

NOACs and VKA What are the Difference

FATHI MAKLADY, MD, FRCP
Suez Canal University

POINTS FOR DISCUSSION

- **Burden of Stroke and its Prevention**
- **Warfarrin**
- **Novel Anticoagulants**

What Is the Impact of Stroke?

- Stroke is the third leading cause of death in the United States
 - *On average, someone suffers a stroke every 40 seconds*
 - *About 795,000 Americans suffer a stroke each year*
 - *About every 4 minutes, someone dies of a stroke*

Scope of the Problem ***Number of Strokes Annually***

- 15 million people worldwide suffer stroke annually
- 6 million die; 5 million are permanently disabled
- Burden of stroke is higher in lower and middle income countries
- Worldwide, stroke is the second leading cause of death in those > 60 years, and the fifth leading cause of death in people aged 15 to 59 years old

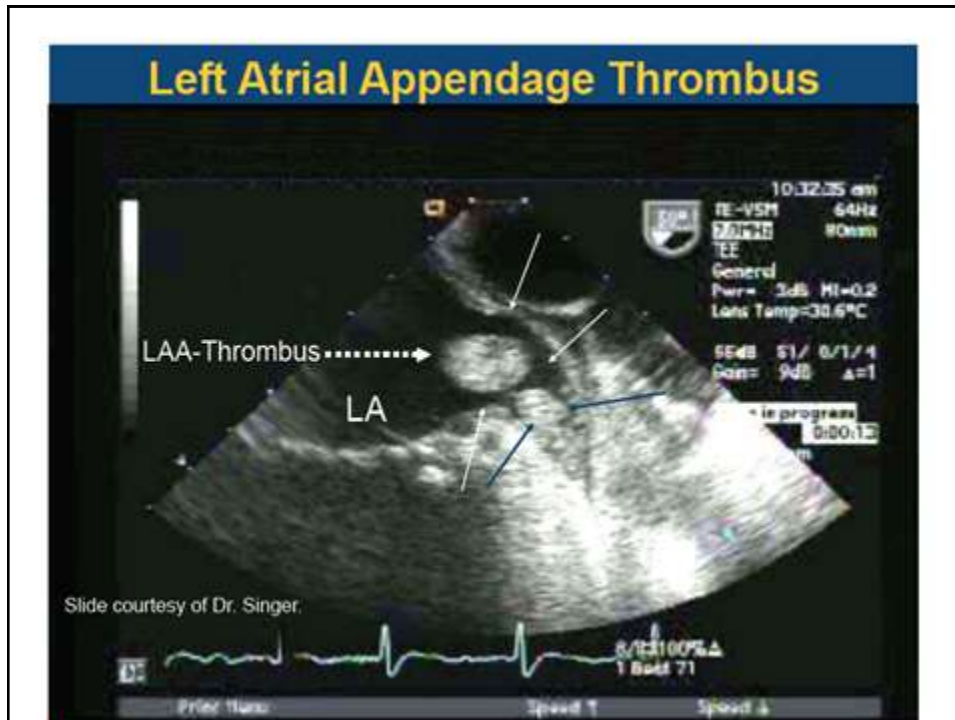
Stroke Recurrence

- Data from US of those 795,000 people who suffer a stroke annually
 - 600,000 of these are first attacks
 - 185,000 are recurrent attacks^a
- TIA: US prevalence (self-reported, physician-diagnosed) approximately 5 million (true prevalence is greater)
- Progression from TIA to stroke
 - Of 1707 TIA patients, evaluated in the ED of Kaiser Permanente Northern California
 - 180 (11%) experienced a stroke within 90 days
 - 91 (5%) had a stroke within 2 days^b

a. Mozaffarian D, et al. *Circulation*. 2016;133:e38-e360; b. Johnston SC, et al. *JAMA*. 2000;284:2901-2906.

