



# Direct Oral Anticoagulants in the frail population

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**PRADAXA**  
SIDE EFFECTS LAWYER  
*wrongful death & internal bleeding lawsuits*

HELP FOR INJURY VICTIMS NATIONWIDE - **1-866-310-9722**

# OAC since world war II

- Vitamin K antagonists
- Inhibition of procoagulant factors II, VII, IX and X, anticoagulants Protein C and S
- Monitoring anticoagulant effect: INR
- Target range 2.0-3.0

## Benefit of VKA

- Recurrence rate of VTE or stroke <10% (much better than aspirin)
- Enormous experience with VKA
- Anticoagulation clinics

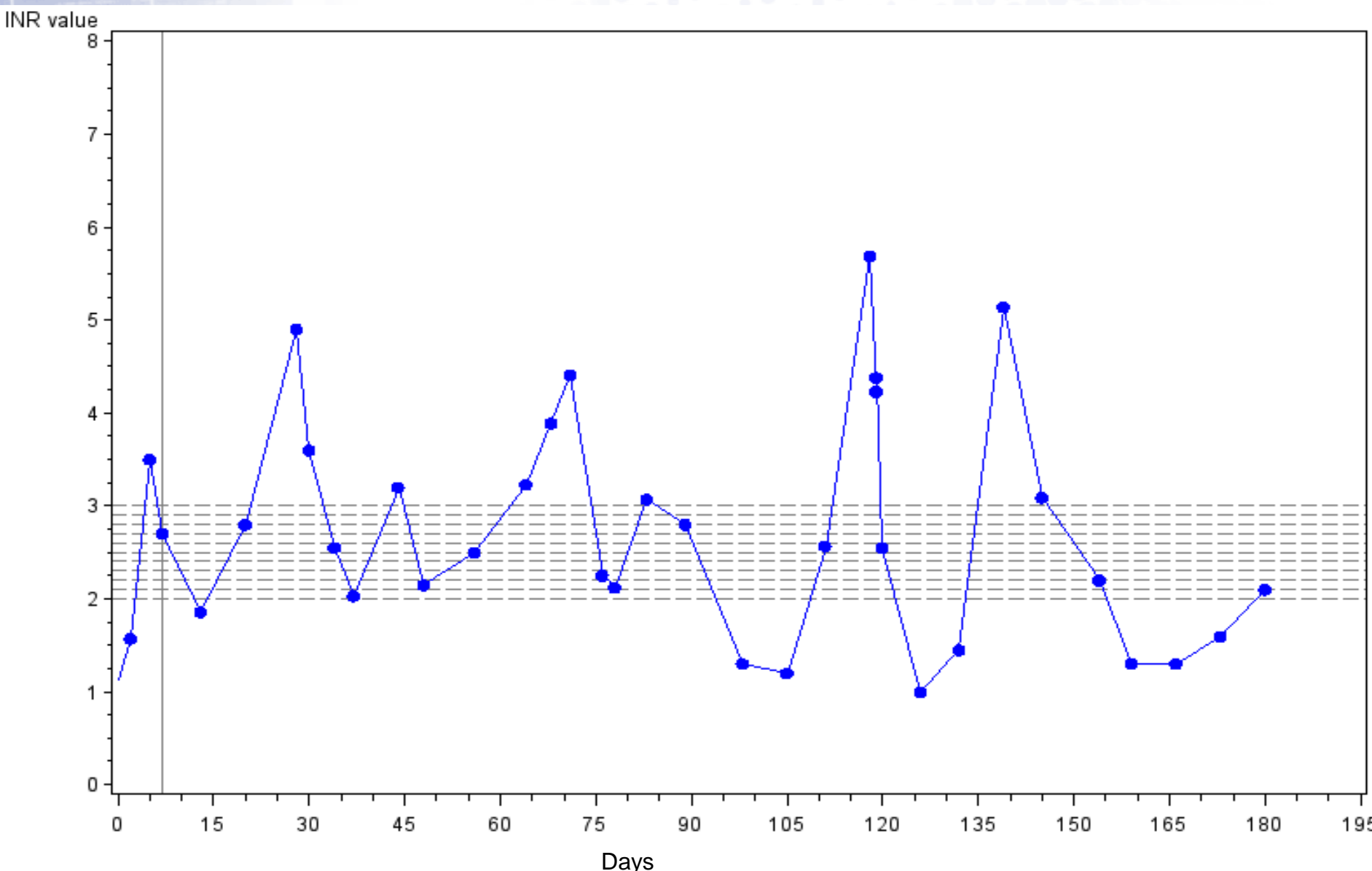
## Drawbacks of VKA

- Unstable and unpredictable effect
- Frequent control of INR
- Interaction with food and medication
- Need for sc injections (VTE)



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# Number of patients on VKA

- Indications: Atrial fibrillation, DVT or pulmonary embolism, mechanical heart valves
- 350.000 patients
- 2.1% of the Dutch population



