



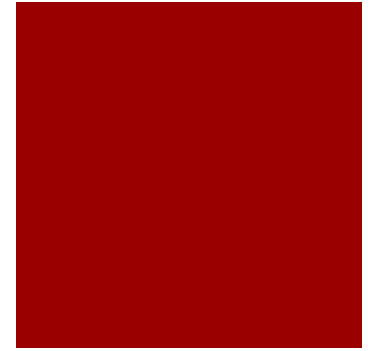
Trials that may affect practice?  
ARISTOTLE and ROCKET AF, Oral Anticoagulants

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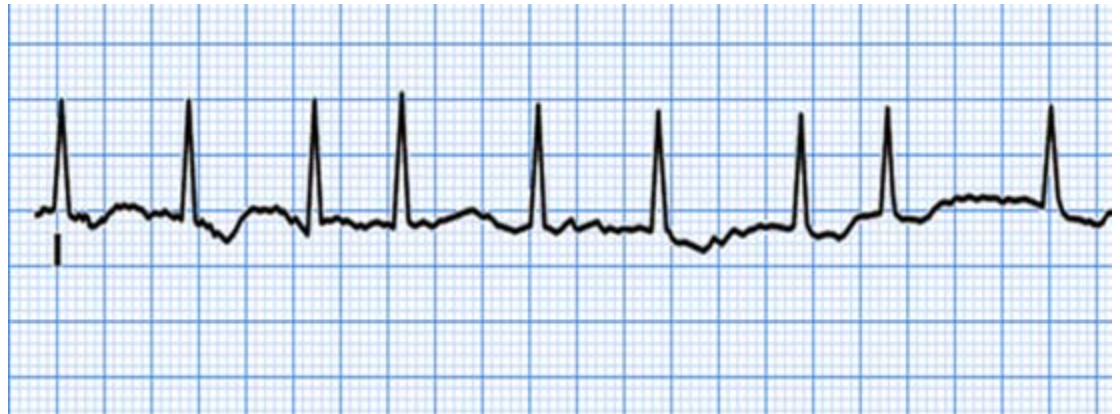
# Disclosures

- None to declare



# Agenda

- Atrial fibrillation (AF) backgrounder
- Brief overview and critical appraisal of ROCKET AF and ARISOTLE trials
- Implications for practice
- Take home points



# ROCKET AF



*The* NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

## Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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ORIGINAL ARTICLE

## Apixaban versus Warfarin in Patients with Atrial Fibrillation

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# Atrial Fibrillation

- Irregular atrial contractions that commonly result in tachycardia if untreated
- Often occurs as an ectopic beat originating from the pulmonary veins, structural and electrical remodeling allow propagation
- Most common sustained arrhythmia
- Life time risk ~ 1 in 4 patients, increases in prevalence dramatically with age