Atrial Fibrillation *Putative Mechanism for Stroke*

AF → Loss of atrial contraction → LA thrombus → Embolism



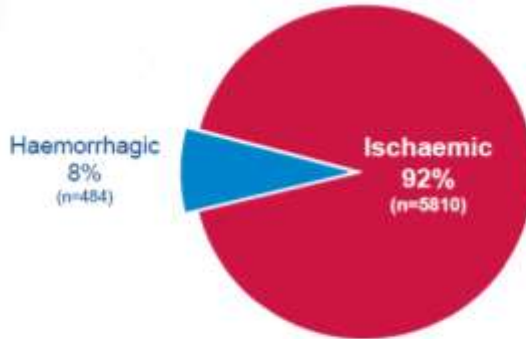
Stroke and Atrial Fibrillation¹⁻⁶

- AF increases stroke risk 5-fold
- 15% of all ischemic stroke patients have AF
- Women have AF-related stroke more often than men
- AF patients with stroke have increased morbidity/mortality
 - 1-year mortality 50%
- One third of AF and stroke patients not known to have AF until admitted for stroke
- More than 50,000 preventable strokes each year due to failure to use appropriate antithrombotic therapy in AF

1. Wolf PA, et al. *Stroke*. 1991;22(8):983-988.
2. Go AS. *Am J Geriatr Cardiol*. 2005;14(2):56-61.
3. Hylek AM, et al. *N Engl J Med*. 2003;349(11):1019-1026.
4. Benjamin EJ, et al. *Circulation*. 1998;98(1):946-952.
5. Mead GE, et al. *Stroke*. 2002;33(10):2383-2390.
6. Harrison MJ, Marshall J. *Stroke*. 1984;15(3):441-442.

Most strokes associated with AF are ischaemic

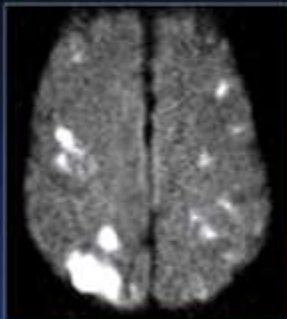
Types of stroke in patients with AF



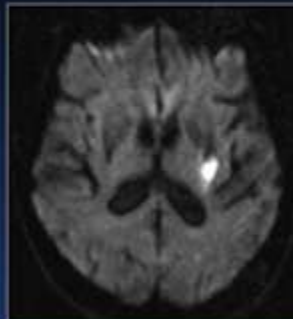
Based on data collected in the Danish National Indicator Project for 39 484 patients hospitalized for stroke (80% of all stroke admissions in Denmark) including 6294 patients with AF; OAC use not recorded
Andersen KK et al. Stroke 2009;40:2068-72

Brain Infarct Topography and Causative Stroke Mechanism

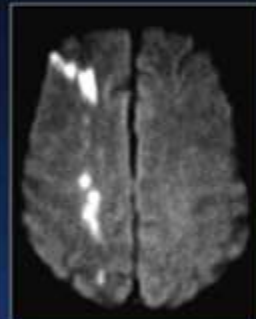
In AF, 70% of strokes are cardioembolic



Cardio-
embolism



Penetrator
Disease



Large Artery
Athero

Lifetime Risk of Developing AF

Lifetime risk of developing atrial fibrillation (AF) for men and women age 40 years and older

Overall: about 1 in 4*

*Based primarily on white individuals.

Lloyd-Jones D, et al. *Circulation*. 2004;110:1042-1046.

Prevention of Thromboembolic complications

Warfarin

Warfarin history

- § 1920's cattle suffered (Northern US) outbreaks of fatal bleeding
 - § Mouldy silage from sweet clover isolated – L.M. Roderick
- § 1940 Karl Link in WI isolated 4-hydroxy coumarin
- § 1952 approved as rodenticide
- § 1954 approved for human use
- § Warfarin name derived from WARF (Wisconsin Alumni Research Foundation), -arin from coumarin.



Oral VKAs

Advantages of warfarin

- Used for more than 60 years
- Well studied
- Fairly effective if INR kept in therapeutic range
- Well-known and defined drug and food interactions
- Relatively inexpensive
- Easy to reverse

