Modeling the Risk of Stroke and Bleeding in Atrial Fibrillation: What Are the Optimal Risk Scores?

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New York, NY

Session II. Weighing the Risks and Benefits of Therapeutic Alternatives

Left Atrial Appendage Closure: Indications, Devices, and Techniques

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Regado Biosciences	Advisory Board
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The Medicines Co.	Research Grant Support (Institutional)

Stroke Prevention in AF

Anticoagulants

Antiplatelet agents

Non-antithrombotic drugs

VKAs

Novel anticoagulants

Aspirin ± Clopidogrel

AntiHTN **Statins** **Anti-arrhythmic**

Warfarin

Non-warfarin VKAs
• **Tecarfarin**

Direct thrombin inhibitors
• **Ximelagatran**
• **Dabigatran**

Factor X inhibitors
• **Apixaban**
• **Betrixaban**
• **Edoxaban**
• **Rivaroxaban**

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Clinical-Decision Making in Afib
Medicine is the ART of "Balance"

Bleeding

Stroke

Optimal Outcome for the Patient

The CHADS$_2$ Index
Stroke Risk Score for Atrial Fibrillation

	Score (points)	Prevalence (%)*
Congestive Heart failure	1	32
Hypertension	1	65
Age >75 years	1	28
Diabetes mellitus	1	18
Stroke or TIA	2	10
Moderate-High risk	≥2	50-60
Low risk	0-1	40-50

VanWalraven C, et al. *Arch Intern Med* 2003; 163:936.
•Nieuwlaat R, et al. (EuroHeart survey) *Eur Heart J* 2006 (E-published).
•Comparison of 12 risk stratification schemes to predict stroke in patients with non-valvular atrial fibrillation. *Stroke 2008;39:1901-1910*.

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CHA$_2$DS$_2$VASc is a newer scoring system

- **CHA$_2$DS$_2$VASc, developed by Lip et al, is a refinement of the older CHADS$_2$ Score which includes additional stroke risk factors and puts greater emphasis on age as a risk factor[1]**

	Condition/Risk Factor	Points
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥75 years	2
D	Diabetes mellitus	1
S$_2$	Previous stroke or TIA	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Sex (female gender)	1
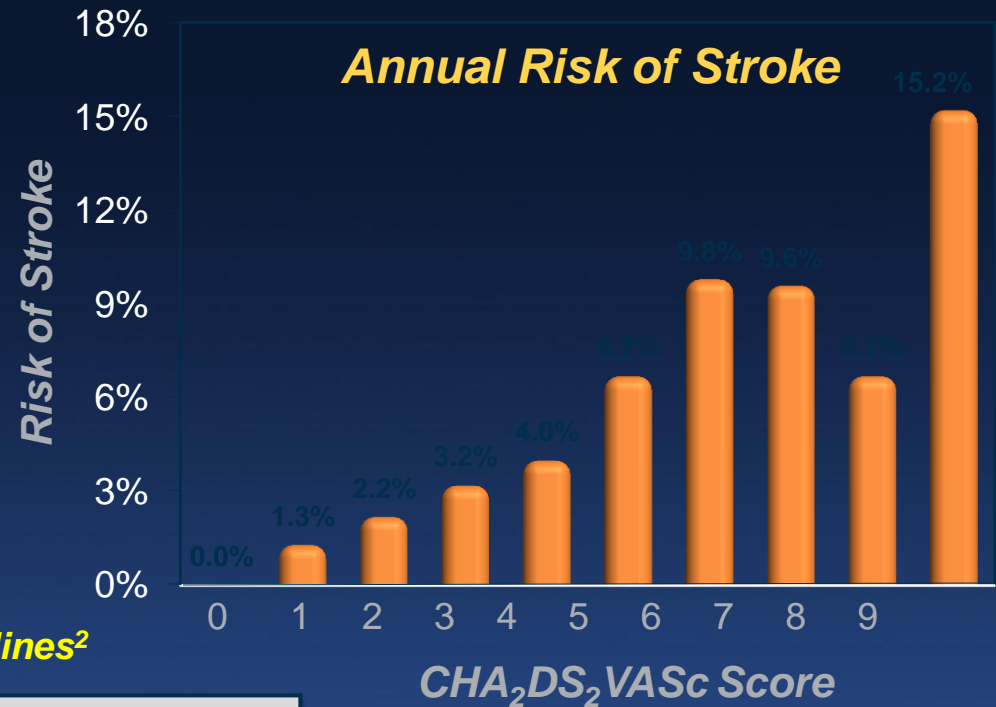
European Society of Cardiology Guidelines[2]

CHA$_2$DS$_2$-VASc Score	Treatment
0	No treatment
1	Aspirin or warfarin or dabigatran
≥2	Warfarin or dabigatran

Annual Risk of Stroke

Risk of Stroke vs CHA$_2$DS$_2$VASc Score:
- 0: 0.0%
- 1: 1.3%
- 2: 2.2%
- 3: 3.2%
- 4: 4.0%
- 5: 6.7%
- 6: 9.8%
- 7: 9.6%
- 8: 6.7%
- 9: 15.2%