# Hospitalisation due to medication complications

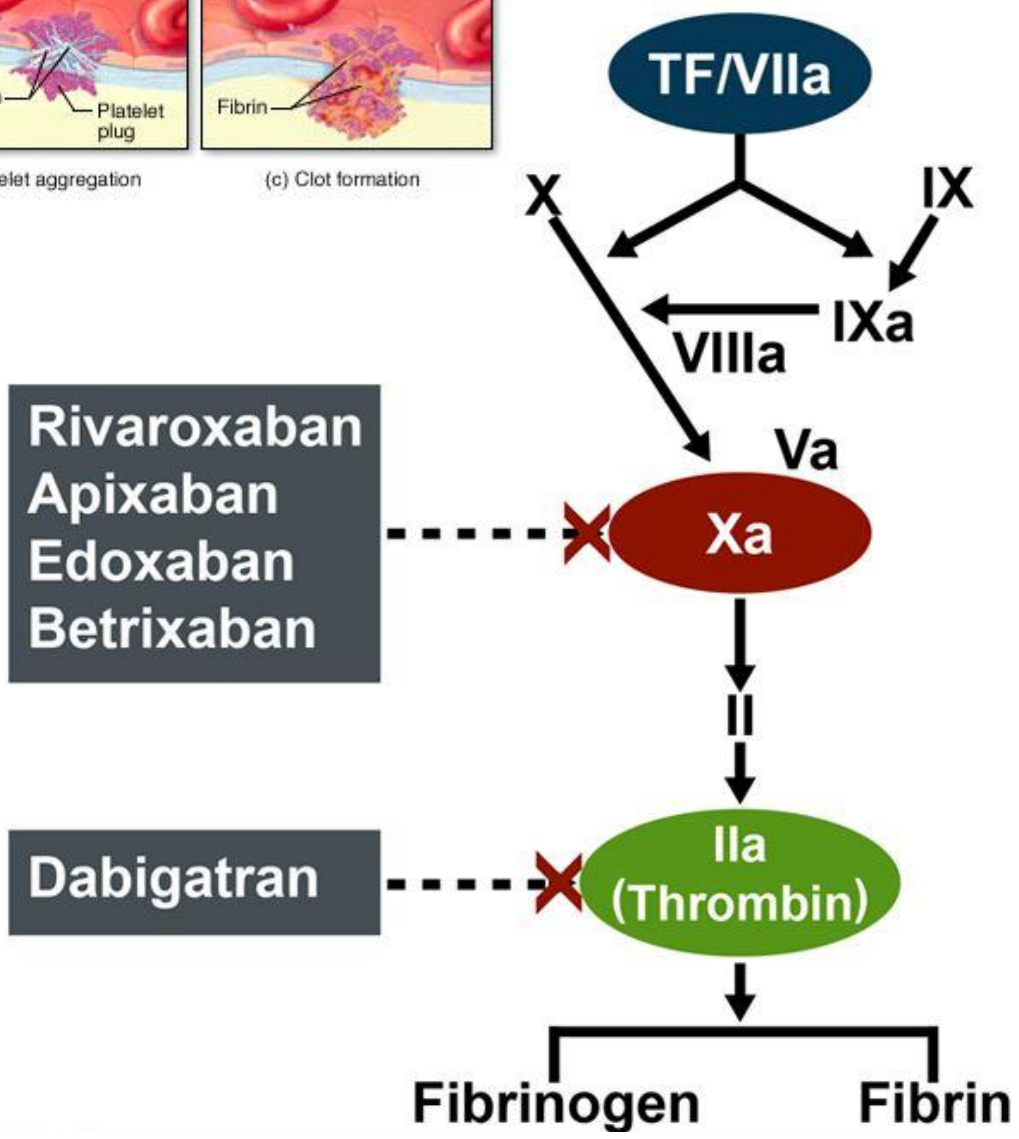
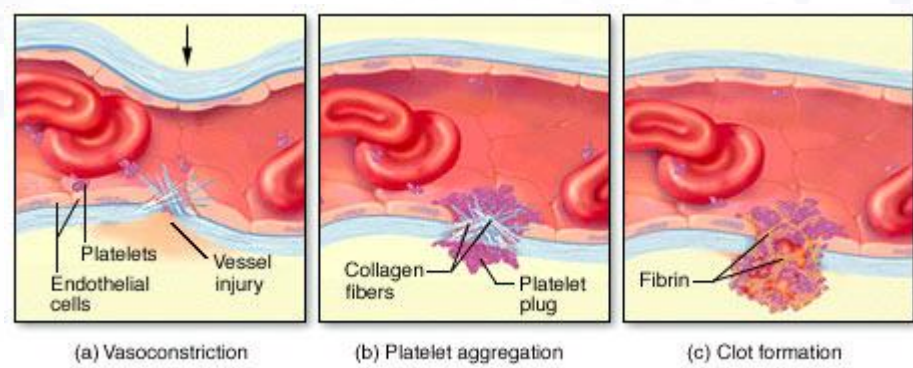
omschrijving ATC groep	Aantal	Percentage
Trombocytenaggregatieremmers	29	8,7%
Vitamine K-antagonisten	21	6,3%
NSAID's	17	5,1%
Psychofarmaca (waaronder anxiolytica, hypnotica en sedativa)	17	5,1%
Insulines en analoga	16	4,8%
Orale Bloedglucoseverlagende middelen	15	4,5%
"High ceiling" diuretica/lisdiuretica	15	4,5%
Corticosteroïden, oraal	13	3,9%
Antimicrobiële middelen	11	3,3%
Anti-epileptica	9	2,7%
Vitamine K-antagonist met NSAID	6	1,8%
Combinatie van verschillende geneesmiddelen	99	29,8%
Overige geneesmiddelen	64	19,3%
Totaal	332	100,0%

# “New” oral anticoagulants

- Since 2009 on the market (Canada, USA)
- Stable anticoagulant effect
- Fixed dosis
- Less interaction with medication or food

## What's in a name.....

- New oral anticoagulants (NOACs)
- Novel oral anticoagulants (NOACs)
- Direct oral anticoagulants (DOACs)
- Target-specific oral anticoagulants (TSOACs)
- Non-VKA oral anticoagulants (NVOACs?)



# Pharmacology DOACs

	Apixaban	Dabigatran	Endoxaban	Rivaroxaban	Warfarin
Thrombin/factor Xa inhibitor	factor Xa	thrombin	factor Xa	factor Xa	VKA
Bioavailability (%)	50	6.5	50	90 - 100	100
Plasma protein binding (%)	87	35	40-59	95	99.5
Half-life (hours)	10 - 14	14 - 17	9 - 11	7 - 11	40
Dosage	bid	bid	od	od	od
T <sub>max</sub> (hours)	3 - 4	1 - 2	1 - 2	3	4
Liver metabolism (%)	N.A.	20	N.A.	66	99%
Renal elimination (%)	25	80	35	33	1%

Abbreviations: VKA: vitamin K antagonist; N.A.: data not available in the literature; od: once daily; bd: twice daily; T<sub>max</sub>: time to peak plasma concentration.