# Atrial Fibrillation - Sequelae

*Cause of significant morbidity and mortality*

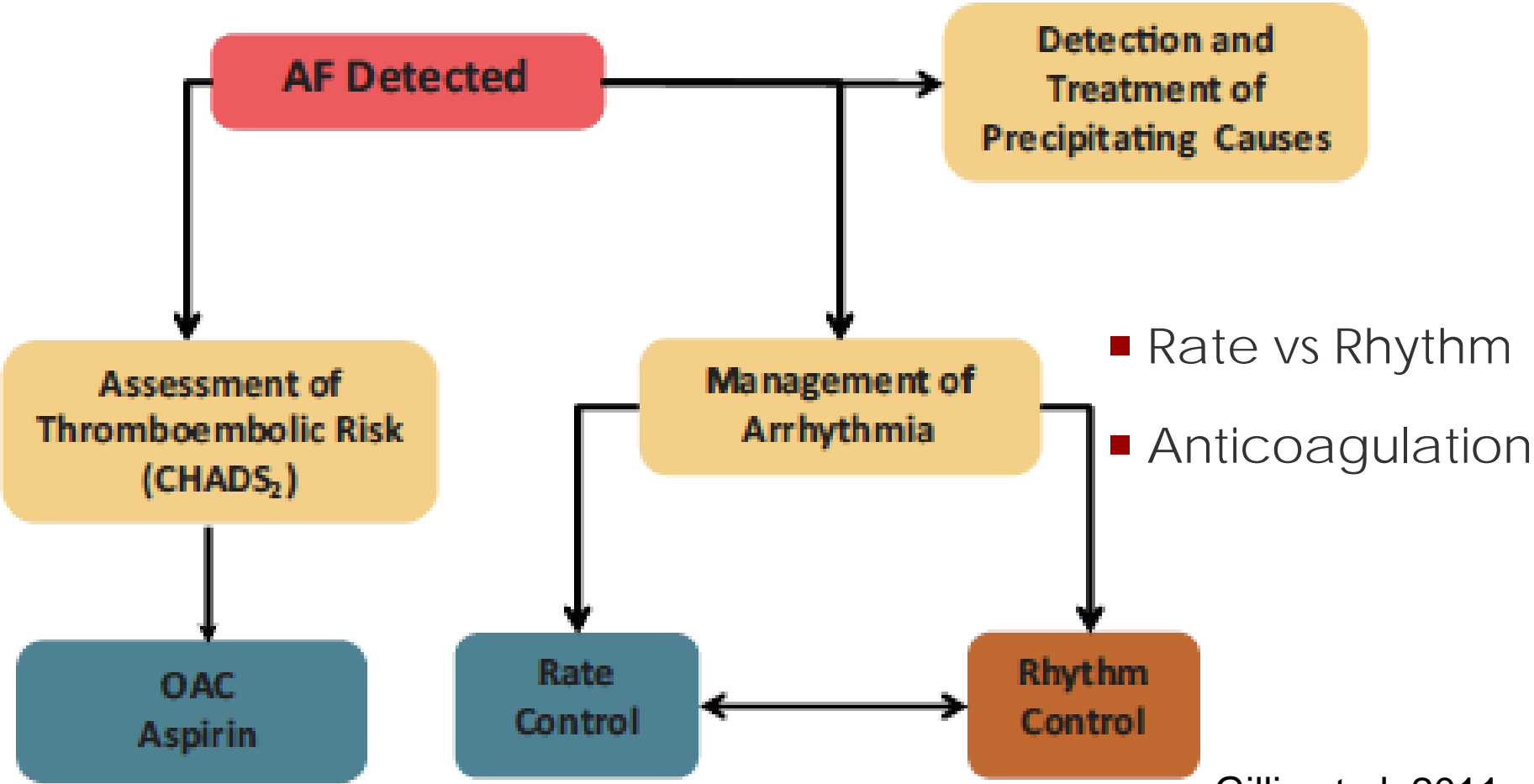
- **Stroke risk** ~1.5% at age 50–59 years and > 23% at age 80–89
- Independent increases the risk of heart failure and the risk of death by 1.5–2x
- Increase incidence of dementia in patients with a history of stroke





# Atrial Fibrillation - Treatment

## Overview of AF Management



Gillis et al. 2011.

# Atrial Fibrillation - Stroke Risk



	CHADS <sub>2</sub> risk criteria	Score
C	Congestive heart failure	1
H	Hypertension	1
A	Age >75 years	1
D	Diabetes mellitus	1
S <sub>2</sub>	(Prior) stroke or TIA	2

CHADS2 score	Adjusted stroke rate (%/year; 95% CI)
0	1.9 (1.2–3.0)
1	2.8 (2.0–3.8)
2	4.0 (3.1–5.1)
3	5.9 (4.6–7.3)
4	8.5 (6.3–11.1)
5	12.5 (8.2–17.5)
6	18.2 (10.5–27.4)



# Current Stroke Prophylaxis

- ASA
- Warfarin
- Dabigatran – Pradax<sup>®</sup>
- **Me too?**
  - **Apixaban**
  - **Rivaroxaban**



# At a glance

	<b>Apixaban</b>	<b>Rivaroxaban – Xarelto®</b>
Mechanism of Action	Direct Factor Xa Inhibitor	
Notice of Compliance	None	DVT for prophylaxis only (2009)
INR Monitoring	None	
Relevant Pharmacokinetics	f ~ 66% t <sub>1/2</sub> 8-15h E: 75% fecal	f ~ 100% t <sub>1/2</sub> 5-13h E: > 60 % renal
Drug Interactions:	? CYP 3A4 inhibitors	? Potent CYP 3A4 and PGP inhibitors