Disadvantages of warfarin

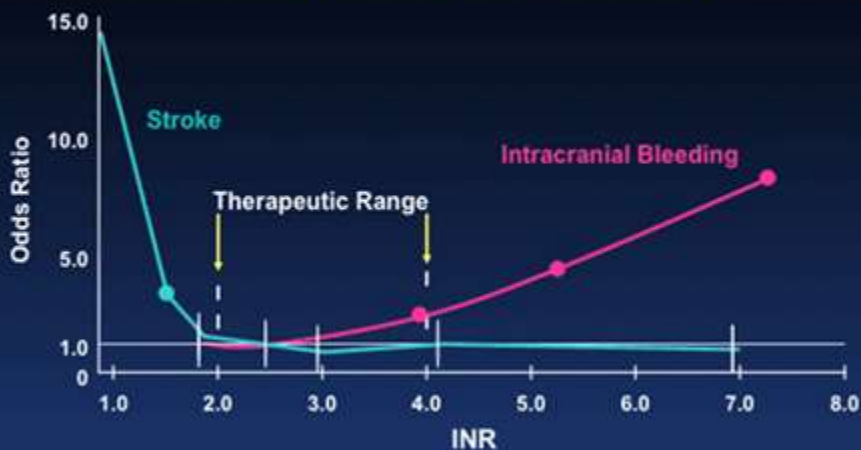
- Requires frequent monitoring to keep in therapeutic range
- Multiple medication adjustments often required
- Significant interactions with multiple medications and foods
- Patient reluctance
- Bad reputation among healthcare providers

VKAs, vitamin K antagonists.

Ansell J, et al. *Chest*. 2008;133(6 suppl):160S-198S.

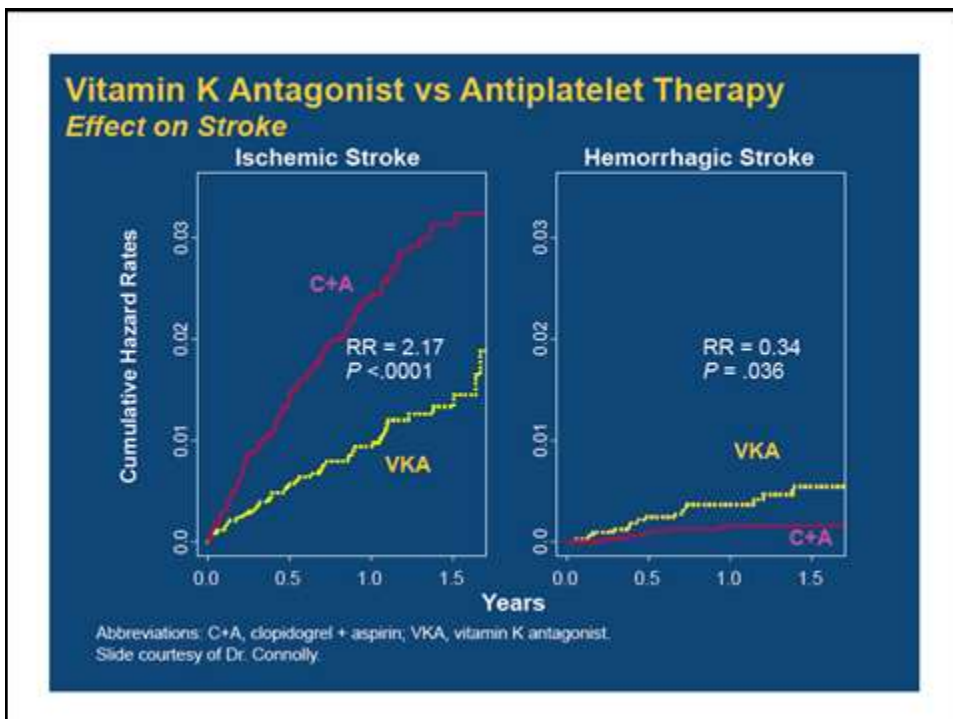
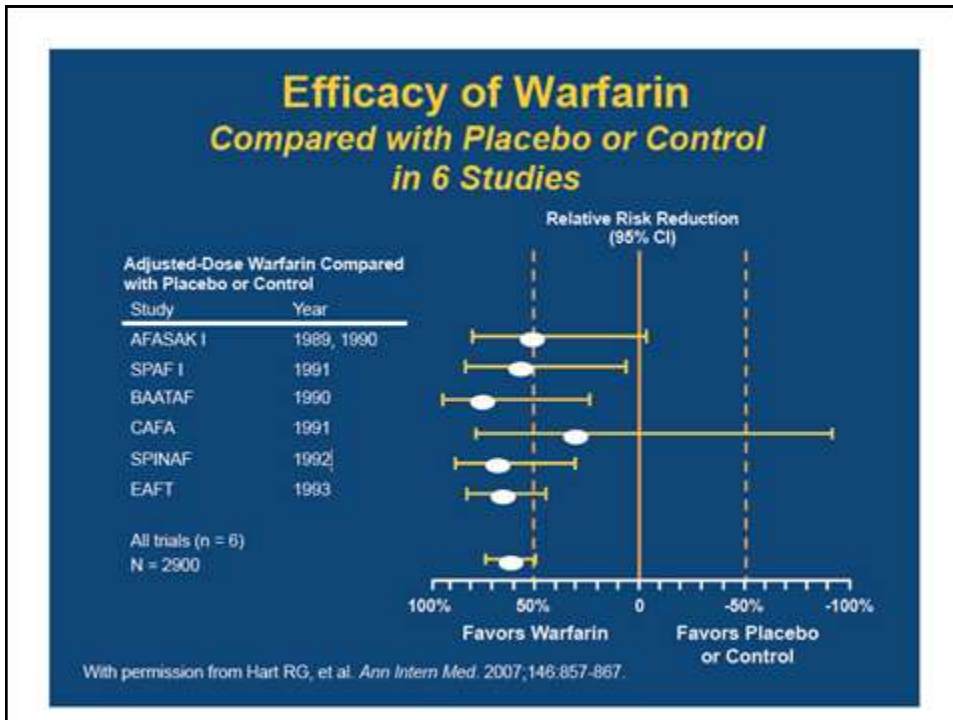
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Therapeutic Range for Warfarin: Balancing Safety and Efficacy^{1,2}