**Table 1. Approved indications for use of novel oral anticoagulants**

Drug/region	Prevention of stroke/systemic embolism in nonvalvular atrial fibrillation	Prevention of VTE after hip/knee replacement surgery	Treatment of acute VTE	Prevention of VTE recurrence
<b>Dabigatran</b>				
United States	✓			
Canada	✓	✓		
Europe	✓	✓		
<b>Rivaroxaban</b>				
United States	✓	✓	✓	✓
Canada	✓	✓	✓	✓
Europe	✓	✓	✓	✓
<b>Apixaban</b>				
United States	✓			
Canada	✓	✓		
Europe	✓	✓		

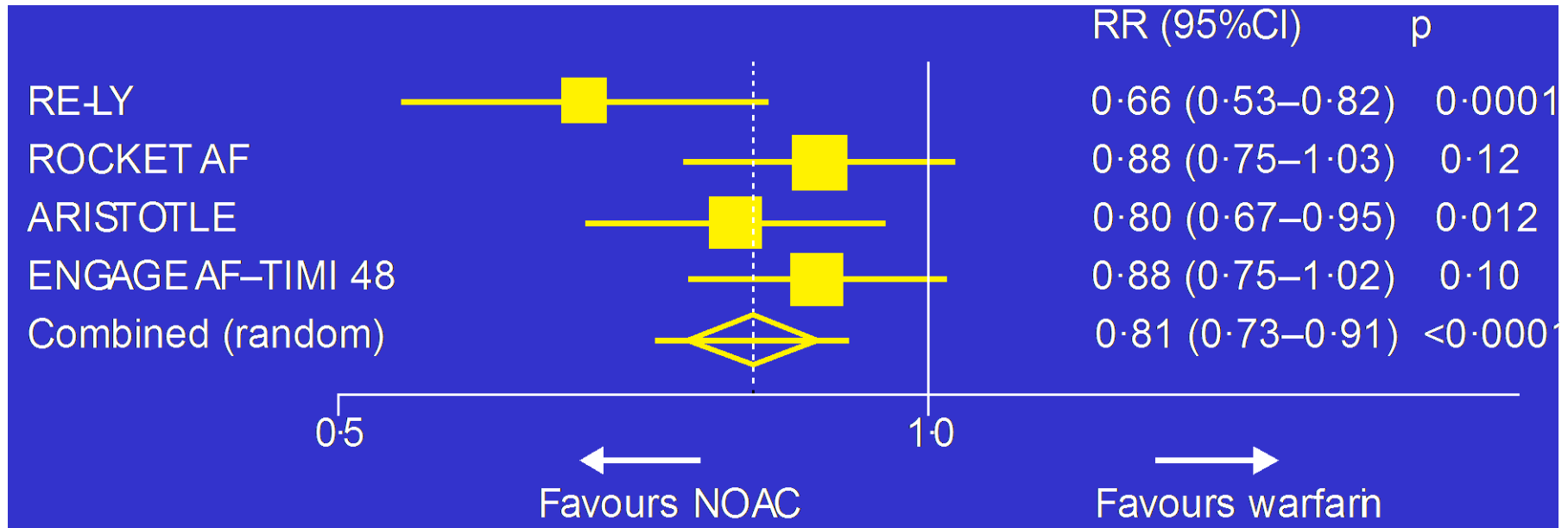
VTE, venous thromboembolism.