# Methods



	Apixaban – ARISTOTLE	Rivaroxaban – ROCKET AF
Design	Double-blind RCT	Double-blind RCT
Intervention	Apixaban 5mg BID + Placebo vs warfarin (Target INR 2-3) + Placebo (<5% given 2.5mg dose)	Rivaroxaban 20mg daily + Placebo vs. warfarin (Target INR: 2-3) + placebo
Outcome analysis	Non-Inferiority 50% Margin Intention to treat	Non-Inferiority 46% margin ? <i>a priori</i> ITT and PP analysis

# Methods – Primary Outcomes



	<b>Apixaban – ARISTOTLE</b>	<b>Rivaroxaban – ROCKET AF</b>
Primary Efficacy Endpoint	Stroke or systemic embolism	Composite of stroke, and systemic embolism
Primary safety endpoint	ISTH Major bleeding	Composite of major and non-major clinically significant bleeds

# Methods

	Apixaban – ARISTOTLE	Rivaroxaban – ROCKET AF
Inclusion Criteria	Non-valvular AF + min. one risk factor for stroke	Non-valvular AF + CHADS score of 2 or more
Exclusion Criteria	Reversible AF, mod-severe mitral stenosis, other anticoag. indications, <b>dual or high dose antiplatelet therapy</b> , CrCl < 25mL, stroke < 7 days prior	Reversible AF, Significant mitral stenosis, Active internal bleeding, History of severe disabling stroke, intracranial hemorrhage or other hemorrhagic disorders