1. Lip GY et al, Chest. 2010;137(2):263-72
2. Camm AJ et al, Eur Heart J. 2012 doi: 10.1093/eurheartj/ehs253

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Risk Stratification and Anticoagulation
Stroke Reduction with Warfarin Instead of Aspirin
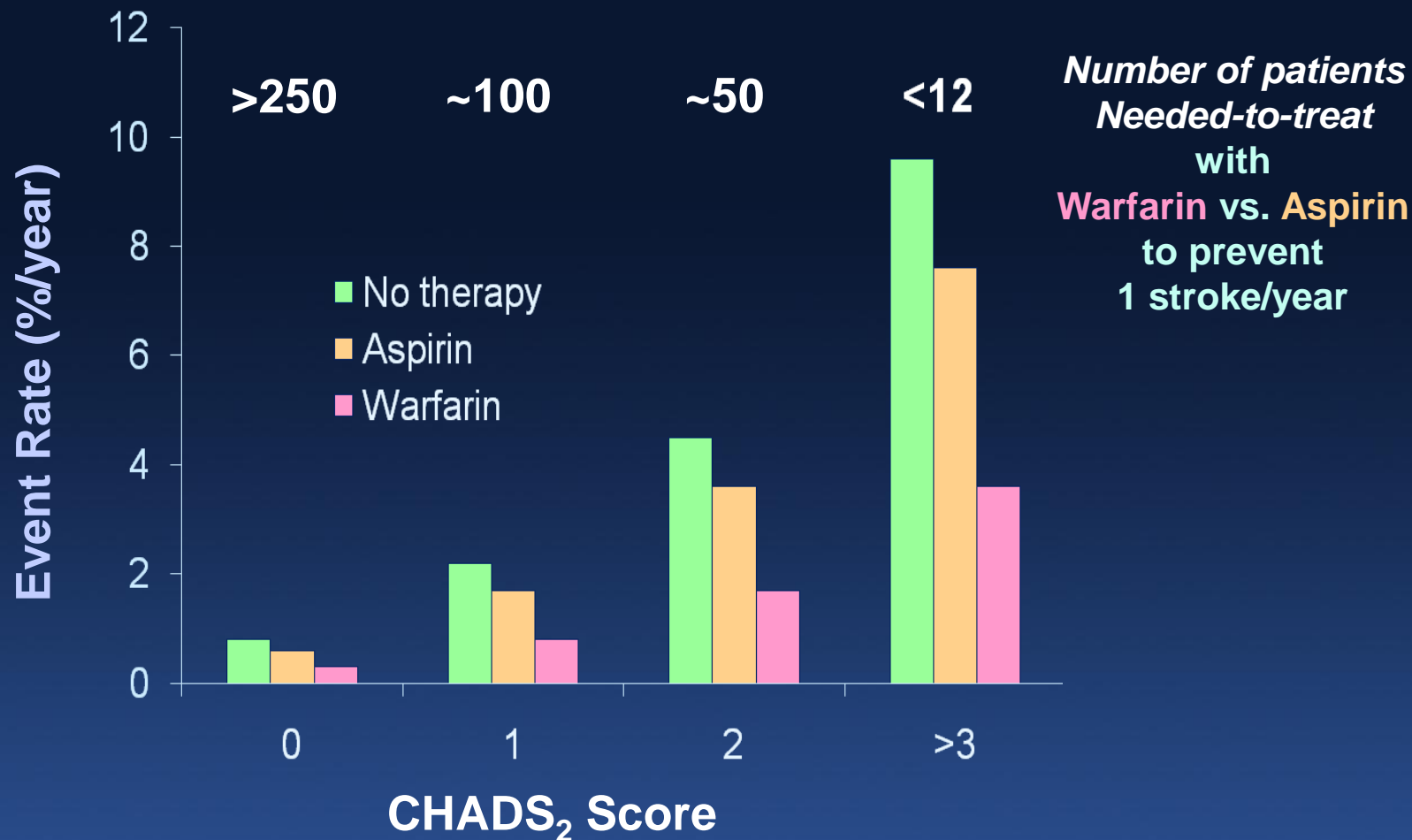
How do the two CHADS scores compare?

Generally, they result in similar treatment recommendations
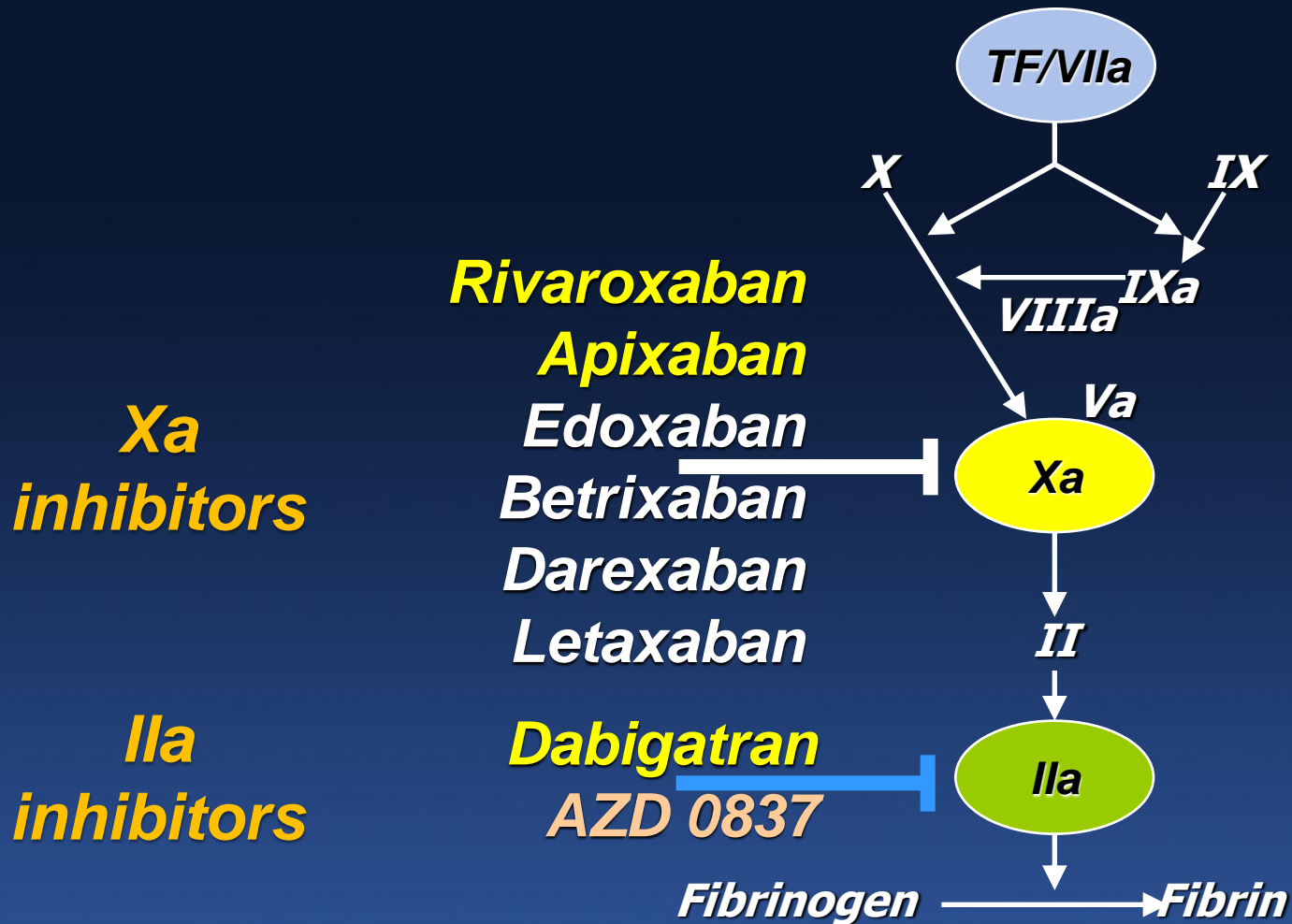
Where they are the same:

- *Both CHADS systems assign 1 "point" each for presence of congestive heart failure (any), hypertension and diabetes*
- *Both CHADS systems assign 2 points for prior TIA or stroke*

Where they differ:

- *CHA_2DS_2VASc puts greater emphasis on age, assigning 1 point for age between 65-74 years, and 2 points for age $\geq$75 years. $CHADS_2$ only assigns one point for age $\geq$75 years*
- *CHA_2DS_2VASc adds 1 point each for presence of any vascular disease and female gender, which are not included in the $CHADS_2$ score*

New Agents for Atrial Fibrillation
Oral direct inhibitors

Xa inhibitors

Rivaroxaban
Apixaban
Edoxaban
Betrixaban
Darexaban
Letaxaban

IIa inhibitors

Dabigatran
AZD 0837

TF/VIIa

X

IX

IXa

VIIIa

Va

Xa

II

IIa

Fibrinogen → Fibrin

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New Oral Anticoagulants: Phase III AF Trials
Primary Endpoint - Stroke or Systemic Emboli

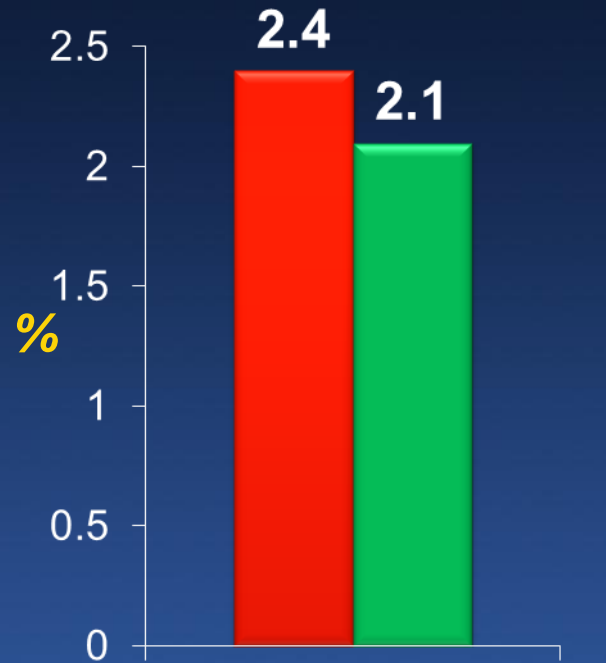### Powered for non-inferiority – P<0.001 for all NI comparisons