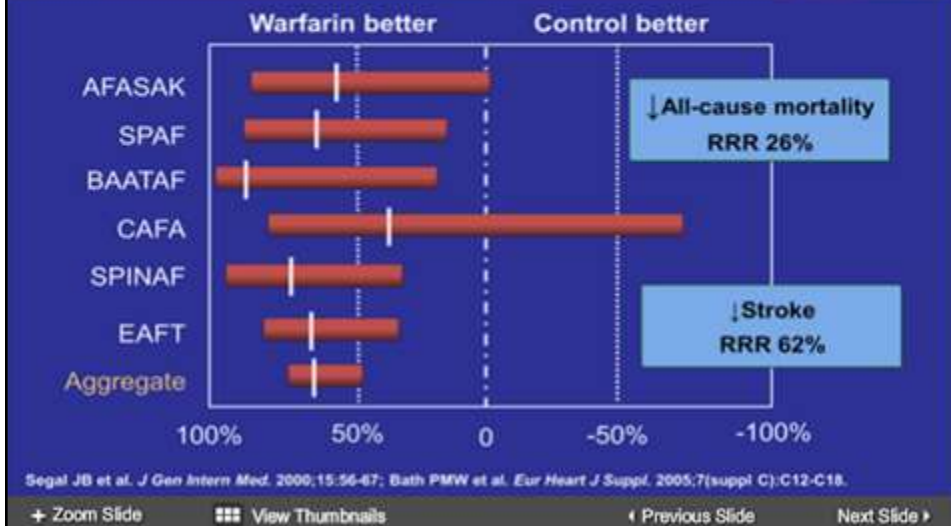


1. Hylek EM, Singer DE. *Ann Intern Med*. 1994;120(11):897-902.
2. Hylek EM, et al. *N Engl J Med*. 2003;349(11):1019-1026.

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Warfarin Anticoagulation in AF Stroke Risk Reductions



Considerations with Warfarin

- Risk of hemorrhage
- Multiple interactions with diet and drugs
- High variability within and between patients
- Narrow therapeutic range
- Need for lifelong monitoring of international normalized ratio and frequent dose adjustment

Role for Warfarin Still Persists

- Hypersensitivity to NOAC
- Severe renal insufficiency
- Severe valvular disease
- Mechanical heart valves
- Clinically significant active bleeding
- High out-of-pocket cost for NOACs

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Role of Warfarin

Recommendation	Class	Level
Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis	I	B
With prior stroke, TIA, or CHA ₂ DS ₂ VASc score ≥ 2, oral anticoagulants are recommended. Options include		
• Warfarin	I	A
• Dabigatran, rivaroxaban, apixaban	I	B
With CHA ₂ DS ₂ VASc score ≥ 2 and end-stage CKD (CrCl < 15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation	IIa	B