# Summary of Phase III studies

- >50.000 patients, mainly AF
- Direct comparison with VKA (INR 2-3)
- Efficacy: Stroke, recurrent VTE
- Safety: Bleeding

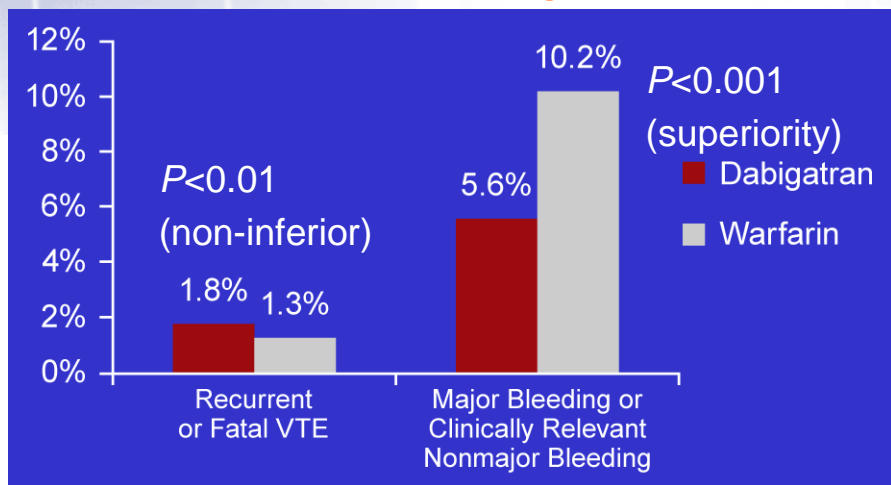


## Stroke or systemic embolic events in large NOAC trials, vs warfarin

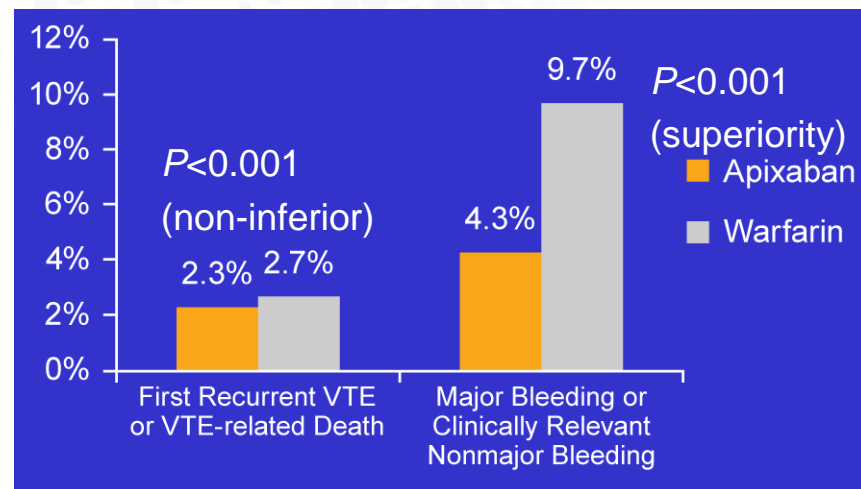


## VTE Treatment

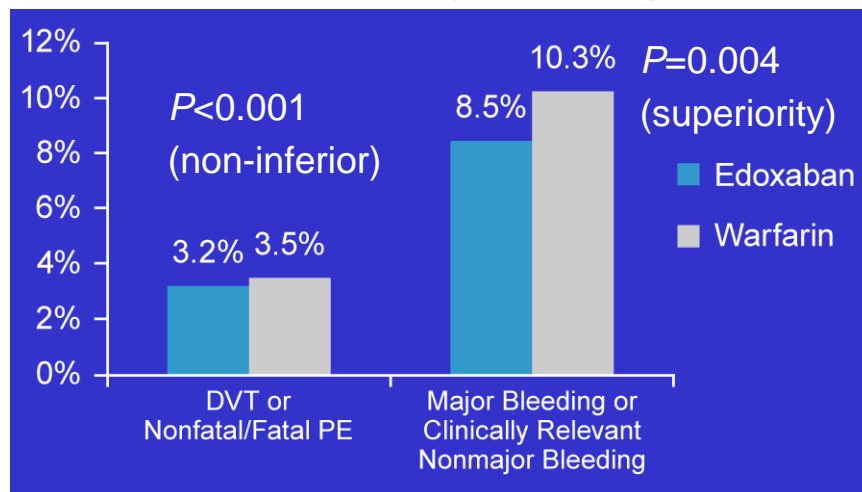
