

Atrial Fibrillation: Stratifying Stroke Risk and Determining Anticoagulant Therapy

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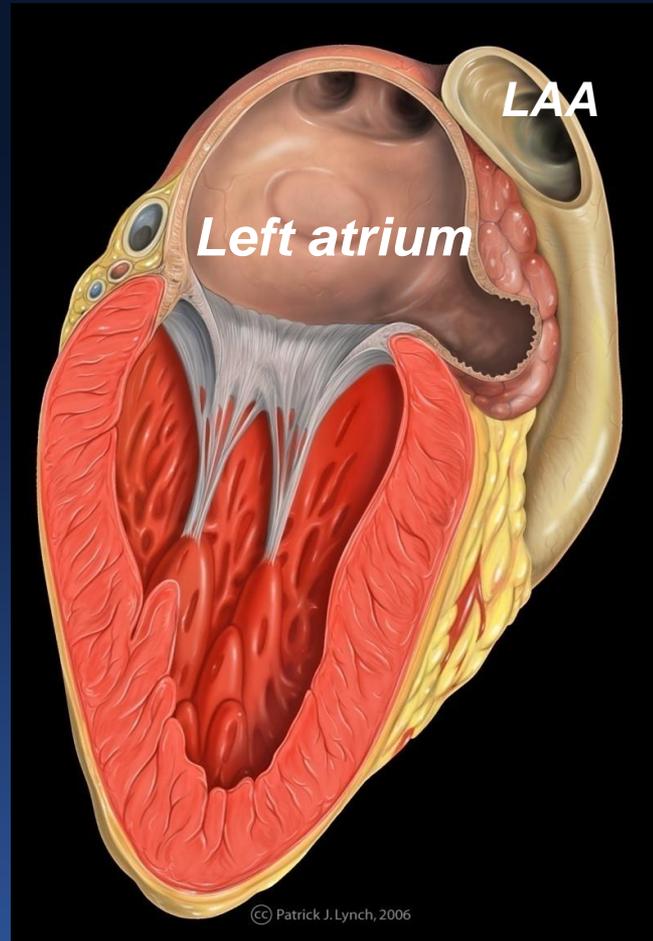
Disclosure Statement of Financial Interest

I, Asma Hussaini DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Atrial Fibrillation and Stroke

- AF is a very common, often asymptomatic condition that can present for the first time as a devastating stroke.
- Stroke rate with atrial fibrillation (AF) varies between 1% and 20% annually (mean 4.5% per year) depending on comorbidities and history of prior cerebrovascular events.¹
- Stratification of stroke risk important, as the major risk of anticoagulation therapy is bleeding.

LAA is the source of thrombus in over 90% of AF patients



CHADS₂ Score

Item	Points		CHADS ₂	Stroke rate (95% CI)*
Congestive heart failure	1	 <p>Add points together</p>	6	18.2 (10.5–27.4)
Hypertension	1		5	12.5 (8.2–17.5)
Age ≥75 years	1		4	8.5 (6.3–11.1)
Diabetes mellitus	1		3	5.9 (4.6–7.3)
Stroke/TIA	2		2	4.0 (3.1–5.1)
			1	2.8 (2.0–3.8)
			0	1.9 (1.2–3.0)

*Per 100 patient-years without antithrombotic therapy

Gage *et al*, JAMA 2001

ACC/AHA/HRS 2012 guidelines: based on CHADS₂ Score

	Recommended therapy
CHADS ₂ score	ACC/AHA/HRS 2012
0	ASA 81–325 mg/day
1	WF (INR 2–3) or ASA 81–325 mg/day
≥2	WF (INR 2–3)

CHADS₂-VASc: a further refinement of CHADS₂

Risk factor	Points
Congestive heart failure/LV dysfunction*	+1
Hypertension	+1
Age ≥75 years	+2
Diabetes mellitus	+1
Previous stroke/TIA/thromboembolism	+2
Vascular disease (MI, aortic plaque, peripheral artery disease)	+1
Age 65–74 years	+1
Sex category (female)	+1
Maximum score	9

*Left ventricular ejection fraction ≤40%; #Including prior revascularization, amputation due to peripheral artery disease or angiographic evidence of peripheral artery disease

Camm *et al*, *Eur Heart J* 2010; Lip *et al*, *Chest* 2010

Many stroke risk factors are also risk factors for bleeding

	Risk factor for stroke*	Risk factor for anticoagulant-related bleeding*
Advanced age ¹⁻⁴	✓	✓
History of hypertension ^{1,3,4}	✓	✓
History of MI or ischemic heart disease ^{1,3}	✓	✓
Cerebrovascular disease ¹⁻⁴	✓	✓
Anemia ^{3,4}		✓
Previous history of bleeding ^{3,4}		✓
Kidney or liver dysfunction ⁴		✓
Concomitant use of antiplatelets ^{3,4}		✓

