Alternative Anticoagulation Strategies in Atrial Fibrillation: Issues and Answers?

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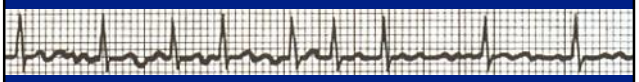
Speaker: sanofi aventis,

*clinical trial steering committee
**clinical trial DSMB

Characterizing Atrial Fibrillation



- Atrial Fibrillation (AF) is the most common sustained arrhythmia in the Western world
- > 80% of individuals with AF are ≥ 65 years of age
- At present, just > 50% of individuals with AF are ≥ 75 years of age
- Soon, 50% of individuals with AF will be ≥ 80 years of age
- Projected prevalence of AF 5.6 to 16 million Americans by 2050
- Lifetime incidence of AF: 1 in 4 individuals > 40 years of age

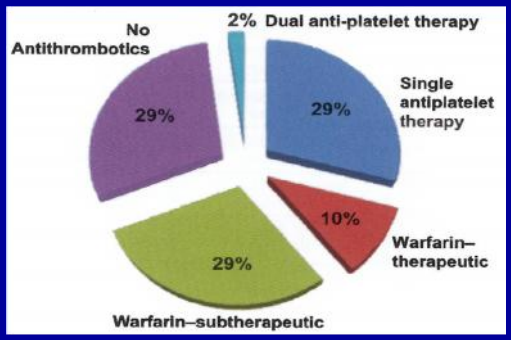
Go AS, et al. *JAMA.* 2001;285:2370-2375.
Lloyd-Jones DM et al. *Circulation.* 2004;110:1042- 1046.
Miyasaka Y, et al. *Circulation.* 2006;114:119-125.

Problems With Warfarin

- Delayed onset/offset of action
- Narrow therapeutic range
- Unpredictable dose response
- Metabolized by CYP450s (especially 2C9)
- Common genetic polymorphisms (especially 2C9) affect dose requirements
- Numerous drug–drug, drug–food interactions
- Variable anticoagulant response necessitates coagulation monitoring and dose adjustments
- Slow reversibility
- Inconvenience for patient and physician
- The above most likely contribute to warfarin underuse

Modified after Ansell et al. *Chest.* 2001;119:22S-38S. Hirsh et al. *Chest.* 2001;119:64S-94S.

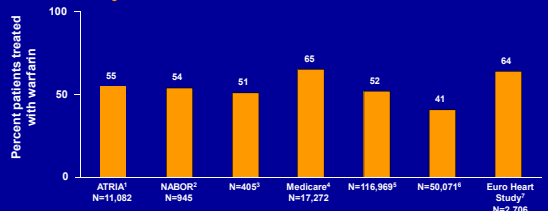
Preadmission Medications for Patients with Known AF Admitted with Stroke



Gladstone DJ et al. Stroke 2009;40:235-40

Prevalence of Eligible AF Patients Receiving Warfarin Therapy

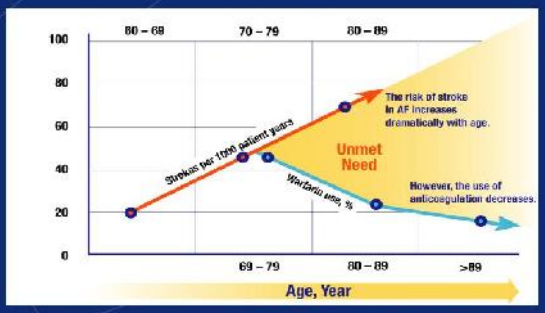
Warfarin is prescribed for only 41% to 65% of eligible patients with AF, *many of whom are considered "warfarin-unsuitable"*



ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation,
NABOR=National Anticoagulation Benchmark and Outcomes Report

1.Go AS et al. *Ann Intern Med.* 1999;131:927-934.
2.Waldo AL et al. *J Am Coll Cardiol.* 2005;46:1729-1736.
3.Hylek EM et al. *Stroke.* 2006;37:1075-1080.
4.Birman-Deych E et al. *Stroke.* 2006;37:1070-1074.
5.Walker AM, Bennett D. *Heart Rhythm.* 2008;5:1365-1372.
6.Williams CJ et al. American College of Cardiology 58th Annual Scientific Session; March 29-31, 2009; Orlando, FL.
7.Nieuwlaat R et al. *Eur Heart J.* 2006;27:3018-3026.

