: Stroke or Systemic Embolism	1.27	1.60	0.79 (0.66, 0.95)	<0.001 non-inferiority 0.01
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.01
Ischemic or uncertain type	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic Embolism	0.09	0.10	0.87 (0.44, 1.75)	0.70
All Cause Mortality	3.52	3.94	0.89 (0.80, 0.998)	0.047
Myocardial Infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

† P-values are for superiority, unless otherwise indicated.

Granger *N Engl J Med* 2011;365:981

Bleeding and Net Clinical Outcomes

	Apixaban Event Rate (per 100 patient/years)	Warfarin Event Rate (per 100 patient/years)	HR (95% CI)	P-value
Primary: Major Bleeding	2.13	3.09	0.69 (0.60, 0.80)	<0.001
Intracranial Hemorrhage	0.33	0.80	0.42 (0.30, 0.58)	<0.001
Other Location	1.79	2.27	0.79 (0.68, 0.93)	0.004
Major GI Bleeding	0.76	0.86	0.89 (0.70, 1.15)	0.37
Major or Clinically Relevant Non-Major	4.07	6.01	0.68 (0.61, 0.75)	<0.001
Net Clinical Outcome*	6.13	7.20	0.85 (0.78, 0.92)	<0.001

*Net Clinical Outcome: Stroke, systemic embolism, death, or major hemorrhage

Granger *N Engl J Med* 2011;365:981

Summary of Key Findings for Apixaban

In a population of low-moderate to high risk patients:

Efficacy:

- Apixaban was superior to warfarin for preventing stroke and non-CNS embolism
- Apixaban reduced the risk of hemorrhagic but not ischemic stroke
- Apixaban reduced the risk of overall mortality

Safety:

- Apixaban reduced the risk of major bleeding and ICH compared to warfarin

Granger *N Engl J Med* 2011;365:981

Edoxaban Phase III: ENGAGE AF TIMI-48 Study

Patients with NVAF assessed for eligibility:

Inclusion Criteria

Stroke, TIA or systemic embolus

OR ≥2 risk factors: CHF, hypertension, age ≥75, diabetes

~20,500 patients randomized
from 1400 centres in 46 countries

Randomization stratified by:
1. $CHADS_2$ 2-3 vs. 4-6
2. Increased drug exposure

Warfarin
INR 2.0-3.0

Edoxaban Low Dose
30 mg QD

Edoxaban High Dose
60 mg QD

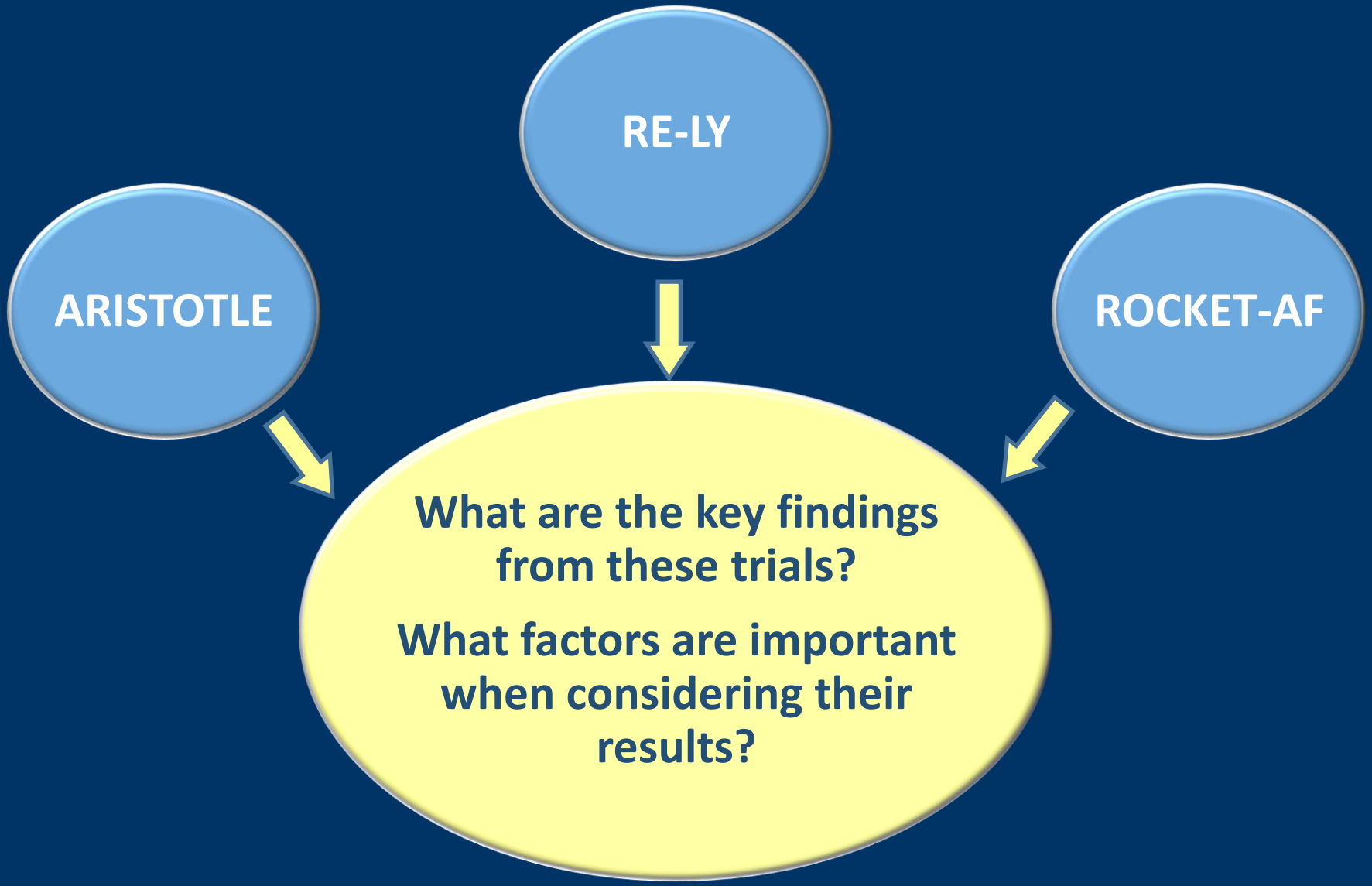
Estimated completion: March 2012

Treatment period 24 months

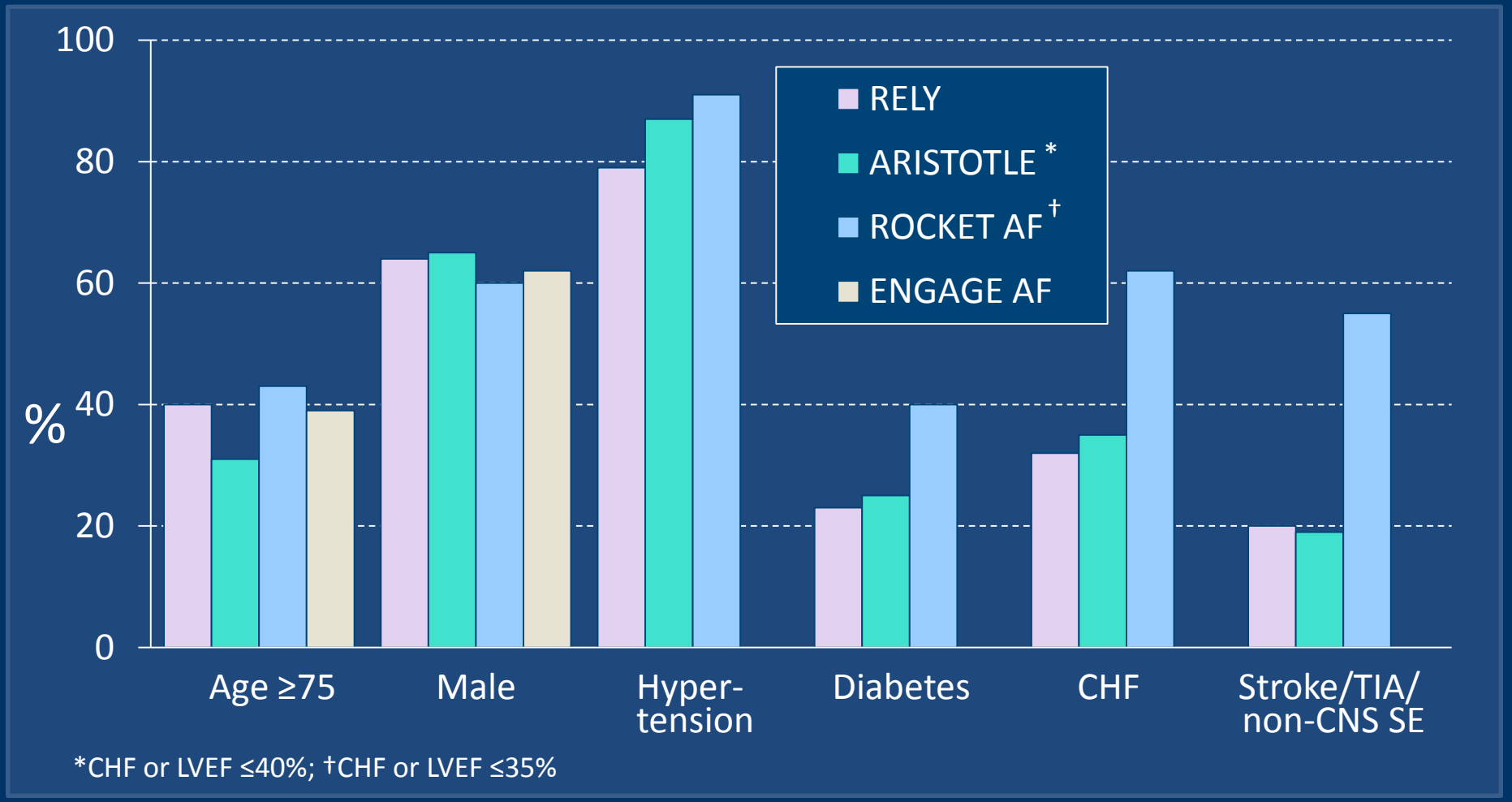
- Non-inferiority, double-blind, double-dummy
- Primary outcome measures: Stroke or systemic embolism; Major bleeding, hepatic function