*Not exhaustive

The relationship between stroke risk and bleeding risk complicates the evaluation of benefit–risk

1. Lip *et al*, *Chest* 2010; 2. Hylek *et al*, *Ann Intern Med* 1994; 3. Hughes *et al*, *QJM* 2007; 4. Pisters *et al*, *Chest* 2010

HAS-BLED score

Clinical characteristic	Points
Hypertension (SBP >160 mm Hg)	1
Abnormal renal or liver function	1 + 1
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age >65 years)	1
Drugs or alcohol	1 + 1
Cumulative score	Range 0–9

Pisters *et al*, *Chest* 2010

1-year risk of major bleeding increases with HAS-BLED score

Score	No	No of Bleed	Bleeds Per 100 Patient-Years
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.50
6	2	0	0.0
7	0	-	-
8	0	-	-
9	0	-	-

Pisters *et al*, *Chest* 2010

HAS-BLED score

- Should not be used to exclude patients from OAC therapy.
- Allows clinician to identify bleeding risk factors and to correct those that are modifiable, ie, controlling blood pressure, and reducing alcohol.
- Can be used to highlight those patients on OACs in whom caution and regular review is warranted.

Vitamin K Antagonists(Warfarin)

- Multiple trials demonstrate superiority of vitamin K antagonists over antiplatelet therapies for stroke prevention in AF patients.
- Data shows consistent benefit of warfarin across studies with absolute reduction in annual stroke rate from 4.5% for control patients to 1.4% in patients assigned to adjusted-dose warfarin.¹
- This absolute risk reduction translates to 31 ischemic strokes prevented each year for every 1000 patients treated.

Vitamin K Antagonists

- Warfarin is relatively safe, annual rate of major bleeding of 1.3% compared with 1% for placebo or aspirin.¹
- No data to support that increasing intensity of anticoagulation or adding antiplatelet agent provides additional protection against second event for patients who have a stroke while on therapeutic anticoagulation.

Antiplatelet Therapy

- For high-risk patients with AF deemed unsuitable for anticoagulation, dual-antiplatelet therapy with Clopidogrel and aspirin offers more protection against stroke than aspirin alone but with an increased risk of major bleeding.

New Oral Anticoagulants (NOACs)

- No published data comparing Dabigatran, Rivaroxaban, and Apixaban to one another, only comparisons to warfarin.
- The duration of follow-up in the clinical trials was limited.
- Due to their short half-lives, noncompliant patients may be at risk for thromboembolism.

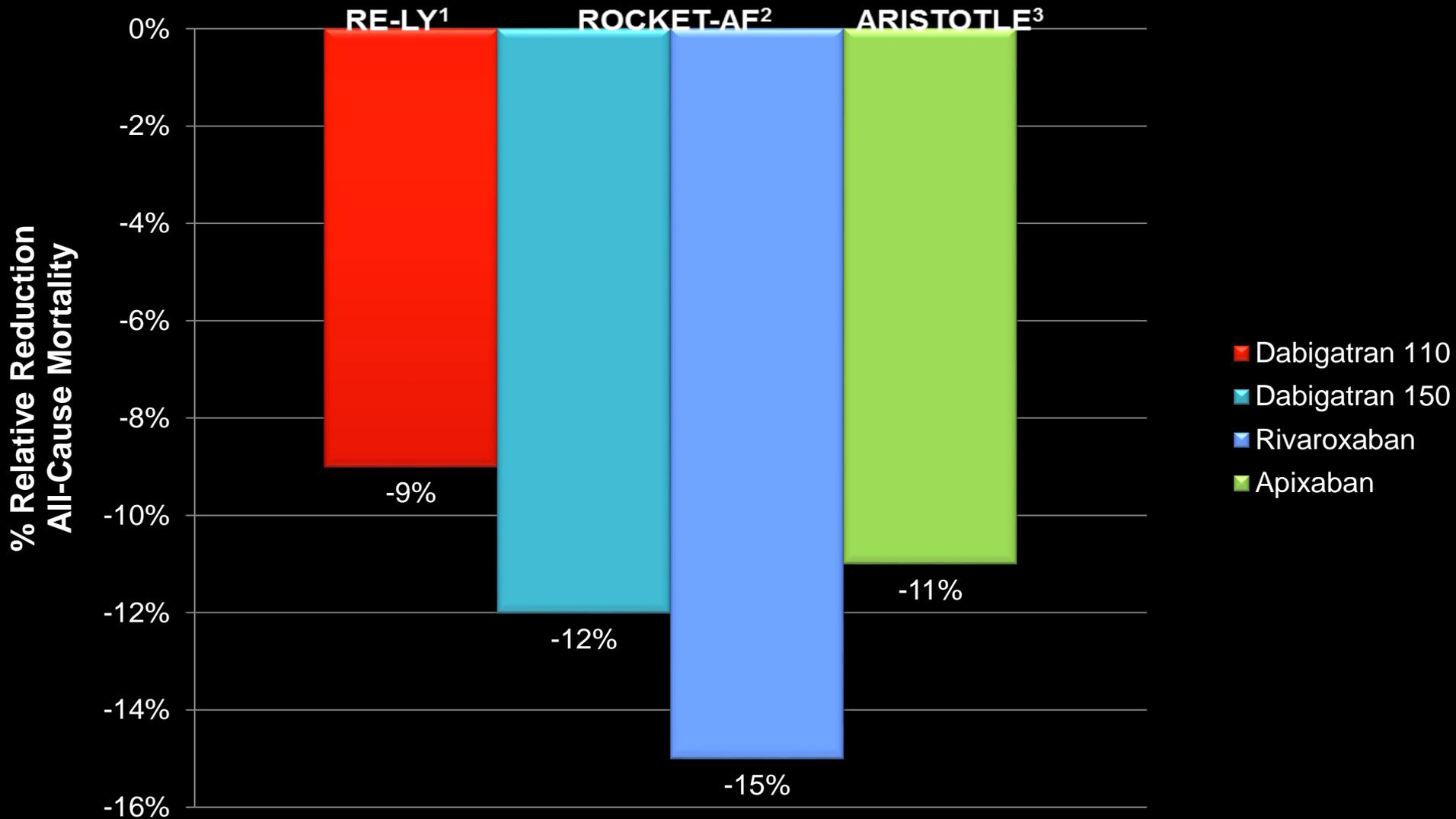
New Oral Anticoagulants (NOACs)