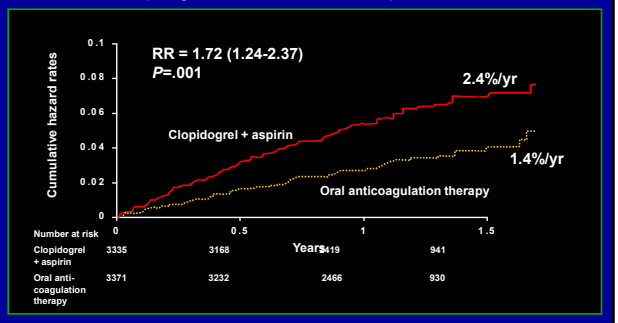
AGE-RELATED TRENDS IN AF



Wolf PA. *Arch Intern Med* 1987;147:1561-4
White RH. *Am J Med* 1999;106:165-71

ACTIVE* W: Cumulative Risk of Stroke

* Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events



Primary outcome: Stroke, Systemic Embolus, MI, Vascular Death

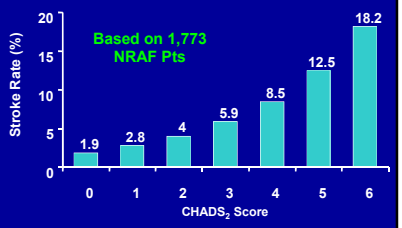
CL+ASA = 5.6% Risk/Year vs W = 3.93% Risk/Year

Connolly S, et al. *Lancet.* 2006;367:1903-1912.

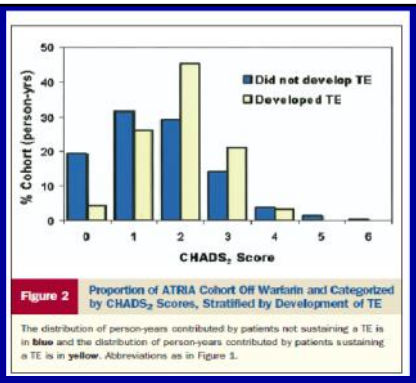
Key AF Stroke Risk Factors: CHADS$_2$ Risk Stratification Scheme

Risk Factor		Points
C	Congestive heart failure (recent)	1
H	Hypertension	1
A	Age 75 years	1
D	Diabetes	1
S_2	Prior stroke or TIA	2

TIA = transient ischemic attack

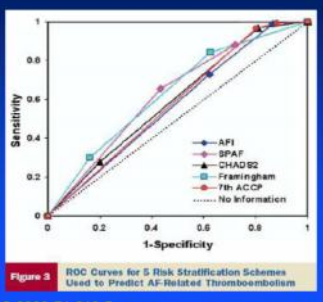


Gage et al. *JAMA.* 2001;285:2864-2870. (A)



Fang M et al. J Am Cardiol 2008;51:810-5

AF Stroke Risk Schemes: ROC Curves*



*Fang et al. JACC 2008;51:810-5

Conclusions

Current risk stratification schemes used to predict thromboembolism in persons with nonvalvular AF have similar discriminatory ability, but the ability is relatively poor. Until better means of risk stratification are available, a large proportion of patients with AF who would not have developed thromboembolism may be exposed to the risks associated with warfarin therapy. In addition, differences across risk schemes could potentially lead to substantial variation in whether or not individual patients are recommended warfarin therapy. Further research is needed to develop more accurate ways to identify prospectively those patients with AF who will sustain a thromboembolic event without warfarin therapy, and similarly, robust methods are needed to identify reliably those patients who will suffer complications when treated with anticoagulants.

Fang MC et al. J Am Coll Cardiol 2008;51:810-5

Conclusions

1. Current risk stratification schemes used to predict TE in persons with nonvalvular AF have similar discriminatory ability, but the ability is relatively poor.
2. Until better means of risk stratification are available, a large proportion of patients with AF who would not have developed TE may be exposed to the risks associated with warfarin therapy.
3. Differences across risk schemes could potentially lead to substantial variation in whether or not individual patients are recommended for warfarin therapy.
4. Need better discriminators to identify for those who will sustain a TE event or who will suffer complications from anticoagulant therapy.

Fang MC et al. J Am Coll Cardiol 2008;51:810-5.

Stroke Risk Stratification in AF

$CHADS_2$

Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	1
Diabetes	1
Stroke	2

Total Score	Annual Risk of Stroke (%)	
0	1.9	0
1	2.8	1.3
2	4.0	2.2
3	5.9	3.2
4	8.5	4.0
5	12.5	6.7
6	18.2	9.8
7		9.6
8		6.7
9		15.2

$CHADS_2$ | CHA_2DS_2-VASc

CHA_2DS_2-VASc

Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	2
Diabetes	1
Stroke	2
Vascular disease (MI, PAD, aortic atherosclerosis)	1
Age 65-74 y	1
Sex category (female)	1

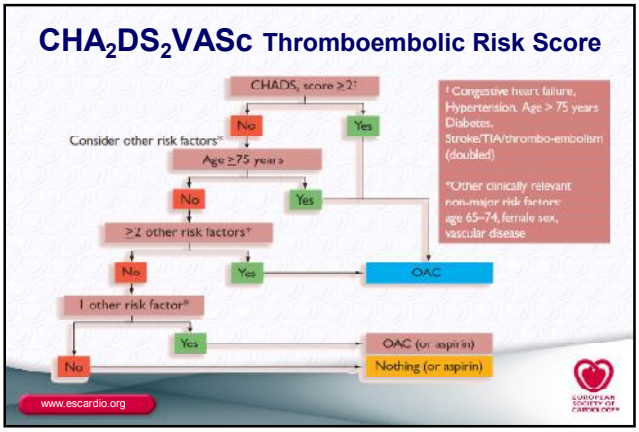
Lip GY, Halperin JL. *Am J Med*. 2010;123(6):484-488.
Camm AJ, et al. *Eur Heart J*. 2010;31(19):2369-2429.