Ruff C *Am Heart J* 2010;160:635

Putting These Results Into Perspective



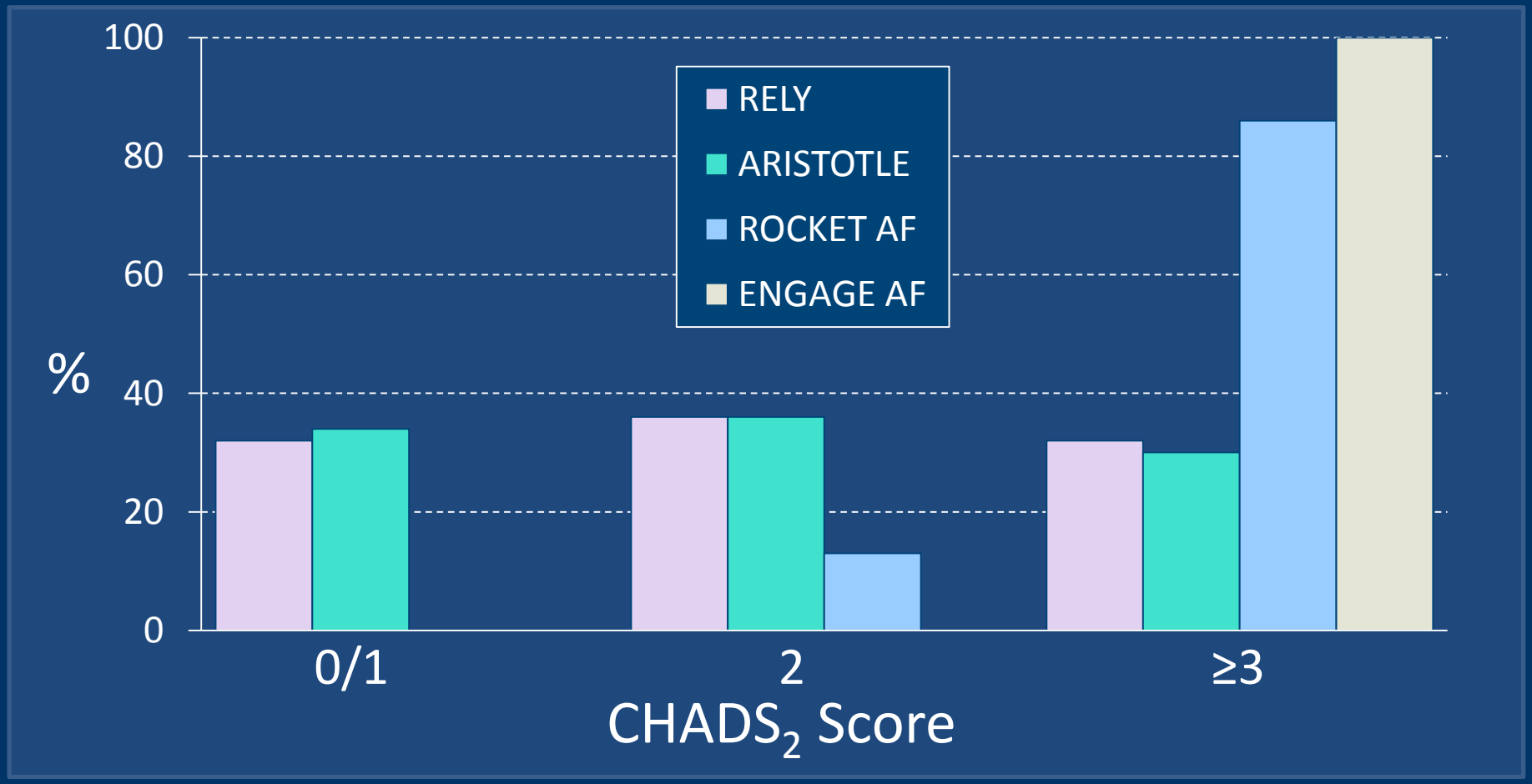
Patient Characteristics Across Trials



- **Notably higher rates of diabetes, CHF, and prior stroke in ROCKET population**

Connolly *N Engl J Med* 2009;361:1139; Patel *N Engl J Med* 2011365:883; Granger *N Engl J Med* 2011;365:981; Ruff *Am Heart J* 2010;160:635