### RE-MEDY (Dabigatran)<sup>1,2</sup>



### AMPLIFY (Apixaban)<sup>1,3</sup>

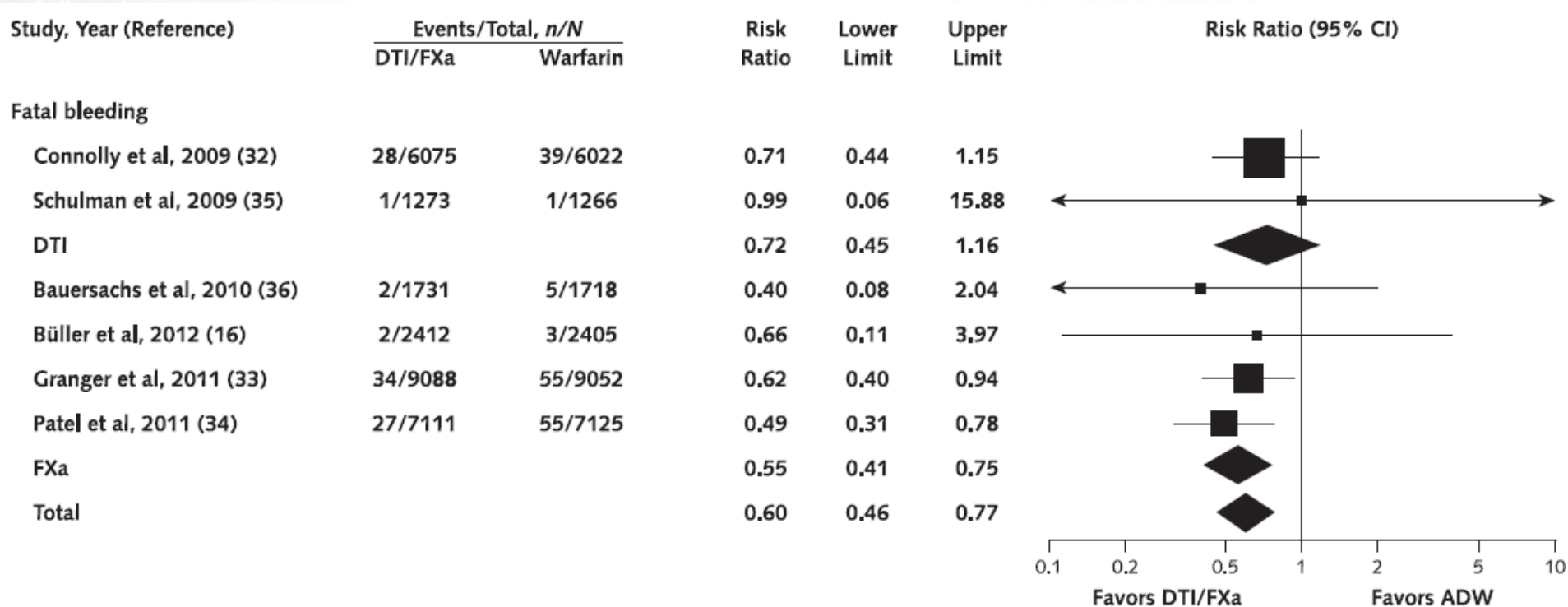


### HOKUSAI-VTE (Edoxaban)<sup>1,4</sup>



1. Cavender MA, Giugliano RP. *Hot Topics in Cardiology*. 2013;8:1-14.
2. Schulman S, et al. *N Eng J Med*. 2013;368:709-718.
3. Agnelli G, et al. *N Engl J Med*. 2013; 369:799-808.
4. Hokusai-VTE Investigators. *N Engl J Med*. 2013;369:1406-1415.