# "Table 1" in a nutshell

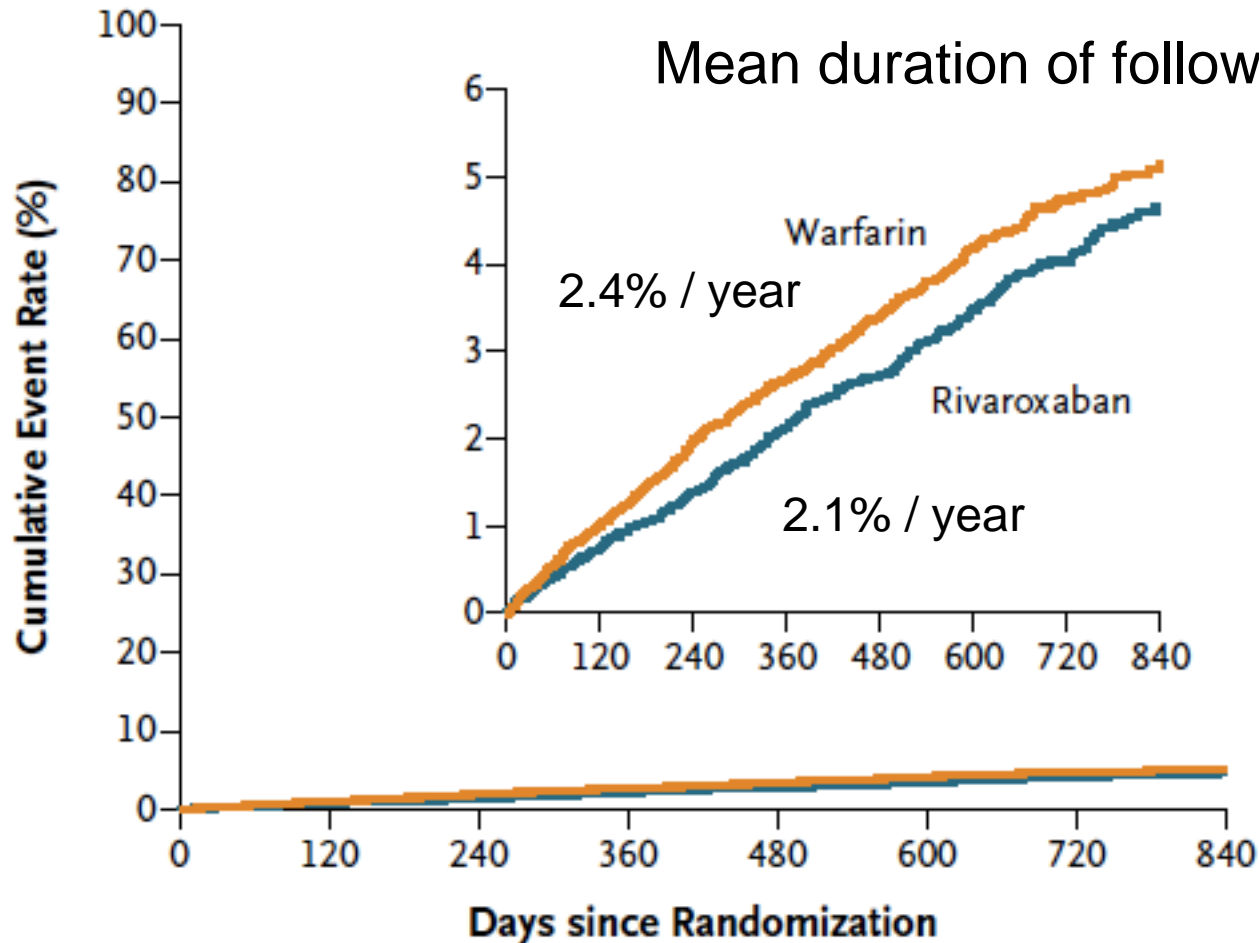


	Apixaban – ARISTOTLE	Rivaroxaban – ROCKET AF
<i>n</i>	18,201	14,262
Sex	~ 35% female	~ 40% female
Mean Age	70	73
Prior H <sub>x</sub> of MI:	~ 14%	~ 17 %
CHADS <sub>2</sub> Score	Mean: 2.1	Mean: 3.5
CrCl (mL/min)	>50 ~ 82%	Median: 67mL/min IQR: ~ 50-90

Even distribution of baseline characteristics in both randomized groups\*

# What happened next? ROCKET AF

## Events in Intention-to-Treat Population



$p < 0.001$  (non-inferiority)

$p = 0.12$   
(superiority)

What about  
the per  
protocol  
analysis?