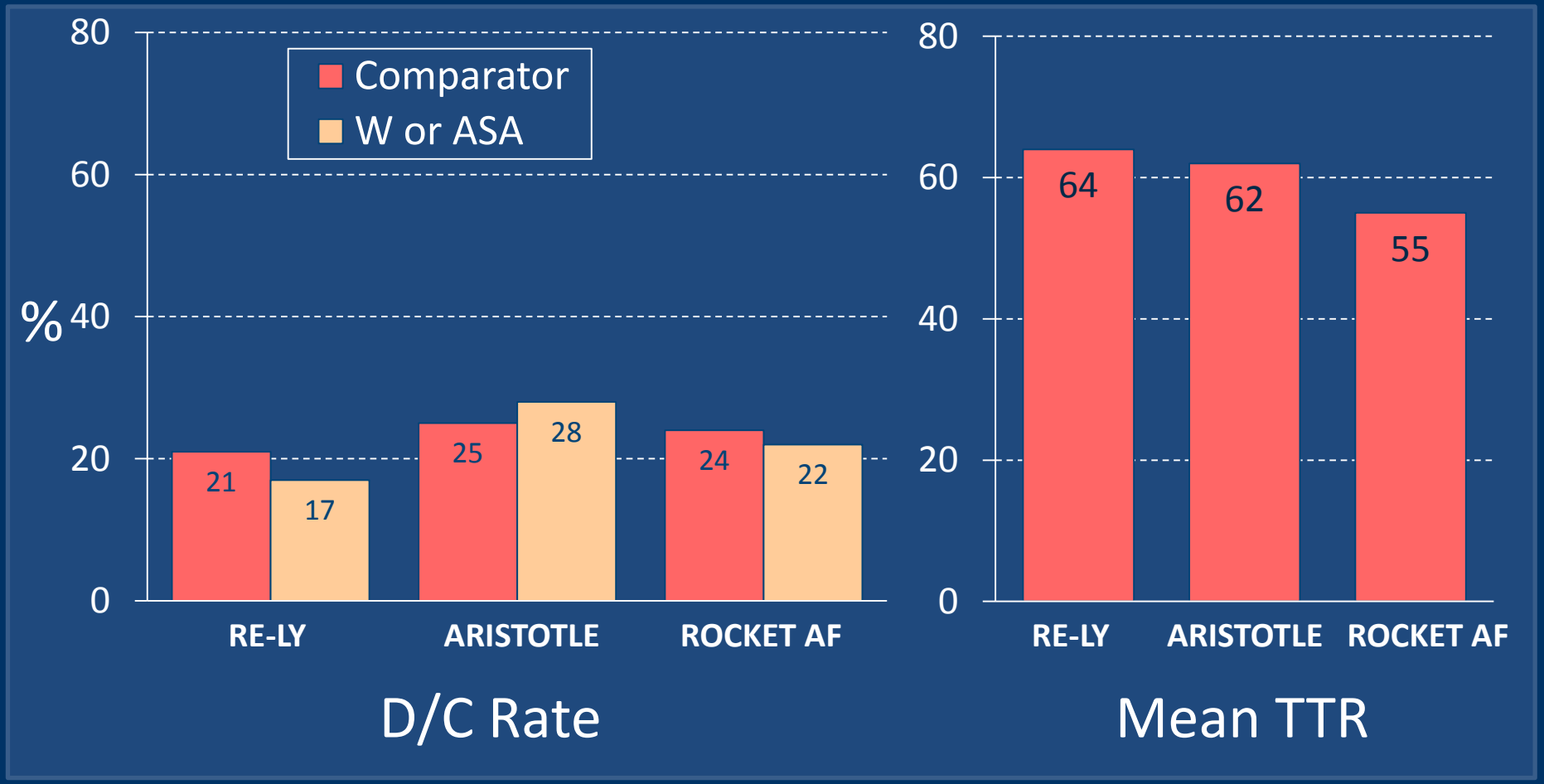
$CHADS_2$ Distribution Across Trials



- **Dabigatran and apixaban: evaluated across a spectrum of stroke risk categories**
- **Rivaroxaban and edoxaban: evaluated in patients at high risk of stroke**

Connolly *N Engl J Med* 2009;361:1139; Patel *N Engl J Med* 2011365:883; Granger *N Engl J Med* 2011;365:981; Ruff *Am Heart J* 2010;160:635

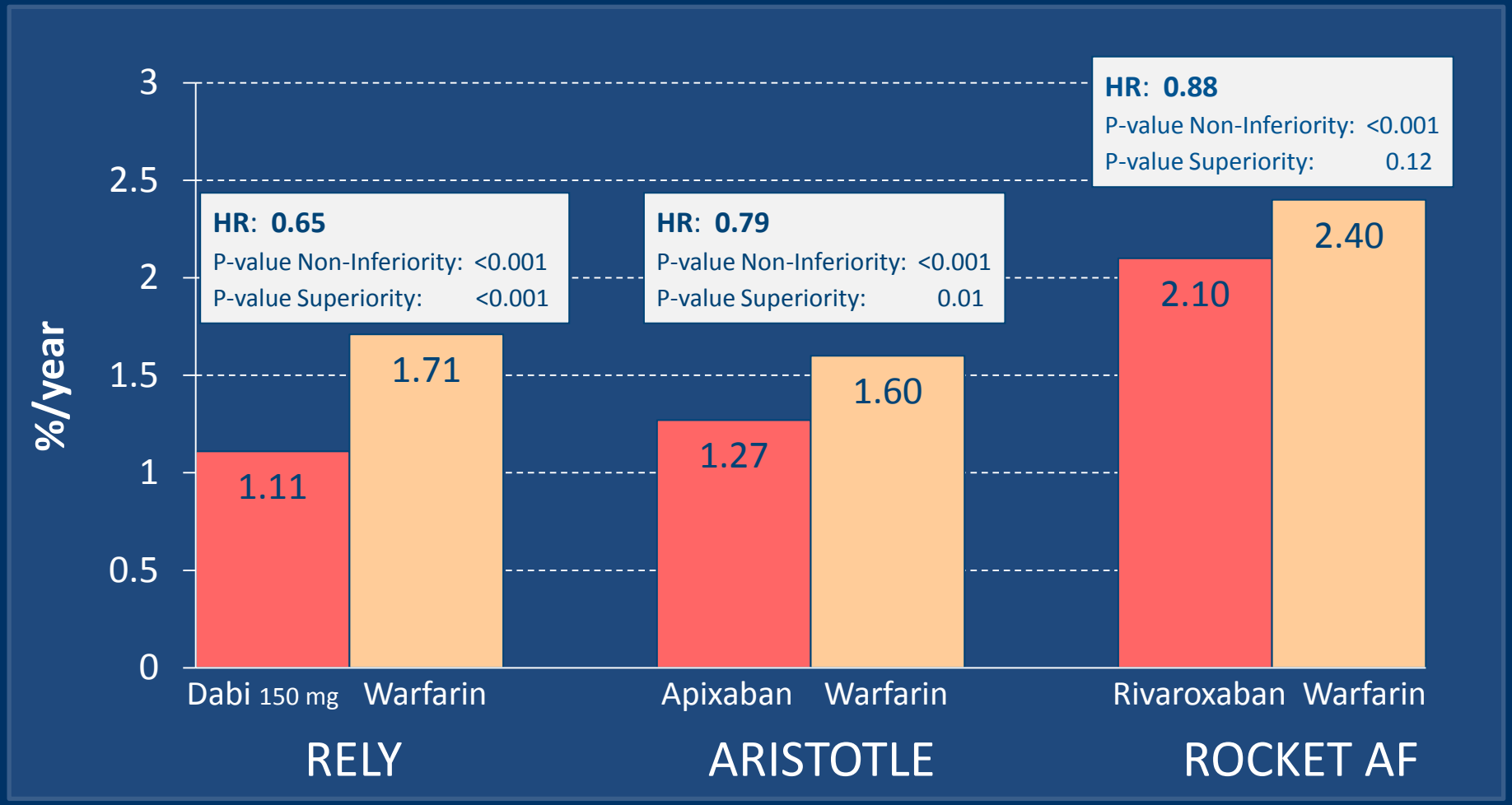
Discontinuation Rates and INR Control



- **Discontinuation rates were generally similar across trials**
- **Time in therapeutic range in ROCKET was lower than in RELY and ARISTOTLE**

Connolly *N Engl J Med* 2009;361:1139; Patel *N Engl J Med* 2011365:883; Granger *N Engl J Med* 2011;365:981