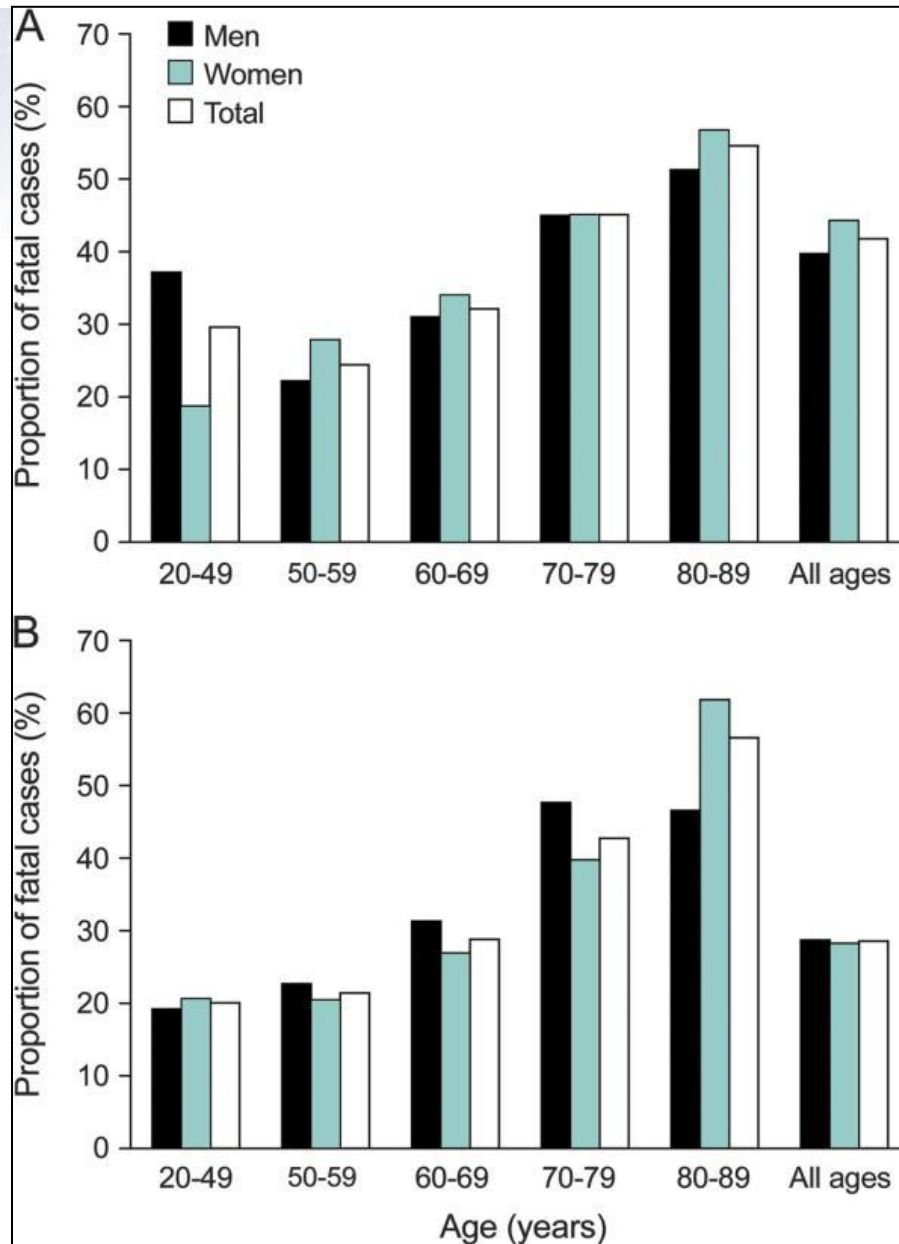
# Fatal bleeding



# Intracerebral bleeding



# Mortality < 30 days



**intracerebral  
bleeding**

**subarachnoidal  
bleeding**

González-Pérez A. Neurology 2013

Table 2. Numbers Needed to Treat in Comparison With Warfarin Sodium for the Prevention of Intracranial Hemorrhage