ISC 2010: "AF: Who Should Be Anticoagulated"

Conclusion:

- Current risk-based approach is OK, but not as good as we'd like
- Need better predictors of ischemic stroke, hemorrhage
- Quality of warfarin anticoagulation is very important
- New anticoagulants may change our approach

CHA_2DS_2VASc Thromboembolic Risk Score

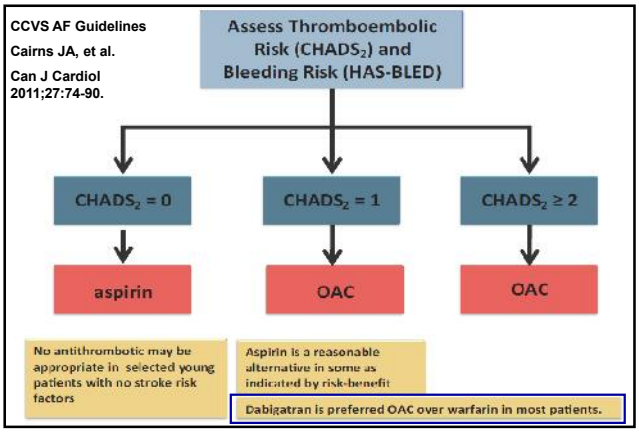


Risk Factor / CHA_2DS_2VASc and Therapy

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥ 2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

www.escardio.org

CCVS AF Guidelines
Cairns JA, et al.
Can J Cardiol 2011;27:74-90.



Assessment of Bleeding Risk

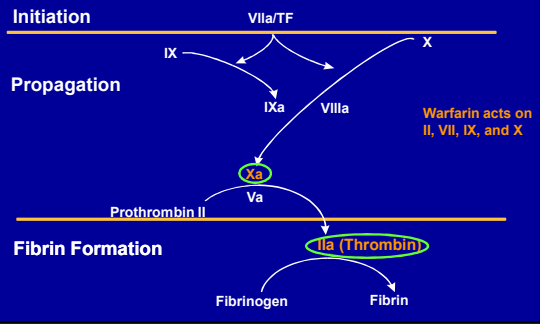
HAS-BLED Score	Score
Hypertension (SBP > 160 mm Hg)	1
Abnormal renal/liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age > 65)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

HAS-BLED score of ≥ 3 suggests increased bleeding risk and warrants some caution and/or regular review.

SBP = systolic blood pressure; INR = international normalized ratio.

Pisters R et al. Chest 2010; pub online March 18. DOI:10/1378/chest.10-0134.

Coagulation Cascade



New Oral Anticoagulants

- Unmet Clinical Needs in the Treatment of AF
  - 29% of all strokes are due to AF
  - Stroke risk can be reduced by 70% with treatment
  - Warfarin grossly underused
  - Use of new, effective, and safe oral agents offers the prospect of simplified (fixed) dosage, rapid onset of action, absence of need for monitoring, and few drug – drug and drug – food interactions

Modified after Turpie AG Eur Heart J 2008;29:155-65

New Anticoagulants:

Comparison Of RCTs

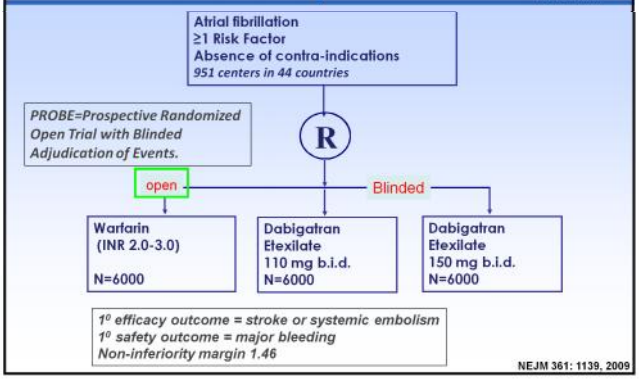
	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose Investigated (mg) Dose Frequency	150, 110 Twice daily	20 Daily	5 Twice daily	60, 30 Daily
Drug Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Subjects	18,113	14,266	~15,000	~16,500
Design	Open label	Double blind	Double blind	Double blind
Primary Efficacy Endpoint	Stroke/SEE	Stroke/SEE	Stroke/SEE	Stroke/SEE
Dose Adjustment For Drug Clearance (mg)	No	Yes 20 → 15	No	Yes 60 → 30 30 → 15
Non-Inferiority HR Margin	1.46	Not published	1.38	1.38