Rates = per yr FU

RE-LY
- Warfarin
- Dabigatran 110 mg

0.91 (0.74–1.11), P=0.34
0.66 (0.53–0.82), P<0.001

Bar chart (%):
- Warfarin: 1.7
- Dabigatran: 1.5
- (green): 1.1

ROCKET AF
- Warfarin
- Rivaroxaban 20 mg

0.88 (0.75–1.03), P=0.12

Bar chart (%):
- Warfarin: 2.4
- Rivaroxaban: 2.1

ARISTOTLE
- Warfarin
- Apixaban 5 mg

0.79 (0.66–0.95), P=0.01

Bar chart (%):
- Warfarin: 1.6
- Apixaban: 1.3

Connolly SJ, et al. NEJM 2009;361:1139-51; Patel MR et al, NEJM 2011; Granger CB et al. NEJM 2011
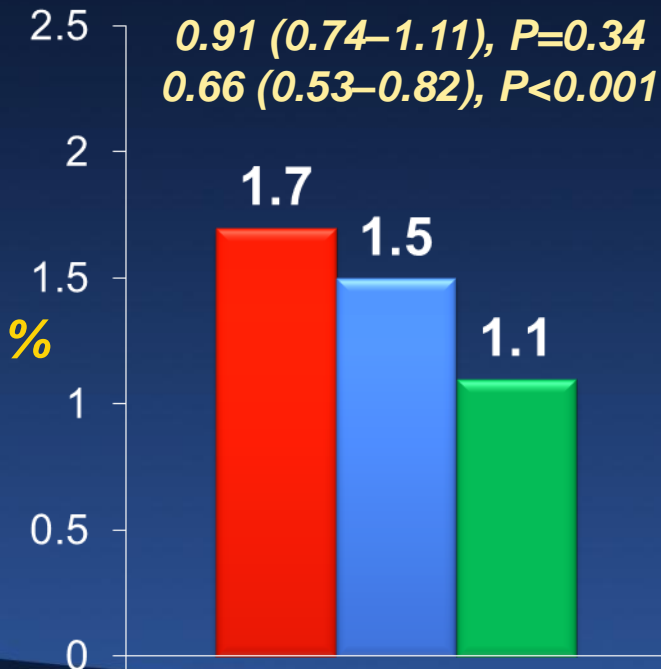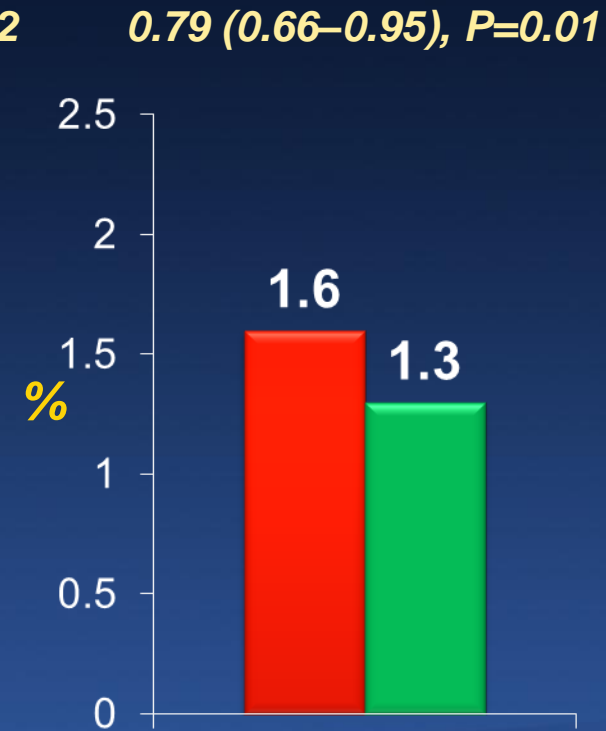
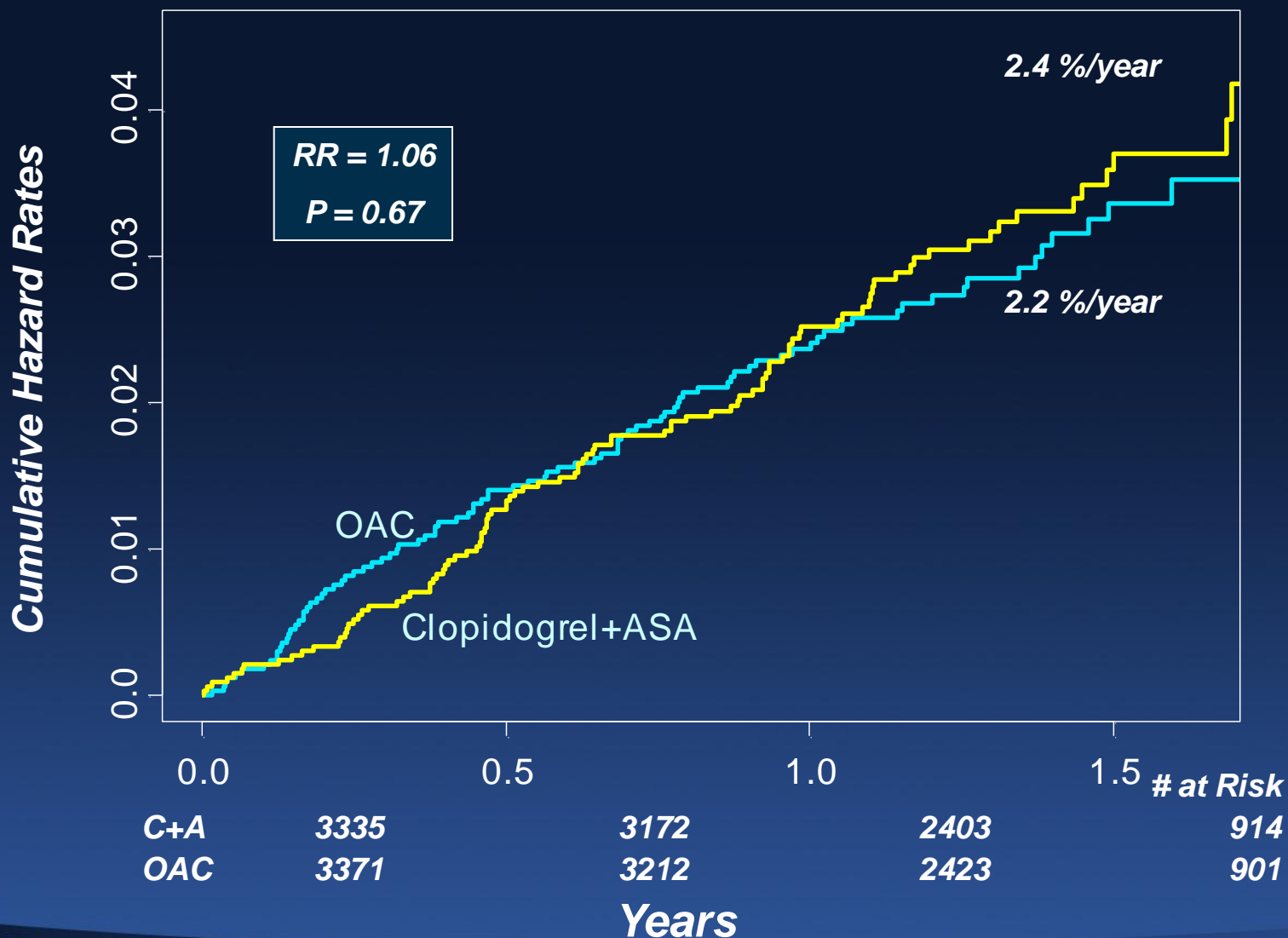# Primary Endpoint of Stroke or Systemic Embolism: Non-inferiority Analysis

Non Inferiorirty p vs warfarin

RE-LY			ITT Analysis
Dabigatran 110 mg	1.53% per year	HR = 0.91	p<0.001
Dabigatran 150 mg	1.11% per year	HR = 0.66	p<0.001
Warfarin	1.69% per year		
ROCKET AF			Modified ITT
Rivaroxaban 20 mg	1.7% per year	HR = 0.79	p<0.001
Warfarin	2.2% per year		
ARISTOTLE			ITT Analysis
Apixaban 5 mg	1.27% per year	HR = 0.79	p<0.001
Warfarin	1.60% per year		

No ITT analysis is available for non-inferiority in Rocket AF. An on treatment or per-protocol analysis is generally performed in the assessment of non-inferiority. If numerous patients come off of study drug, this biases the trial towards a non-inferior result in an ITT analysis. This is the basis for performing a per-protocol analysis in a non-inferiority assessment.

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med 2011

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Major Bleeding: Dual antiplatelet vs Warfarin

RR = 1.06
P = 0.67

2.4 %/year

2.2 %/year

OAC

Clopidogrel+ASA

Cumulative Hazard Rates

	0.0		0.5	1.0	1.5	# at Risk
C+A	3335		3172	2403		914
OAC	3371		3212	2423		901

Years

ACTIVE Investigators. *Lancet*. 2006;367;1903-1912.