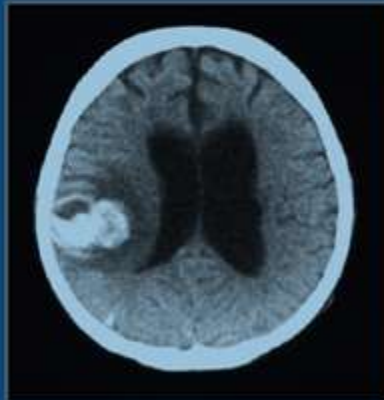
January CT, et al. *J Am Coll Cardiol*. 2014;64:e1-e76.^[29]

Conclusions

Unmet Medical Need

- Warfarin is effective against stroke in AF, but has major limitations
 - Warfarin use is low, especially in elderly
 - Time in therapeutic range is only 55% in US clinical practice
- Warfarin increases hemorrhagic stroke even while reducing ischemic stroke

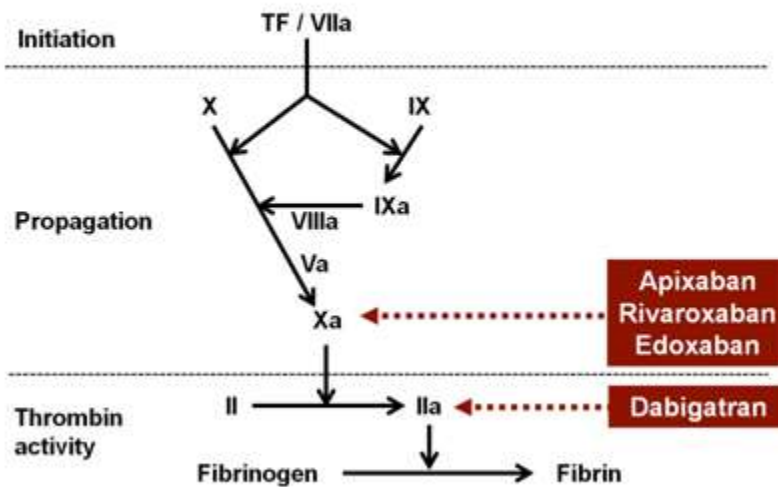
CT Scan of Intracerebral Hemorrhage During Anticoagulation



Slide courtesy of Dr. Hart.

New Oral Anticoagulants

Sites of Action in Coagulation System Novel Factor Xa and DT Inhibitors



Weitz JI, Bates SM. *J Thromb Haemost.* 2005;3:1843-1853.^[1]

NOACs

Important Comparative Features

Dabigatran

- Oral direct thrombin inhibitor
- Twice-daily dosing
- Renal clearance 80%

Rivaroxaban

- Direct factor Xa inhibitor
- Once daily
- Renal clearance 33%

Apixaban

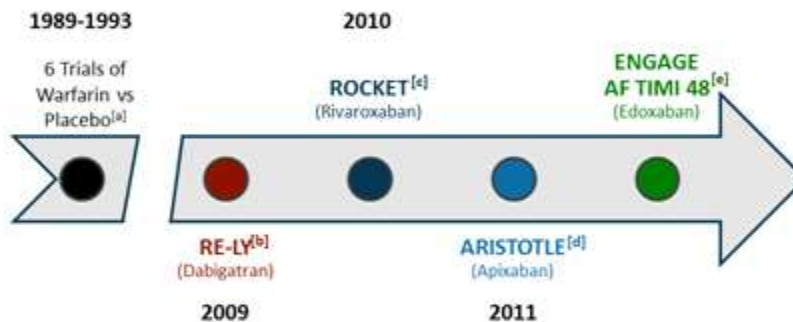
- Direct factor Xa inhibitor
- Twice-daily dosing
- Renal clearance 25%