Stroke or Systemic Embolism:
Annual Event Rates

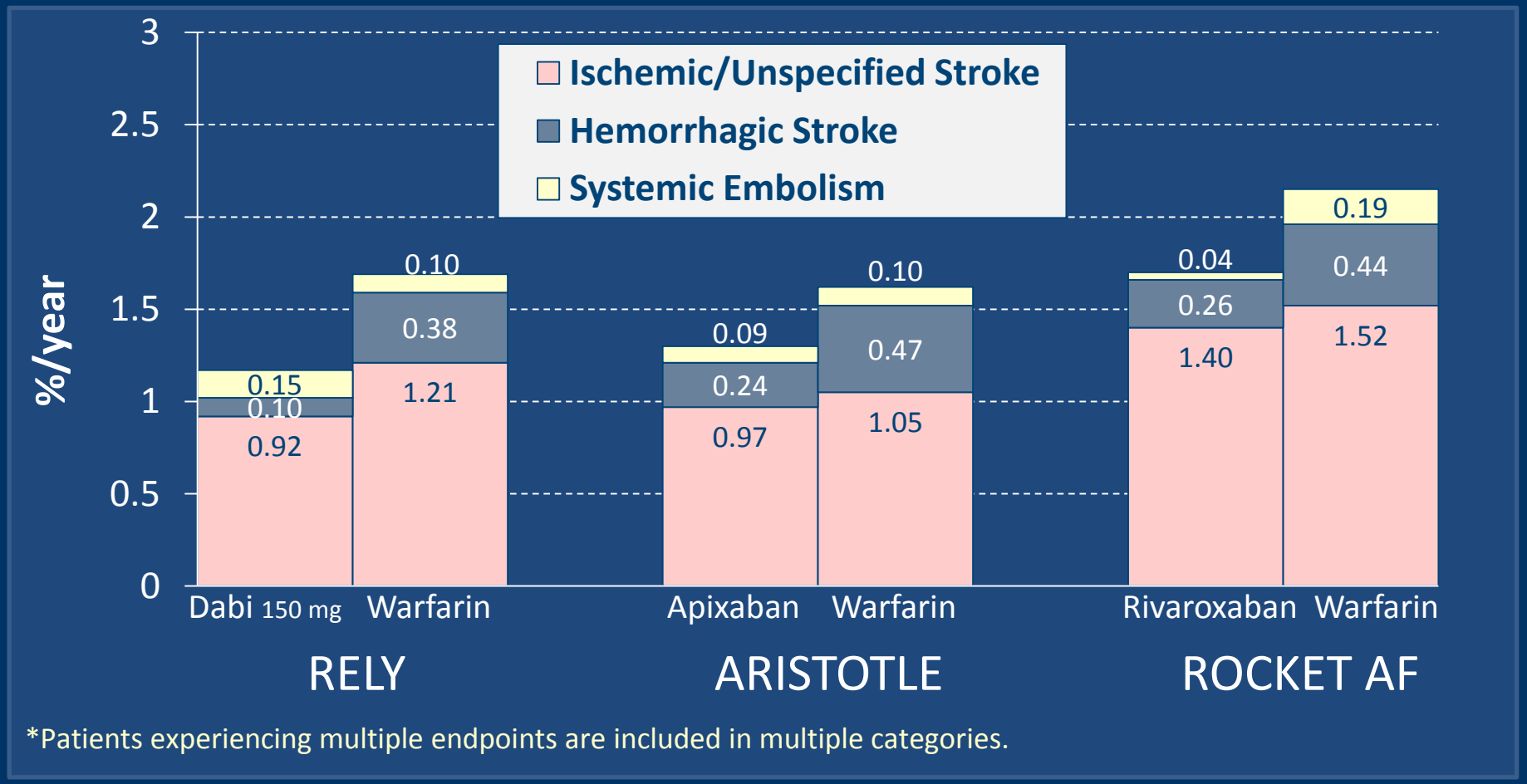


- **Dabigatran and apixaban were superior to warfarin in reducing stroke/systemic embolism**

Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

Elements of Primary Endpoint:*

Annual Event Rates

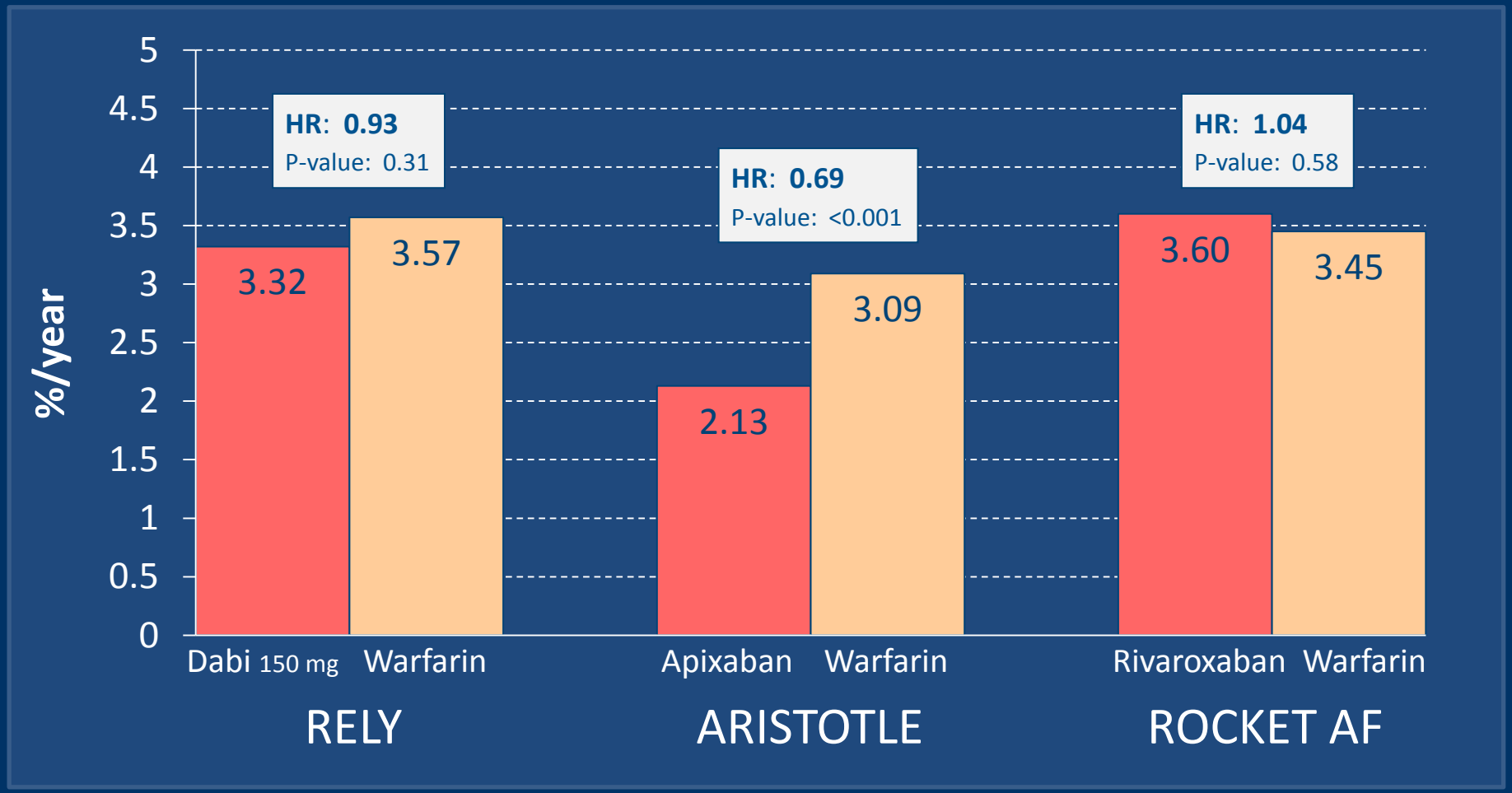


*Patients experiencing multiple endpoints are included in multiple categories.

- All 3 agents reduced hemorrhagic stroke vs. warfarin
- Dabigatran also reduced ischemic stroke

Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

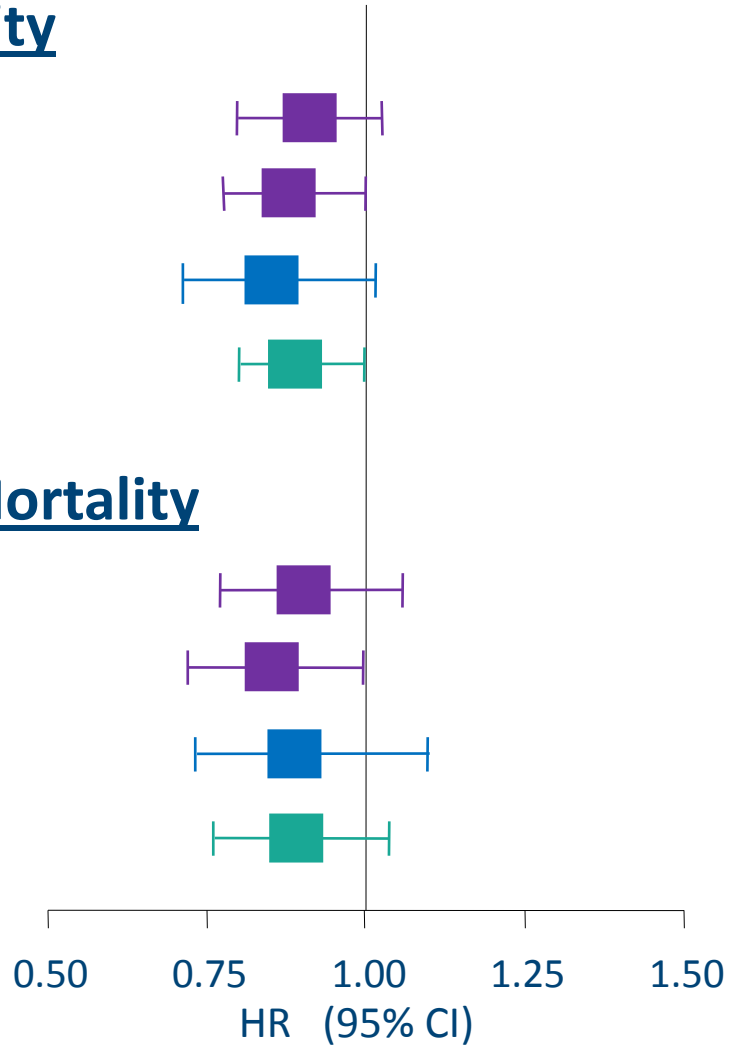
ISTH Major Bleeding:
Annual Event Rates



- **Apixaban reduced ISTH major bleeding**

Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

Mortality



	Superiority p-value
All-Cause Mortality	
Dabigatran 110 mg BID	0.13
Dabigatran 150 mg BID	0.051
Rivaroxaban 20 mg QD	0.073
Apixaban 5 mg BID	0.047
Cardiovascular Mortality	
Dabigatran 110 mg BID	0.21
Dabigatran 150 mg BID	0.04
Rivaroxaban 20 mg QD	0.29
Apixaban 5 mg BID	NR

NR: Not Reported

Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

Similarities Across the 3 Novel Oral Anticoagulants: Dabigatran, Rivaroxaban, and Apixaban Vs. Warfarin

- All 3 agents were non-inferior to warfarin in reducing the risk of stroke / systemic embolism
- All 3 agents reduced ICH
- The 3 agents seem to demonstrate a consistent trend towards mortality reduction
  - RRR approximates 10%/year

Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

Key Differentiators:

Dabigatran, Rivaroxaban, and Apixaban Vs. Warfarin

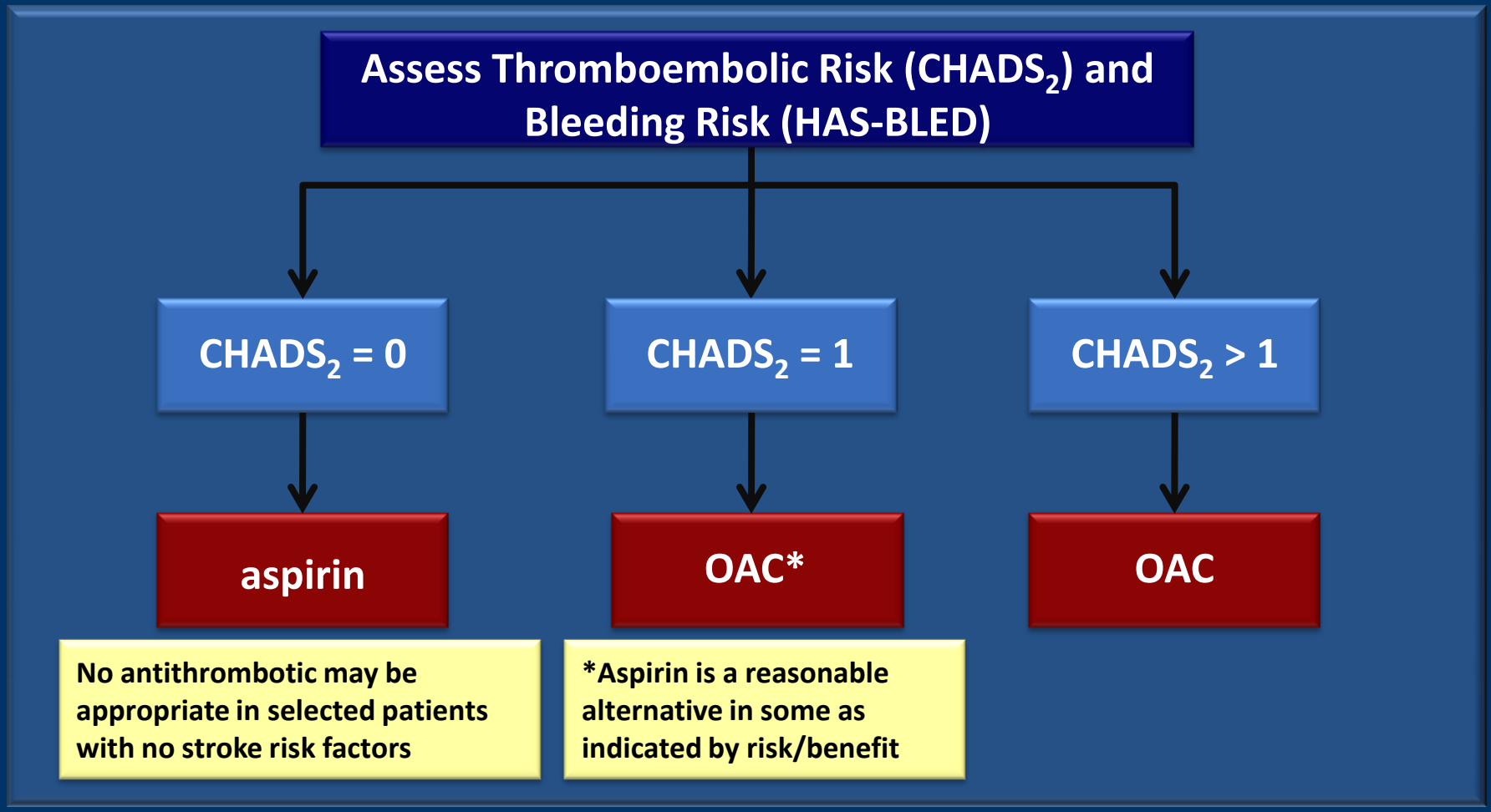
- Dabigatran at 150 mg BID reduced ischemic stroke
- Apixaban and Dabigatran at 100 mg BID reduced major bleeding
- Rivaroxaban is dosed once, rather than twice, daily

Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

Considerations When Comparing Trials:
Differences In Patient Populations

- Rivaroxaban was evaluated in patients at much higher risk:
  - 30-34% with $CHADS_2$ of 0/1 in RELY/ARISTOTLE, vs. none of these patients in ROCKET
  - 19-20% with prior stroke/TIA in RELY/ARISTOTLE, vs. 55% in ROCKET
- TTR in the warfarin arm was lower in ROCKET than in RELY/ARISTOTLE
  - Higher risk status of the ROCKET patients may have contributed

Contemporary Stroke Prevention in AF:
Canadian Cardiovascular Society (CCS) Guidelines



Dabigatran and rivaroxaban† are preferred OAC over warfarin in most patients

† Being added to 2012 update

Practical Considerations :

Starting Patients on One of the New Oral Anticoagulants

- Start patients not currently on any OAC immediately
- Switching from warfarin to a new OAC:
  - Stop warfarin
  - Initiate dabigatran or rivaroxaban once INR <2.0 or 3.0
- Switching from a new OAC to a parenteral one
  - Wait 12 hours after the last dose of dabigatran
  - Wait 24 hours after the last dose of rivaroxaban
- Switching from a parenteral to a new anticoagulant
  - Start 0-2 hours prior to the time that the next dose of the alternate therapy would be due

Based on best available information; expert recommendations; *Pradax Product Monograph (Canada)*, 26 Oct 2010 rev., 8 Nov 2010; *Xarelto Product Monograph* (United States), November 2011

Practical Considerations :

Patient Follow-up

- Patients require regular, ongoing monitoring:
  - Assess and reinforce adherence to their anticoagulant
  - Monitor renal function
    - No dabigatran if CrCl < 30 ml/min (role of 75 mg BID dose?)
    - No rivaroxaban if CrCl < 15 ml/min (15 mg OD for CrCl 15-50)
  - Monitor other relevant clinical and laboratory parameters