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New Oral Anticoagulants: Phase III AF Trials
Major Bleeding

Rates = per yr FU

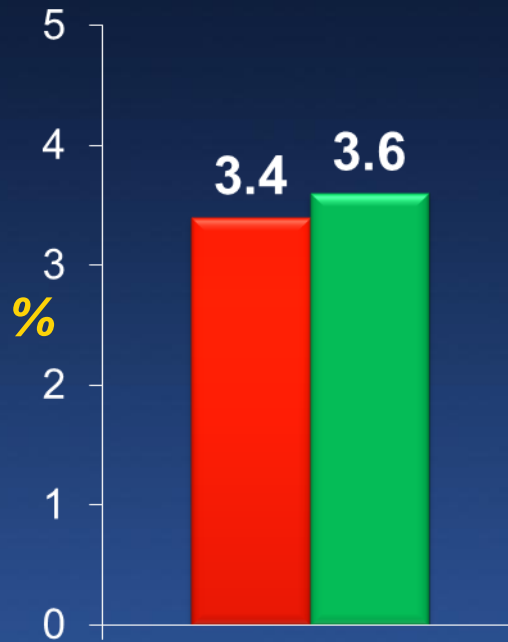### RE-LY

- Warfarin
- Dabigatran 110 mg
- Dabigatran 150 mg

0.80 (0.69–0.93), P=0.003
0.93 (0.81–1.07), P=0.31

Bar chart (%): Warfarin 3.4, Dabigatran 110 mg 2.7, Dabigatran 150 mg 3.1
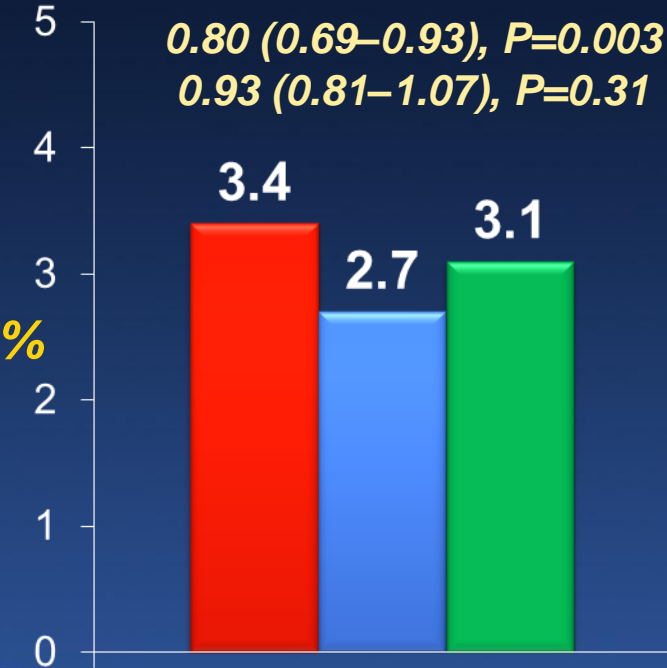
ROCKET AF

- Warfarin
- Rivaroxaban 20 mg

1.04 (0.90–1.20), P=0.58

Bar chart (%): Warfarin 3.4, Rivaroxaban 20 mg 3.6

ARISTOTLE

- Warfarin
- Apixaban 5 mg

0.69 (0.60–0.80), P<0.001

Bar chart (%): Warfarin 3.1, Apixaban 5 mg 2.1

Connolly SJ, et al. NEJM 2009;361:1139-51; Patel MR et al, NEJM 2011; Granger CB et al. NEJM 2011
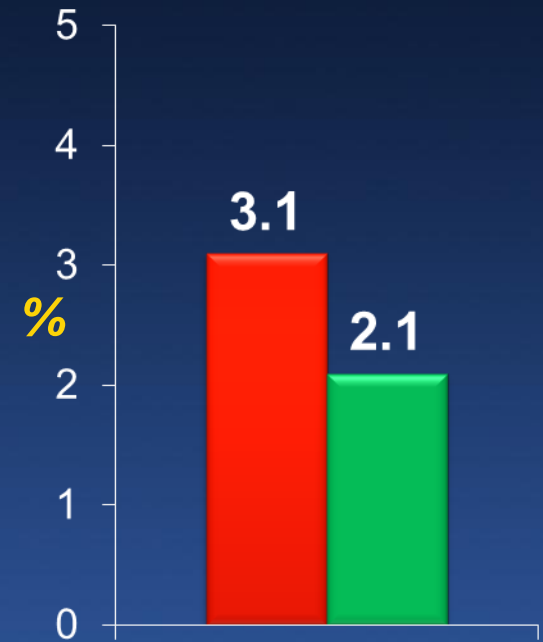
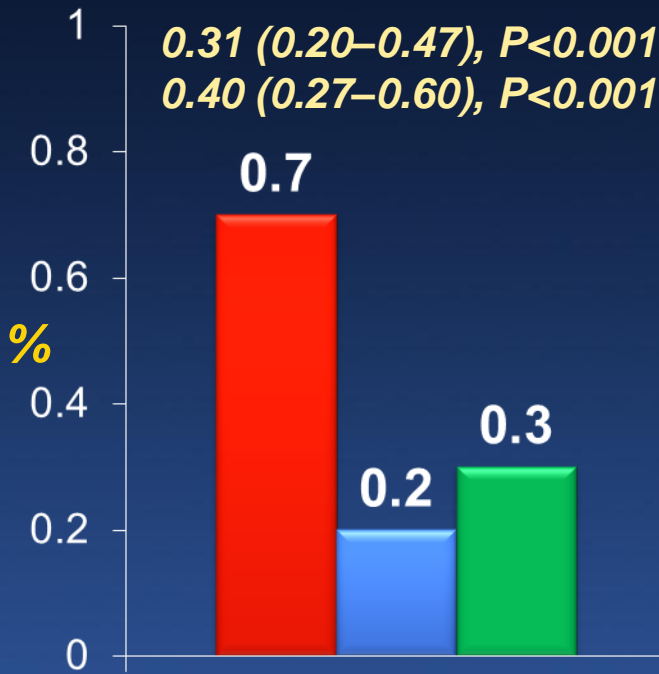# New Oral Anticoagulants: Phase III AF Trials
Intracranial Hemorrhage