Edoxaban

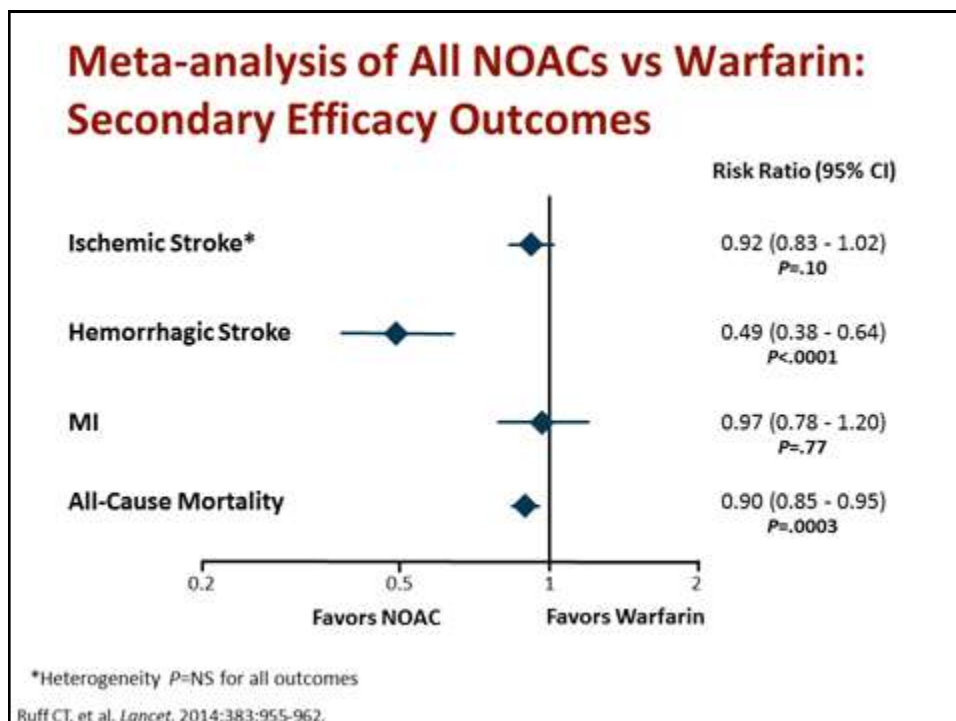
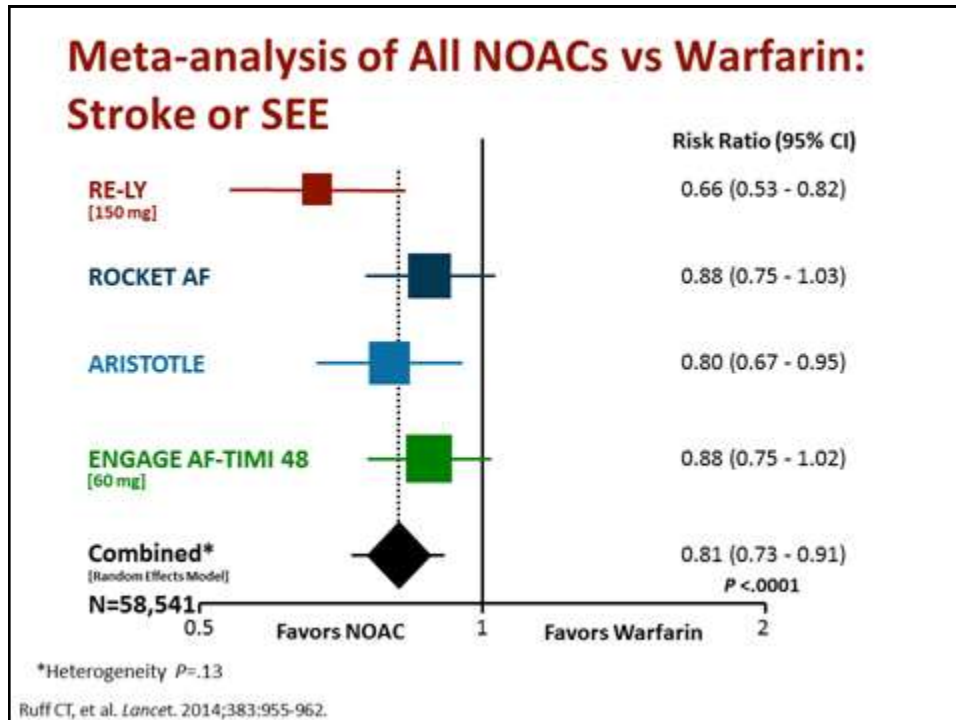
- Direct factor Xa inhibitor
- Once-daily dosing
- Renal clearance 35%