Dabigatran Etexilate

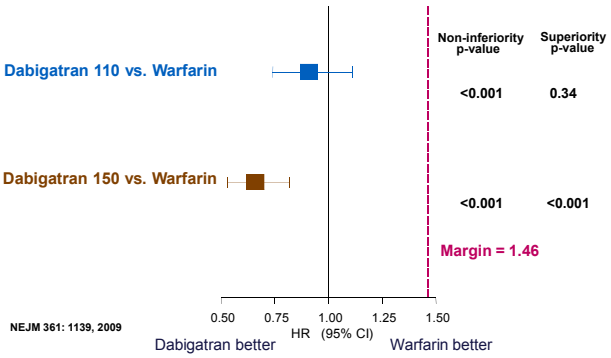
- Competitive inhibitor of thrombin
- Prodrug - converted completely to active dabigatran
- Orally active; peak plasma concentration at 2 hours post-dose; T ½: 12 – 17 hours
- Extensively metabolized, mainly by CYP3A; proton pump inhibitors reduce absorption; bioavailability is increased by meals
- Eliminated predominantly by kidneys (80%)
- Phase 2 data identified 110 mg BID and 150 mg BID as viable doses

Stangier J et al. J Clin Pharmacol 2005;45:555-563; Liesenfeld KH et al. Br J Clin Pharmacol 2006;62:527-537; Stangier J et al. Br J Clin Pharmacol 2007;64:292-303

RE-LY: A Non-inferiority Trial

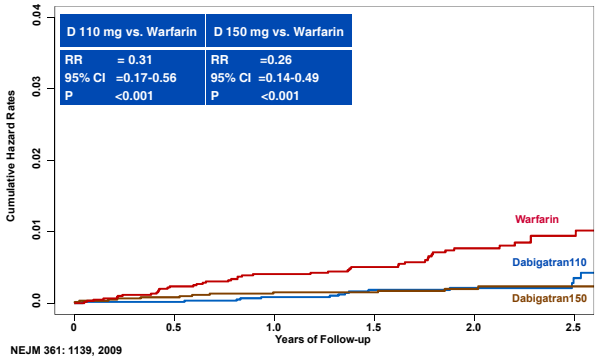


Stroke or Systemic Embolism



NEJM 361: 1139, 2009

Hemorrhagic Stroke



NEJM 361: 1139, 2009

Bleeding

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Total	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major	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	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Gastro-intestinal Major	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001

Major bleeding = ↓HGB ≥ 20 g/L, transfusion ≥ 2 units, or sympt. bleeding in a critical area or organ

NEJM 361: 1139, 2009

Cardioversion in RE-LY

- Cardioversions (n=1,983) were performed in 1,270 pts: 647 pts on 110 mg bid, 672 pts on 150 mg bid, and 664 pts on warfarin.
  - DC: 536, 550, 553; and pharmacologic: 91, 122, 111, respectively.
  - TEE was performed in 25.5%, 24.1%, and 13.3% of D110, D150, and warfarin, respectively, with 1.8%, 1.2%, and 1.1% positive, respectively.
- Stroke and systemic embolism by 30 days occurred in 0.77, 0.30, and 0.60 % of pts, respectively.
  - These were not statistically different (with p=0.40 for 150 bid vs warfarin and p=0.71 for 110 bid vs warfarin), but the RE-LY trial was not powered for this analysis.
  - There were no differences in major bleeding.
  - There were no differences with vs without TEE
  - This is the largest cardioversion experience published to date!

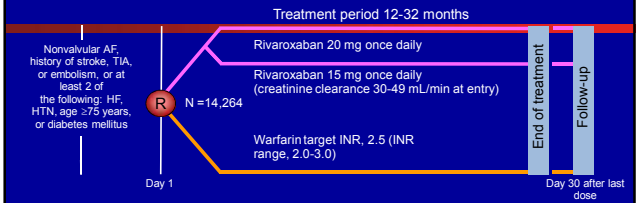
Nagarakanti et al. Circulation 2011; 123:131-136

Rivaroxaban

- Direct inhibitor of coagulation Factor Xa
- Well tolerated
- Half-life up to 12 hrs in elderly subjects; up to 9 hrs in healthy subjects
- No direct effect on platelet aggregation
- Potently inhibits free and clot-associated Factor Xa activity
- Rapid onset of action (T_{max} 2 - 4 hrs)
- Elimination – 1/3 renal (unchanged); 2/3 liver metabolism
- Low propensity for clinically relevant drug-drug interactions

Turpie ACG Eur Heart J E Pub Dec.17, 2007

ROCKET AF Trial: Rivaroxaban



- In AF patients with a moderate to high risk of stroke, does rivaroxaban reduce the risk of major vascular events compared with warfarin?
- **1º study end point**: composite of all-cause stroke and non-CNS systemic embolism
- **2º end points**: composite of TIA, all-cause death, vascular death, and MI
- **1º safety end point**: composite of major and clinically relevant nonmajor bleeding events
- Randomization completed in June 2009; follow-up completed 2010
- Follow-up: up to 4 years (until 405 primary outcome events have been observed)