Rates = per yr FU

RE-LY

- Warfarin
- Dabigatran 110 mg
- Dabigatran 150 mg

0.31 (0.20–0.47), P<0.001
0.40 (0.27–0.60), P<0.001

%

0.7	0.2	0.3

ROCKET AF

- Warfarin
- Rivaroxaban 20 mg

0.67 (0.47–0.93), P=0.02

%

0.7	0.5
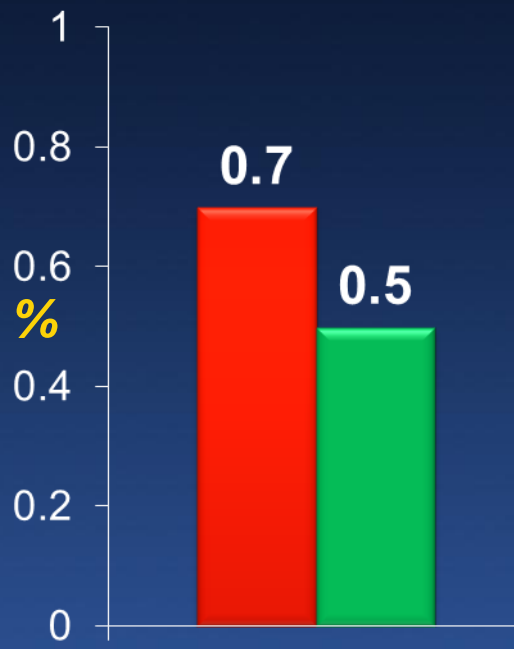
ARISTOTLE

- Warfarin
- Apixaban 5 mg

0.42 (0.30–0.58), P<0.001

%

0.8	0.3
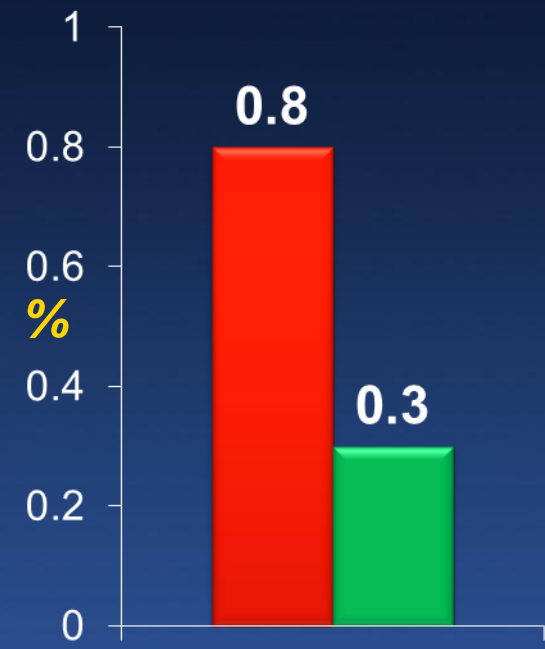
ROCKET AF: *Fatal bleeding reduced from 0.5% to 0.2%, 0.50 (0.31–0.79), P=0.003*

Connolly SJ, et al. NEJM 2009;361:1139-51; Patel MR et al, NEJM 2011; Granger CB et al. NEJM 2011

Hemorrhagic Stroke

RELY		HR	ITT P-value
Dabigatran 110 mg	0.12% / yr	0.31	<0.001
Dabigatran 150 mg	0.10% / yr	0.26	<0.001
Warfarin	0.38% / yr		
ROCKET		HR	mITT P-value
Rivaroxaban 20 mg	0.26% / yr	0.59	0.024*
Warfarin	0.44% / yr		
ARISTOTLE		HR	ITT P-value
Apixaban 5 mg	0.24% / yr	0.51	<0.001
Warfarin	0.47% / yr		

In an ITT analysis in Rocket AF Hemorrhagic Stoke rates were 0.26% / yr for rivaroxaban and 0.44% / yr for warfarin, p=0.012. No on treatment analysis is available from RE-LY.

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

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Definitions of Major Bleeding in Clinical Trials: Main Components

Clinical Events

- Intracranial / intracerebral bleeding
- Intraocular bleeding
- Bleeding causing hemodynamic compromise
- Cardiac tamponade
- Retroperitoneal hematoma
- Hematoma
- Surgical intervention for bleeding
- Blood product transfusion

Laboratory Parameters

- Decrease in Hgb ≥3 g/dL *with* overt source of bleeding
- Decrease in Hgb ≥4 g/dL *w/o* overt source of bleeding
- Decrease in Hgb ≥5 g/dL *with or w/o* overt source of bleeding
- Decrease in Hct ≥15% *with* overt source of bleeding

Definitions of Major or Severe Bleeding in Randomized Controlled Clinical Trials

Type of bleeding	GUSTO	TIMI phase I	TIMI phase II	REPLACE-2	OASIS-5 ESSENCE	CURE	STEEPLE	ACUITY HORIZONS	PLATO
Intracranial/intracerebral	+	+	+	+	+	+	+	+	+
Intraocular	-	-	-	+	+	+	+	+	+
Retroperitoneal	-	-	-	+	+	+	+	+	-
Bleeding causing hemodynamic compromise	+	-	-	-	-	+	+	-	+
Cardiac tamponade	-	+	+	-	-	-	-	-	+
Bleeding requiring surgical intervention	-	-	-	-	-	+	+	+	+
Hematoma >5cm at the puncture site	-	-	-	-	-	-	-	+	-
Transfusion, units	≥1	≥1	≥1	≥2	≥2	≥2	≥1	≥1	≥4
Decrease in Hgb *with* overt bleeding, g/dL	-	≥5.0*	≥3.0	≥3.0	≥3.0	-	≥3.0	≥3.0	≥5.0
Decrease in Hgb *without* overt bleeding, g/dL	-	-	-	≥4.0	-	≥5.0	-	≥4.0	-

*Or decrease in Hct ≥15%

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BARC Bleeding Definitions

BARC

- **Type 0:** No bleeding
- **Type 1:** Bleeding that is not actionable
- **Type 2:** Any overt, actionable sign of hemorrhage requiring nonsurgical intervention leading to hospitalization or increased level of care
- **Type 3a:**
  - Overt bleeding plus hemoglobin drop of 3 to <5 g/dl
  - Transfusion with overt bleeding
- **Type 3b:**
  - Overt bleeding plus hemoglobin drop ≥5 g/dl
  - Cardiac tamponade
  - Bleeding requiring surgical intervention or vasoactive agents
- **Type 3c:**
  - Intracranial hemorrhage
  - intraocular bleeding compromising vision
- **Type 4:** Coronary artery bypass grafting-related bleeding
- **Type 5:** Fatal bleeding

Mehran R et al. *Circulation.* 2011;123:2736-47.