Based on best available information; expert recommendations; *Pradax Product Monograph (Canada)*, 26 Oct 2010 rev., 8 Nov 2010; *Xarelto Product Monograph* (United States), November 2011

Practical Considerations:
The Importance of Patient Education

- Patient education, a key element of care, includes:
  - Education about AF stroke risk and the need to prevent it by **taking anticoagulant therapy exactly as prescribed**
  - If it is withheld (eg, for procedures), instruction about **promptly restarting** the drug afterwards
  - Counselling about **never stopping the drug due to side effects** without prior discussion with a physician
  - Instruction about **managing a missed dose**:
    - For dabigatran, take ASAP up to 6 hours prior to the next scheduled dose; beyond 6 hours, omit the missed dose
    - For rivaroxaban, take ASAP the same day
    - Doses should never be doubled to compensate for a missed dose

Based on best available information; expert recommendations; *Pradax Product Monograph (Canada)*, 26 Oct 2010 rev., 8 Nov 2010; *Xarelto Product Monograph* (United States), November 2011

Practical Considerations:
Managing Mild Bleeding

- Hold one dose
- If bleeding continues:
  - Stop any concomitant antiplatelet drugs, if possible
  - Investigate for a local cause
- If bleeding continues, check for drug accumulation
  - Measure aPTT: if prolonged, dabigatran or rivaroxaban is on board
  - Determine creatinine clearance rate
- Consider reducing dose or stopping drug if appropriate

Based on best available information; expert recommendations; *Pradax Product Monograph (Canada)*, 26 Oct 2010 rev., 8 Nov 2010; *Xarelto Product Monograph* (United States), November 2011

Practical Considerations:
Managing Moderate/Severe Bleeding

- Stop treatment and investigate the bleeding source
- Control bleeding with pressure or surgical hemostasis
- Measure aPTT: if prolonged, an OAC is on board
- Although not formally evaluated, consider:
  - Supportive treatment with whole blood, fresh frozen plasma or platelet concentrates (with thrombocytopenia or antiplatelet drugs)
  - Activated prothrombin complex concentrates (e.g., FEIBA); recombinant Factor VIIa; concentrates of coagulation factors II, IX, X

Based on best available information; expert recommendations; *Pradax Product Monograph (Canada)*, 26 Oct 2010 rev., 8 Nov 2010; *Xarelto Product Monograph* (United States), November 2011

Practical Considerations:
Perioperative Management of Anticoagulant Therapy

- **Alteration of oral anticoagulant regimen *may not be necessary for most patients undergoing low risk procedures:***
  - Dental procedures, joint and soft tissue injections, arthrocentesis, cataract surgery, upper endoscopy or colonoscopy with/without biopsy

- **For other invasive and surgical procedures, oral anticoagulation needs to be withheld:**
  - Decision on whether to pursue an aggressive strategy of perioperative administration of IV heparin or SQ low molecular-weight heparin should be individualized based on an estimation of the patient's risks of thromboembolism and bleeding and the patient's preference

Douketis J, et al. Chest 2008;133:299S-339S;
Dunn AS and Turpie AGG. Arch Intern Med 2003;163:901-908

Practical Considerations:

Perioperative management – Summary of CCS Guidelines

Patients with Very Low to Moderate Stroke Risk ($CHADS_2$ ≤2):

- In patients with **low bleeding risk**:
  - Continue antithrombotic therapy
- In patients with **high bleeding risk:**
  - Stop antithrombotic therapy pre-procedure and reinstitute when risk of bleeding is reduced

Patients with High Stroke Risk ($CHADS_2$ ≥3):

- In patients with **low bleeding risk**:
  - Continue antithrombotic therapy or provide bridging therapy perioperatively
- In patients with **high bleeding risk:**
  - Stop antithrombotic therapy and provide bridging therapy perioperatively

Cairns *et al*. *Can J Card* 2011 27:74-90

Practical Considerations:
Cardioversion / Ablation

- Patients can be maintained on dabigatran while being cardioverted
- It is reasonable to assume that dabigatran can be safely given the day after AF ablation (based on limited data*)
- It is also reasonable to assume that both the above will apply to rivaroxaban

Based on best available information, expert recommendations and *Pradax Product Monograph*, 26 Oct 2010 rev., 8 Nov 2010

*Eitel et al., Dabigatran in patients undergoing catheter ablation for atrial fibrillation. *Europace Journal* 2011 ; 13 (3), Abstract P1051

Practical Considerations:
Antithrombotic Therapy for Patients with CAD

Stable CAD

- Includes patients with a history of prior ACS and/or PCI who are without CHF, angina, etc.
- Aspirin is suggested for patients at very low risk of stroke ($CHADS_2$=0)
- Warfarin or dabigatran (and likely rivaroxaban) monotherapy is suggested for patients with $CHADS_2 \geq 1$

Recent ACS and/or PCI

- Aspirin plus clopidogrel alone is suggested for patients at low risk of stroke (CHADS2≤1)
- Triple antithrombotic therapy is suggested for patients with $CHADS_2 \geq 2$
- Warfarin (or rivaroxaban?) is preferred in these patients

Based on best available information, expert recommendations, and Cairns *et al*. *Can J Card* 2011 27:74-90

A Cardiologist's Perspective:
On The Evolving Treatment Paradigm for SPAF

- Compared with warfarin, each of the 3 new agents:
  - Are at least as effective in preventing stroke/systemic embolism
  - Reduce intracranial bleeding
- Differences among agents will play a role in selecting treatment strategies for individual patients, based on:
  - Patient characteristics (e.g., renal impairment, bleeding risk)
  - Patient values (e.g., preventing ischemic stroke vs. once daily dosing)
- Many patients will benefit from the advantages offered by these drugs that ideally should be started by primary care/emergency department physicians rather than cardiologists

Thank You