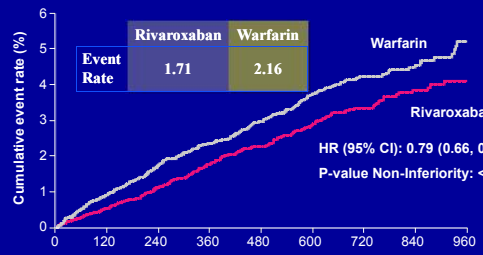
TIA = transient ischemic attack; ROCKET = Randomized, Double-Blind Study Comparing Once Daily Oral Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation. ROCKET AF Study Investigators. *Am Heart J*. 2010;159(3):340-347.e1.

Rocket-AF: Baseline Demographics

	Rivaroxaban (N=7081)	Warfarin (N=7090)
$CHADS_2$ Score (mean)	3.48	3.46
2 (%)	13	13
3 (%)	43	44
4 (%)	29	28
5 (%)	13	12
6 (%)	2	2
Prior VKA Use (%)	62	63
Congestive Heart Failure (%)	63	62
Hypertension (%)	90	91
Diabetes Mellitus (%)	40	39
Prior Stroke/TIA/Embolism (%)	55	55
Prior Myocardial Infarction (%)	17	18

Based on Intention-to-Treat Population

ROCKET AF: Primary Efficacy Outcome
Stroke and non-CNS Embolism



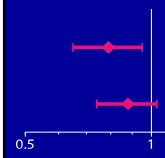
No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

Mahaffey KW et al. AHA presentation Chicago 11/15/2010

ROCKET AF: Primary Efficacy Outcome
Stroke and Non-CNS Embolism



	Rivaroxaban* Event Rate	Warfarin Event Rate	HR (95% CI)	*P*-value
On Treatment N= 14,143	1.70	2.15	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.12	2.42	0.88 (0.74,1.03)	0.117

TTR 57.8%

Average $CHADS_2$ score 3.7

*Rivaroxaban is not FDA-approved.
Event rates are per 100 patient-years. Based on safety on treatment or ITT thru site notification populations.
ITT = intention to treat.
Califf RM. Presented at: American Heart Association 2010 Scientific Sessions; November 15, 2010; Chicago, IL.

ROCKET-AF

Outcome	Rivaroxaban (n=7081)	Warfarin (n=7090)	Hazard ratio (95% CI)	p
•Primary end point, noninferiority	1.71	2.16	0.79 (0.66–0.96)	<0.001
•Primary end point, on-treatment superiority	1.70	2.15	0.79 (0.65–0.95)	0.015
•Primary end point, intention-to-treat superiority	2.12	2.42	0.88 (0.74–1.03)	0.117
•Vascular death, stroke, embolism	3.11	3.63	0.86 90.74–0.99)	0.034
•Hemorrhagic stroke	0.26	0.44	0.59 (0.37–0.93)	0.024
•Ischemic stroke	1.34	1.42	0.94 (0.75–1.17)	0.581
•Unknown stroke	0.06	0.10	0.65 (0.25–1.67)	0.366

Mahaffey KW et al. AHA presentation Chicago 11/15/2010

ROCKET AF: Key Secondary Efficacy Outcomes

	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	*P*-value
Vascular Death, Stroke, Embolism	4.51	4.81	0.94 (0.84, 1.05)	0.265
Stroke Type				
Hemorrhagic	0.26	0.44	0.58 (0.38, 0.89)	0.012
Ischemic	1.62	1.64	0.99 (0.82, 1.20	0.916
Unknown type	0.15	0.14	1.05 (0.55, 2.01)	0.871
Non-CNS Embolism	0.16	0.21	0.74 (0.42, 1.32	0.308
MI	1.02	1.11	0.91 (0.72, 1.16)	0.464
All Cause Mortality	4.52	4.91	0.92 (0.82, 1.03)	0.152
Vascular	2.91	3.11	0.94 (0.81, 1.08)	0.350
Nonvascular	1.15	1.22	0.94 (0.75, 1.18)	0.611
Unknown cause	0.46	0.57	0.80 (0.57, 1.12)	0.195

Event rates are per 100 patient-years.
Based on ITT population.