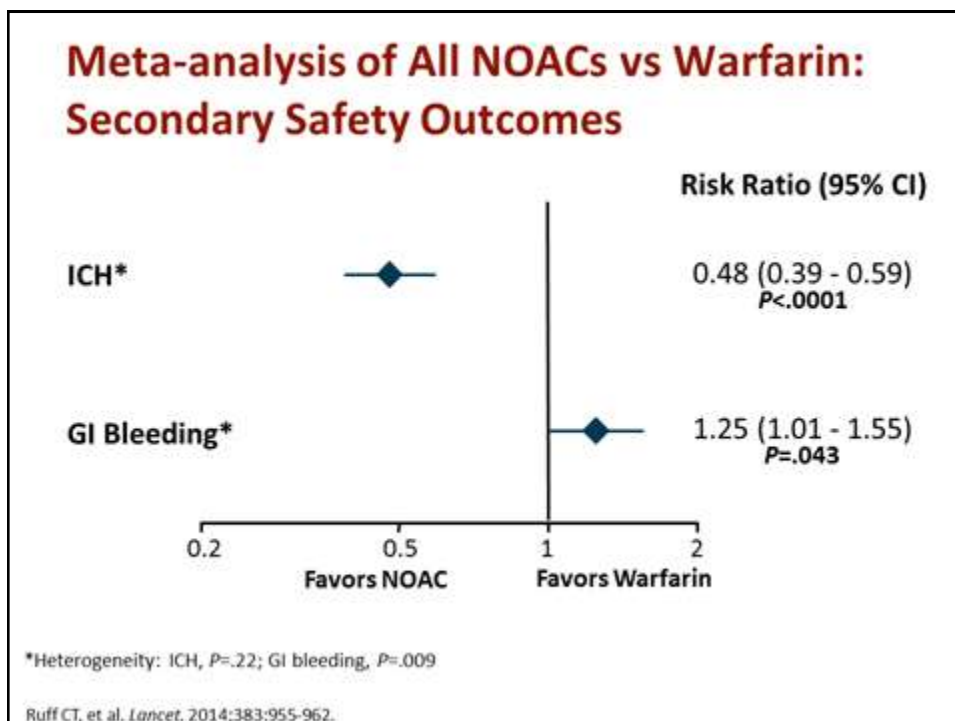
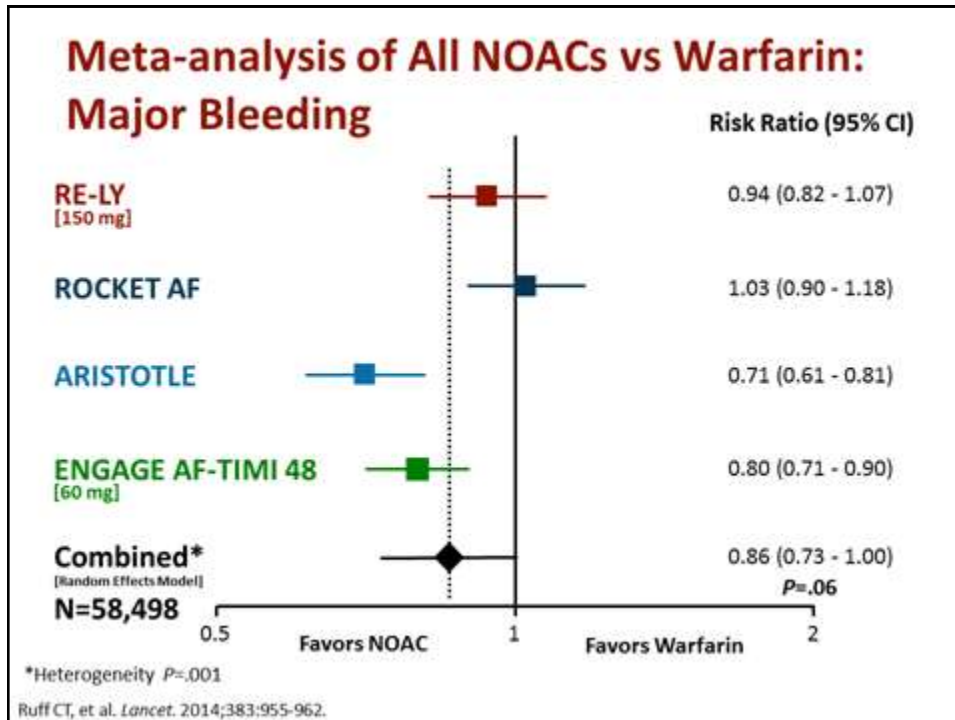
Eikelboom JW, Weitz JI. *Circulation*. 2010;121:1523-1532.^[6]

Major Advances in Direct NOACs for AF



a. Hart RG et al. *Ann Intern Med*. 1999;131:492-501; b. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151; c. Patel MR, et al. *N Engl J Med*. 2011;365:883-891; d. Granger CB, et al. *N Engl J Med*. 2011;365:981-992; e. Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.