- Treatment decisions should account for differences in costs, which may affect compliance.
- Drug activity presently cannot be assessed in routine clinical practice, this can lead to risk of undertreating or overtreating.
- There are no antidotes to emergently reverse these medications in the setting of hemorrhage.

Comparison of Key Studies of NOACs

	RE-LY ²⁶	ROCKET-AF ⁵²	ARISTOTLE ⁵⁸
Agent	Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg or 2.5 mg BID*
Comparator	Warfarin	Warfarin	Warfarin
Blinding	Open label	Double blind	Double blind,
Sample size	18 113	14 264	18 201
Mean age, y	72	73	70
Female, %	36	40	35
CHADS score	2.1	3.5	2.1
0–1, %	32	0	34
2, %	35	13	36
3–6, %	33	87	30
Previous stroke, %	20	34	19
Event rate vs comparator, %†	1.1 vs 1.7 (P<0.001)	2.1 vs 2.4 (P=0.12‡)	1.3 vs 1.6 (P<0.001)
HR vs comparator†	0.66 (0.53–0.82)	0.88 (0.74–1.03)‡	0.79 (0.66–0.95)
No. needed to treat	167	Noninferior	303
Major bleeding vs comparator, %	3.1 vs 3.4	3.6 vs 3.4	2.1 vs 3.1
ICH vs comparator, %	0.3 vs 0.7	0.5 vs 0.7	0.2 vs 0.5

Total Mortality Relative Reduction (vs warfarin)



¹Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs f-up

²Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs f-up, ITT

³Granger, C NEJM 2011; 365:981-992 – 1.8 yrs f-up

Dabigatran

- Dabigatran is useful as an alternative to warfarin for the prevention of stroke in AF patients who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (CrCl <15 mL/min), or advanced liver disease (impaired baseline clotting function).

Apixaban

- Apixaban 5 mg twice daily is a relatively safe and effective alternative to warfarin in patients with nonvalvular AF deemed appropriate for vitamin K antagonist therapy who have at least 1 additional risk factor and no more than 1 of the following characteristics: Age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL.

Rivaroxaban

- Rivaroxaban 20 mg/d is reasonable as an alternative to warfarin.
- Should not be used if $\text{CrCl} < 25$ mL/min.
- Also approved for treatment and prophylaxis of DVT/PE

Conclusions

- Warfarin and the newer anticoagulant agents (Dabigatran, Rivaroxaban, Apixaban) are effective in reduction of ischemic stroke risk in AF patients.
- Clinicians often overestimate the risk of bleeding with OACs, and underestimate risk of stroke in AF.
- Stroke and bleeding risk assessment tools such as CHADS₂ and HAS-BLED can help guide the decision of OAC to use and the management plan.