Mahaffey KW et al. AHA presentation Chicago 11/15/2010

ROCKET-AF

Outcome	Rivaroxaban (n=7081)	Warfarin (n=7090)	Hazard ratio (95% CI)	p
Major and nonmajor bleeding	14.91	14.52	1.03 (0.96–1.11)	0.442
Major bleeding	3.60	3.45	1.04 (0.90–1.20)	0.576
•>2 g/dL hemoglobin drop	2.77	2.26	1.22 (1.03–1.44)	0.019
•Transfusion	1.65	1.32	1.25 (1.01–1.55)	0.044
•Critical organ bleeding	0.82	1.18	0.69 (0.53–0.91)	0.007
•Bleeding causing death	0.24	0.48	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	0.49	0.74	0.67 (0.47–0.94)	0.019

Mahaffey KW et al. AHA presentation Chicago 11/15/2010

Rocket-AF: Summary

- **Efficacy:**
  - Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism.
  - Rivaroxaban was superior to warfarin while patients were taking study drug.
  - By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.
- **Safety:**
  - Similar rates of bleeding and adverse events.
  - Less ICH and fatal bleeding with rivaroxaban.
- **Conclusion:**
  - Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with AF.

$CHADS_2$ Scores: RE-LY and ROCKET-AF

	RE-LY (a)			ROCKET-AF (b)	
$CHADS_2$ Score	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Rivaroxaban	Warfarin
Mean	2.1	2.2	2.1	3.48	3.46
0-1	32.6%	32.2%	21.0%	0	0
2	34.7%	35.2%	37.0%	13%	13%
3-6	32.7%	32.6%	32.1%	87%	87%

a) Connolly SJ et al. N Engl J Med 2009;361:1139-1151

b) Data presented by Mahaffey KW. AHA; 2010; Chicago.

ROCKET AF Compared with RE-LY

	ROCKET AF	RE-LY
N	14,171	18,113
VKA naive	37%	50%
Design	Randomized, double-blind, double-dummy study	PROBE design
Treatment	Rivaroxaban 1 dose (with dose adaptation for moderate renal impairment)	Dabigatran 2 doses
Regimen	Once daily	Twice daily
Primary outcome	Efficacy: Composite of all-cause stroke and non-CNS systemic embolism Safety: Composite of major and clinically relevant nonmajor bleeding events	Efficacy: Incidence of stroke (including hemorrhagic) and systemic embolism Safety: Major bleeding events
Secondary outcome	Each category of bleeding events, and adverse events Composite of TIA, all-cause death, vascular death, and MI	Incidence of stroke (including hemorrhagic), systemic embolism, all death, pulmonary embolism, MI, TIA, vascular deaths (including deaths from bleeding), and hospitalizations

ROCKET AF Investigators. *Am Heart J*. 2010;159:340-7.e1. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-51.

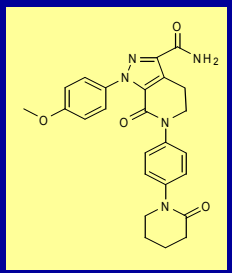
ROCKET AF Compared with RE-LY

	ROCKET AF	RE-LY
TTR (median)	58%	67%
$CHADS_2$ (mean)	3.7	2.1
Previous TIA/CVA	55%	20%
Primary outcome HR	0.79	0.66 (150 dose)
Hemorrhagic CVA rate	0.24	0.24 (150 dose)
Ischemic CVA: HR	0.99	0.75 (150 dose)
Major Bleeding rate	3.6%	3.3% (150 dose)

ROCKET AF Study Investigators. *Am Heart J*. 2010;159:340-347.e1. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.

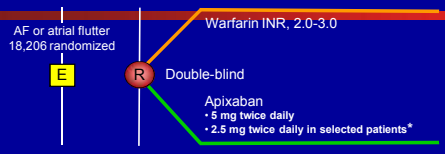
Apixaban

- Oral, direct, selective factor Xa inhibitor
- Produces concentration-dependent anticoagulation
- No formation of reactive intermediates
- No organ toxicity or liver function test abnormalities in chronic toxicology studies
- Low likelihood of drug interactions or QTc prolongation
- Good oral bioavailability
- No food effect
- Balanced elimination (~25% renal)
- $T_{1/2}$: ~12 hours



He K, et al. *Blood*. 2006;108:910. Lassen MR. *Blood*. 2006;108:574

ARISTOTLE Trial: Apixaban



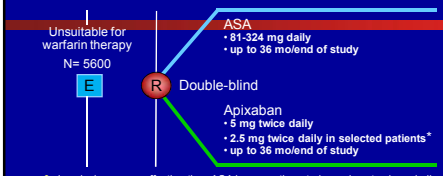
- Is apixaban noninferior to standard therapy (warfarin) in preventing stroke and systemic embolism in moderate- to high-risk (stroke, at least 1 risk factor) AF/AFL patients?
- **1^0 efficacy end point**: confirmed ischemic or hemorrhagic stroke, or systemic embolism
- **2^0 efficacy end points**: composite of confirmed ischemic or hemorrhagic stroke, systemic embolism, and all-cause death
- **1^0 safety end point**: time to first occurrence of confirmed major bleeding
- Treatment period: up to 4 years (until 448 primary outcome events have been observed—>90% power to demonstrate noninferiority)
  - Stratified by warfarin-naïve status

*At least 2 of the following: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL

ARISTOTLE = Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation.