# What happened next? ARISTOTLE

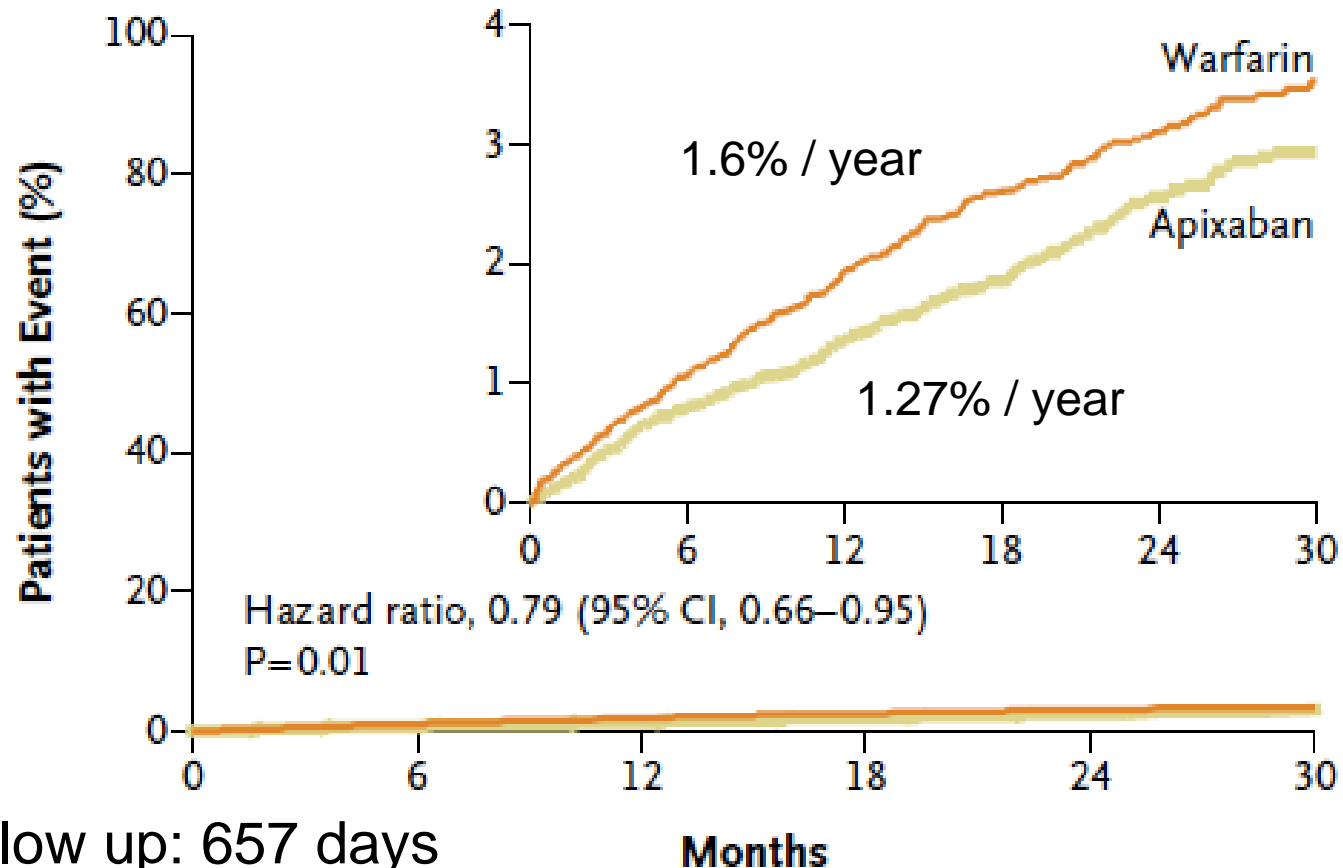
ARR: 0.33%

NNT: 304

$p < 0.001$   
(non-inferiority)

$p < 0.01$   
(superiority)

## Primary Outcome: Stroke or Systemic Embolism



Mean duration of follow up: 657 days



# ARISTOTLE

Notable secondary findings...

- All cause mortality favored apixaban
  - **NNT: 455**
  - AR: 1.8 vs. 2.02% p
- CV mortality favored apixaban
  - **NNT = 239**
  - AR: 3.52 vs 3.94% p = 0.047

# ROCKET AF -Adverse Effects

- Non-significant difference
  - Major and clinically significant bleeding(14.9 vs.14.5 in favor of warfarin)
  - Major bleed ( 3.6 vs. 2.4 favoring warfarin)
- Clinically/statistically significant differences
  - Intracranial hemorrhage **NNH of warfarin 500** (0.7 vs. 0.5% p= 0.02)
  - Major bleed from a GI site **NNH of rivaroxaban 100** (3.2 vs 2.2% p < 0.001)





# ARISOTLE -Adverse Effects

- Clinically significant differences
  - Major bleeding **NNH of warfarin 104** (3.09 vs. 2.13%  $p < 0.001$ )
  - Intracranial hemorrhage **NNH of warfarin 212** (0.80 vs. 0.33%  $p < 0.001$ )



# Strengths

- Large blinded placebo controlled studies
- Risk/benefit outcomes clinically relevant
- INR ranges (mean % in ideal range: 55 ROCKET AF vs 62.2 for ARISTOTLE)



# Weaknesses

- ROCKET AF
  - Per Protocol analysis vs. intention to treat (200 vs. 334)
  - Per protocol  $p < 0.01$  hazard ratio significant for superiority
- ARISTOTLE/ROCKET AF
  - Industry sponsored yet “independently reported”

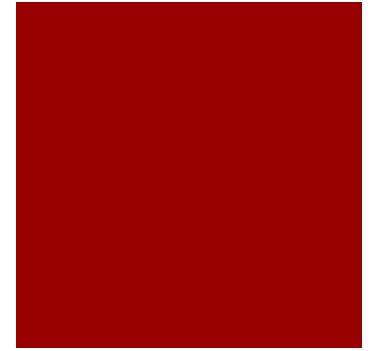


# How do the results affect our patients?



- Results likely to lead to approval in Canada
- Will inevitably be used in our patients
- Counseling and follow up/monitoring as relevant as before
- Results suggest favoritism towards apixaban
- As with dabigatran, in select patients without contraindication these agents may be more appropriate than standard warfarin therapy

# How do the results affect our patients?



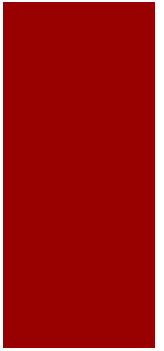
- As with dabigatran...
  - long term safety and rare side effects are currently unknown
  - No reversal agent
  - Perioperative management?
  - Dual and triple therapy risks?
  - Cost? Formulary issues?



## Take Home Points

- Oral anticoagulants dramatically reduce the risk of stroke in patients with AF and are therefore a pharmacotherapy keystone
- Fortunately we have the necessary data and skills to translate clinical trial findings into tangible objective risks and benefits
- This information can be presented to **all parties** involved in order to ultimately enhance patient care

Questions



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