2014 AHA/ACC/HRS Guidelines for the Management of Patients With AF: Role of Warfarin

Recommendation	Class	Level
Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis.	I	B
With prior stroke, TIA, or CHA ₂ DS ₂ -VASc score ≥ 2 , OACs are recommended. Options include:		
<ul style="list-style-type: none"> Warfarin 	I	A
<ul style="list-style-type: none"> Dabigatran, rivaroxaban, apixaban 	I	B
With CHA ₂ DS ₂ -VASc score ≥ 2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation.	IIa	B

January CT, et al. *J Am Coll Cardiol*. 2014;64:e1-76.

ESC Guidelines for Anticoagulation

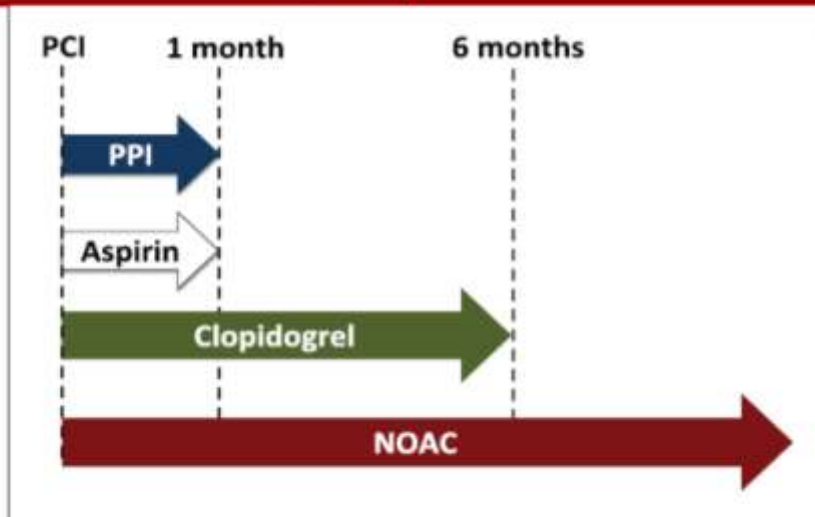
Recommendations	Class	Level
<p>When adjusted-dose VKA (INR 2-3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either:</p> <ul style="list-style-type: none"> a direct thrombin inhibitor (dabigatran); or an oral factor Xa inhibitor (eg, rivaroxaban, apixaban) <p>... is recommended.</p>	I	B
<p>Where OAC is recommended, one of the NOACs, either:</p> <ul style="list-style-type: none"> a direct thrombin inhibitor (dabigatran); or an oral factor Xa inhibitor (eg, rivaroxaban, apixaban) <p>... should be considered rather than adjusted-dose VKA (INR 2-3) for most patients with non-valvular AF, based on their net clinical benefit.</p>	IIa	A

Camm AJ, et al. *Europace*. 2012;14:1385-1413.^[30]

Viewpoint: a proposal for a simple algorithm for managing oral anticoagulation and antiplatelet therapy in patients with non-valvular atrial fibrillation and coronary stents

Ph Gabriel Steg^{1,2,3,4} and Deepak L. Bhatt⁵

From received 20 May 2016; accepted 20 September 2016; 10 September 2016; 20 September 2016



Final Thoughts

- ☞ Imagine if the NOAC's had been around for 70 years and a new drug appeared that:
 - ☞ Was unpredictable in therapeutic response
 - ☞ Had slow therapeutic onset and offset
 - ☞ Had a narrow therapeutic window
 - ☞ Required close monitoring via frequent blood tests
 - ☞ ...next slide

Final Thoughts

Continued...

- Required frequent dose adjustments
- Was plagued by drug-drug and drug-food interactions
- Was associated with more intracranial hemorrhage and worsened the bleeding profile
- Resulted in a 10% increased mortality

Would anyone think it had a chance of getting to market and, if it did, would anyone prescribe it ???? Food for thought...

All Patients Will Use
NOACS Instead of
Warfarin in 10 Years:
Fact or Fiction?

Cash Casey, MD
Advocate Medical Group/
Midwest Heart Specialists
December 3rd, 2016