Lopes RD, et al. *Am Heart J*. 2010;159(3):331-339.

AVERROES Trial

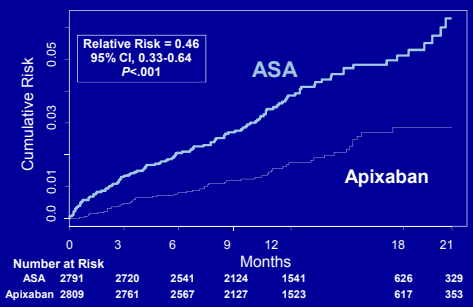


- Is apixaban more effective than ASA in preventing stroke and systemic embolism in moderate to high-risk (stroke, at least 1 risk factor) AF patients?
- **1º efficacy end point**: confirmed ischemic or hemorrhagic stroke or systemic embolism
- **2º study end points**: as above, including MI or vascular death
- **1º safety end point**: major bleeding
- Study period: until 226 primary outcome events have been observed
- **In June 2010, the study was stopped early** because a predefined interim analysis revealed clear evidence of a clinically important reduction in stroke and systemic embolism

* **At least 2 of: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL.**

AVERROES = Apixaban Versus ASA to Reduce the Risk of Stroke.
Eikelboom JW, et al. *Am Heart J.* 2010;159(3):348-353.e1. http://www.theheart.org/article/1087291.do.. Connolly SJ, et al. Presented at: European Society of Cardiology; 2010; Stockholm, Sweden..

AVERROES: Stroke or Systemic Embolic Event



Connolly SJ, et al. *N Engl J Med*. 2011 Feb 10. [Epub ahead of print]

Baseline Characteristics

Characteristic	Apixaban	ASA
Randomized	2809	2791
Age (mean and SD)	70 ±10 yrs	70 ±10 yrs
Male	1661 (59%)	1615 (60%)
CHADS2 score (mean and SD)	2.1 ± 1.1	2.1± 1.1
0-1	1005 (36%)	1017 (37%)
2	1042 (37%)	959 (34%)
3+	760 (27%)	811 (29%)
Prior stroke/TIA	389 (14%)	375 (14%)
Diabetes	537 (19%)	558 (20%)
Hypertension	2424 (87%)	2406 (86%)
CHF	1113 (40%)	1050 (38%)
Baseline ASA	2126 (76%)	2074 (74%)
Prior VKA use and discontinued	1083 (39%)	1089 (39%)

Connolly SJ, et al. *N Engl J Med*. 2011 Feb 10. [Epub ahead of print]

AVERROES: Bleeding Events

Outcome	Apixaban		ASA		Apixaban vs. ASA		
	events	Annual rate	events	Annual rate	RR	95% CI	P
Major	47	1.6	40	1.4	1.18	0.77-1.78	0.45
Clinically Relevant Non-major	92	3.3	80	2.9	1.15	0.85-1.53	0.37
Minor	155	5.7	120	4.4	1.35	1.05-1.78	0.02
Fatal	4	0.1	7	0.2	0.57	0.17-1.96	0.38
Intra-cranial	13	0.4	11	0.3	1.19	0.53-2.66	0.43

Connolly SJ, et al. *N Engl J Med*. 2011 Feb 10. [Epub ahead of print]

AVERROES: 2° and Other Efficacy Outcomes

Outcome	Apixaban		ASA		Apixaban vs. ASA		
	events	Annual rate	events	Annual rate	RR	95% CI	P
Stroke, MI, SEE or Vascular Death	122	4.3	186	6.7	0.65	0.52-0.82	<0.001
MI	22	0.7	27	0.9	0.81	0.46-1.43	0.47
Vascular Death	75	2.6	90	3.2	0.84	0.61-1.14	0.25
CV Hospitalization	339	12.8	423	16.3	0.79	0.68-0.91	0.001
Total Death	103	3.6	134	4.7	0.77	0.59-0.99	0.04

Connolly SJ, et al. *N Engl J Med*. 2011 Feb 10. [Epub ahead of print]

AVERROES: Bleeding Events

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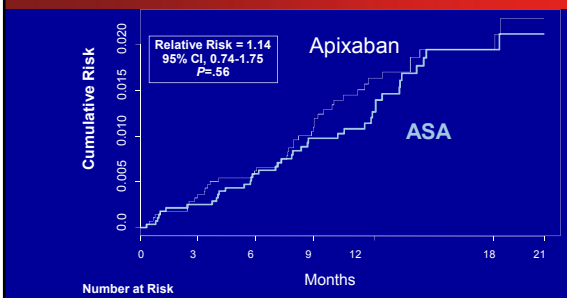
Connolly SJ, et al. *N Engl J Med*. 2011 Feb 10. [Epub ahead of print]

AVERROES: Major Bleeding



Number at Risk							
ASA	2791	2744	2572	2152	1570	642	340
Apixaban	2809	2763	2567	2123	1521	622	357

Connolly SJ, et al. *N Engl J Med*. 2011 Feb 10. [Epub ahead of print].