Are the BARC Bleeding Definitions Valid?

Interventional Cardiology

Validation of the Bleeding Academic Research Consortium Definition of Bleeding in Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

Gjin Ndrepepa, MD; Tibor Schuster, PhD; Martin Hadamitzky, MD; Robert A. Byrne, MB, BCh; Julinda Mehilli, MD; Franz-Josef Neumann, MD; Gert Richardt, MD; Stefanie Schulz, MD; Karl-Ludwig Laugwitz, MD; Steffen Massberg, MD; Albert Schömig, MD; Adnan Kastrati, MD

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Ndrepepa G et al. Circulation. 2012;125:1424-31.

Predictivity of the Multivariable Models Without and After Inclusion of Bleeding in Regard to 1-Year Mortality
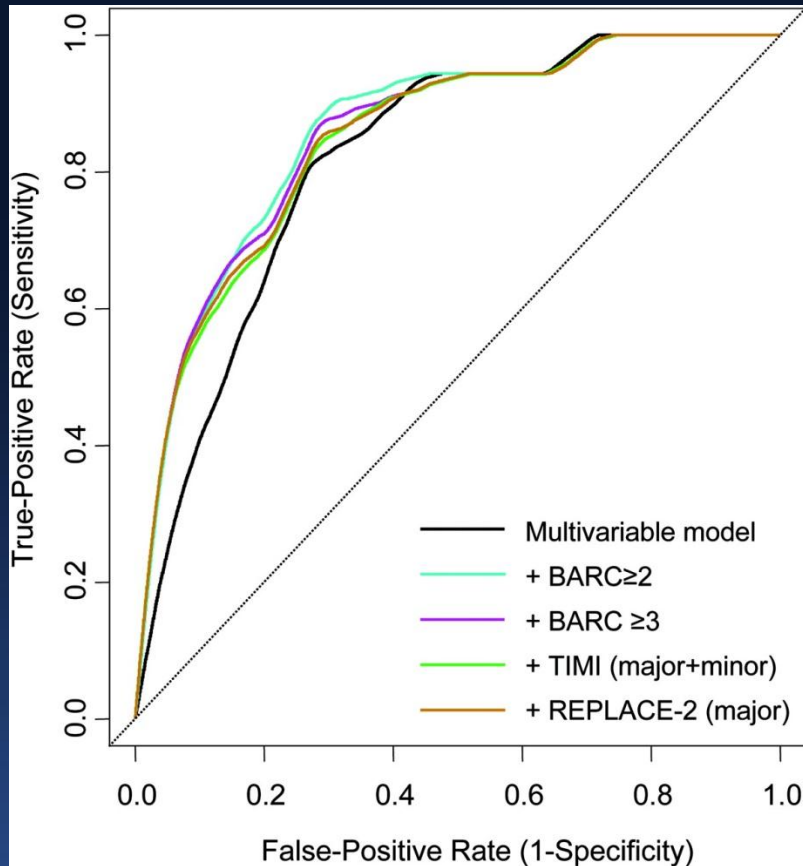
Adjusted receiver operating characteristic curves showing predictivity of the multivariable models in regard to 1-year mortality without and with inclusion of the bleeding events defined by Bleeding Academic Research Consortium (BARC), Thrombolysis in Myocardial Infarction (TIMI), and Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) criteria.

Figure 3. Ndrepepa G et al. Circulation. 2012;125:1424-31.

Although various bleeding risk–prediction tools have been developed in general populations undergoing anticoagulation, only 3 have been initially derived for and validated exclusively in patients with AFib:

- **HEMORR$_2$HAGES** **(Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke)**

- **HAS-BLED** **(Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol)**

- **ATRIA** **(Anticoagulation and Risk Factors in Atrial Fibrillation)**

HEMORR$_2$HAGES

HEMORR2HAGES by adding:

2 points for

- prior bleed

1 point for each of the other risk factors:

- hepatic or renal disease,

- ethanol abuse,

- malignancy,

- older (age > 75 years),

- reduced platelet count or function,

- hypertension (uncontrolled),

- anemia,

- genetic factors,

- excessive fall risk

- stroke

Gage BF et al. AHJ. 2006;713-9.

HAS-BLED risk of bleeding

- *HAS-BLED, developed by Pisters et al, allows clinicians to assess an individual's risk of bleeding based on comorbidities[1]*
- *In determining when oral anticoagulation is appropriate, clinicians must balance the $CHADS_2$ or CHA_2DS_2VASc score against HAS-BLED*
- *Unfortunately, a high CHADS score often correlates with a high HAS-BLED score and these patients do not receive anticoagulation due to the high bleeding risk*

HASBLED

	Condition	Points
H	Hypertension	1
A	Abnormal liver and renal function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age >65)	1
D	Drugs or alcohol (1 point each)	1 or 2

Risk of major bleeding in patients with AF in the Euro Heart Survey

Score	Bleeds Per 100 Patient Years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.7

Hypertension, stroke and age are also variables in the CHADS scores

1. Pisters R et al. Chest 2010;138(5):1093-100

ATRIA
(Anticoagulation and Risk Factors in Atrial Fibrillation)

- **Anemia** (3 points),

- **Severe renal disease** (e.g., eGFR <30 ml/min or dialysis-dependent, 3 points),

- **Age** ≥75 years (2 points),

- **Prior bleeding** (1 point),

- **Hypertension** (1 point).

Fang MC et al. 2011;395-401.