Characteristics of Edoxaban

- Potent and specific inhibitor of factor Xa
- Bioavailability over 45%
- Rapidly absorbed - Cmax 1- 2 hours
- Half-life of 8 to 10 hours
- Multiple pathways of excretion: 30% renal and 65% hepatic
- Linear PK, providing a predictable and consistent exposure
- Exposure to edoxaban increases with renal dysfunction and low body wt (≤ 60 kg)
- It is a substrate for the efflux transporter p-glycoprotein (P-gp) – reduced dosage of edoxaban may be needed when coadministered with strong P-gp inhibitors (e.g., verapamil, quinidine)
- Once daily regimens associated with less bleeding than twice daily regimens

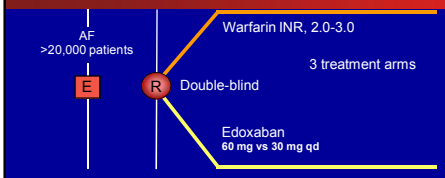
Weitz JI. Presented at the 50th ASH meeting. 12-7-2008 San Francisco, CA; Ruff CT et al. Am Heart J 2010;160:635-41

Summary

1. Once-daily edoxaban dosing regimens are associated with less bleeding than twice-daily regimens
2. Edoxaban, at 30 or 60 mg OD, appears to have a safety profile similar to that of warfarin (target INR of 2 to 3)

Weitz JI. Presented at the 50th American Society for Hematology meeting. 12-7-2008 San Francisco, CA

ENGAGE AF–TIMI 48: Edoxaban



- Is edoxaban noninferior to standard therapy (warfarin) in preventing stroke and systemic embolism in moderate-to-high-risk ($CHADS_2$ score ≥2) AF patients?
- **1⁰ efficacy end point**: composite primary end point of stroke and systemic embolic events
- **2⁰ efficacy end points**: composite clinical outcome of stroke, systemic embolic events, and all-cause mortality; also major bleeding events
- Treatment period: up to 2 years

ENGAGE AF—TIMI = Global Study to Assess the Safety and Effectiveness of DU-176b vs Standard Practice of Dosing With Warfarin in Patients with Atrial Fibrillation.

ClinicalTrials.gov identifier NCT00781391

Clinical Challenges With New Oral Anticoagulants

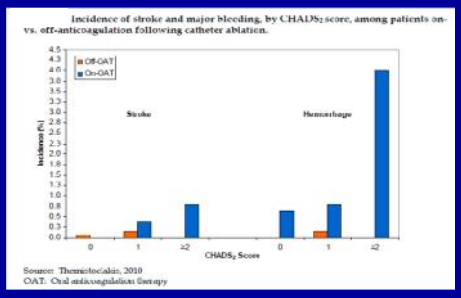
- No validated tests to measure anticoagulation effect
- No established therapeutic range
- No antidote for most agents
- Assessment of compliance more difficult than with vitamin K antagonists
- Potential for unknown long-term adverse events
- Balancing cost against efficacy
- Lack of head-to-head studies comparing new agents

Sobieraj-Teague M, et al. *Semin Thromb Hemost*. 2009;35:515-524.

Baseline Characteristics of the AF Ablation Treated Patients

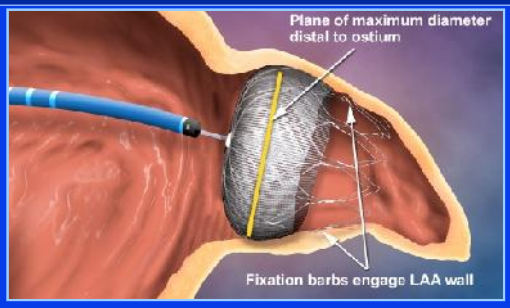
Measure	Total population, % (n=3355)	Off OAC therapy, % (n=2692)	On OAC therapy, % (n=663)	p
AF type				
• Paroxysmal	60	62	51	<0.0001
• Persistent	18	16	26	<0.0001
• Permanent	22	22	22	0.6941
$CHADS_2$				
• 0	53	60	23	<0.0001
• 1	29	27	39	<0.0001
• ≥2	18	13	37	<0.0001

Themistoclakis S, et al. *J Am Coll Cardiol* 2010; 55:735-743.

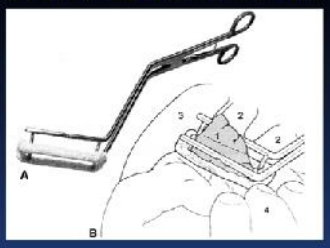


Themistoclakis S, et al. *J Am Coll Cardiol* 2010; 55:735-743.

PROTECT AF Trial: WATCHMAN LAA Closure Device in situ



LAA Clip, Deployment Tool, and Deployment



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