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Performance of the HEMORR2HAGES, ATRIA, and HAS-BLED Bleeding Risk–Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation :

The AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study
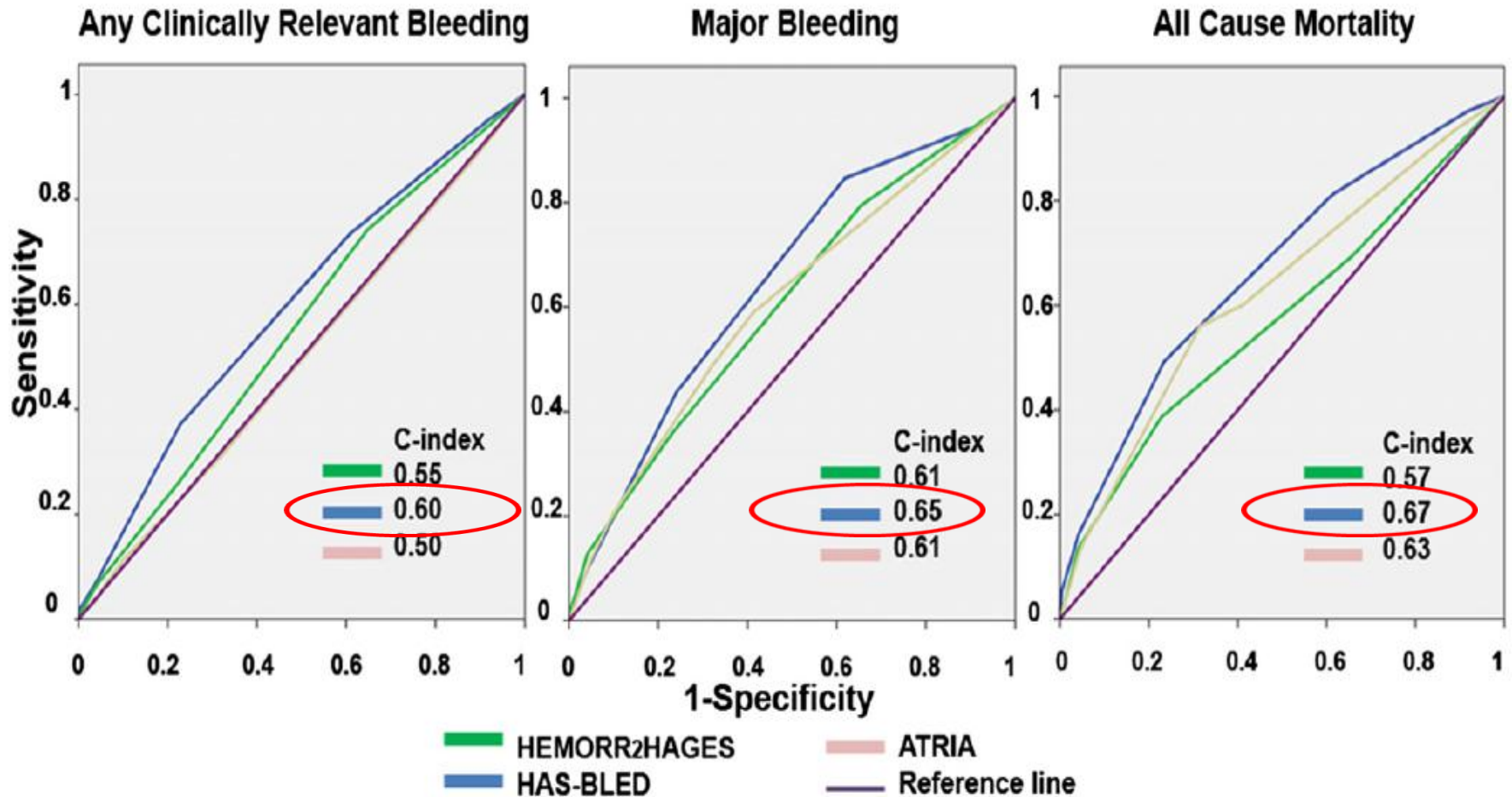
RESULTS

AUC Analysis	Any Clinically Relevant Bleeding			Major Bleeding			Death		
	AUC	95% CI	SE	AUC	95% CI	SE	AUC	95%CI	SE
HEMORR$_2$HAGES	0.55	0.51-0.59	0.019	0.60	0.51-0.69	0.046	0.57	0.50-0.65	0.033
HAS-BLED	0.60	0.56-0.63	0.019	0.65	0.56-0.73	0.043	0.67	0.60-0.73	0.035
ATRIA	0.50	0.46-0.54	0.020	0.61	0.51-0.70	0.048	0.63	0.56-0.69	0.037

Apostolakis S et al. JACC. 2012;861-7.

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Comparison of Bleeding Schemas

Receiver-Operating Characteristic Curves of the Bleeding Risk Schemes for the 3 Outcomes

RESULTS

Score	Any Clinically Relevant Bleeding		Major Bleeding		All-Cause Mortality	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
HEMORR$_2$HAGES >1	1.2 (0.9–1.5)	0.30	1.8 (0.9–3.5)	0.08	2.0 (1.3–3.3)	0.003
HAS-BLED >2	1.9 (1.4–2.4)	<0.001	2.4 (1.3–4.6)	0.006	2.9 (1.9–4.6)	<0.001
ATRIA >3	1.2 (0.8–1.7)	0.50	2.3 (1.1–5.1)	0.03	2.3 (1.3–4.0)	0.005

Conclusions
(Major Bleeding)

- **With respect to major bleeding events, all 3 scores demonstrated significant predictive ability, although their c-indexes were below the cutoff point of what is considered good performance (c-index: <0.70).**

- **No statistically significant differences were observed between the 3 scores in the outcome of major bleeding.**

Modeling Stroke and Bleeding in AF

- **Risk scores allow for identifying patients at risk for the outcome of interest and help in choosing the best therapy for pts with Afib**

- **With respect to Stroke prediction, CHADS Vasc 2 should be used routinely**

- **The HAS-BLED score may be an attractive method for the estimation of oral anticoagulant–related bleeding risk for use in clinical practice**

- **The risk factors for bleeding and stroke are similar (age, gender, CKD, DM), therefore risk scores are needed to evaluate the NET clinical benefit for pts with Afb when choosing best possible therapy for a given patient.**