Drug	NNT vs Warfarin Sodium		
	Median	2.5% CrI	97.5% CrI
Dabigatran etexilate mesylate, 110 mg	29.32	6.56	130.20
Dabigatran etexilate mesylate, 150 mg	34.53	7.57	156.80
Rivaroxaban	59.11	10.98	348.10
Apixaban	35.07	7.85	157.20
Aspirin	39.60	-188.60	376.30

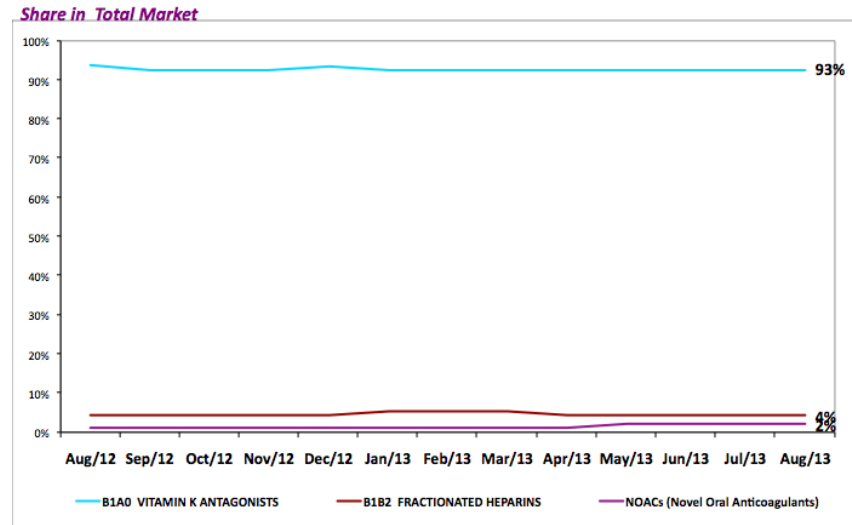
# Conclusion of the Phase III DOACs studies

- Non-inferiority for stroke and VTE compared to warfarin
- Reduction in major/fatal bleeding, ICH
- Without monitoring

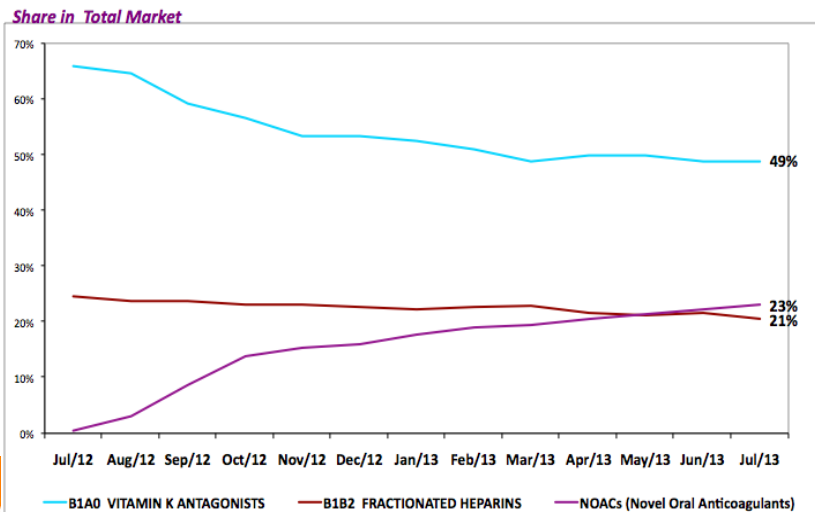


# DOAC use in Netherlands, Belgium and Germany

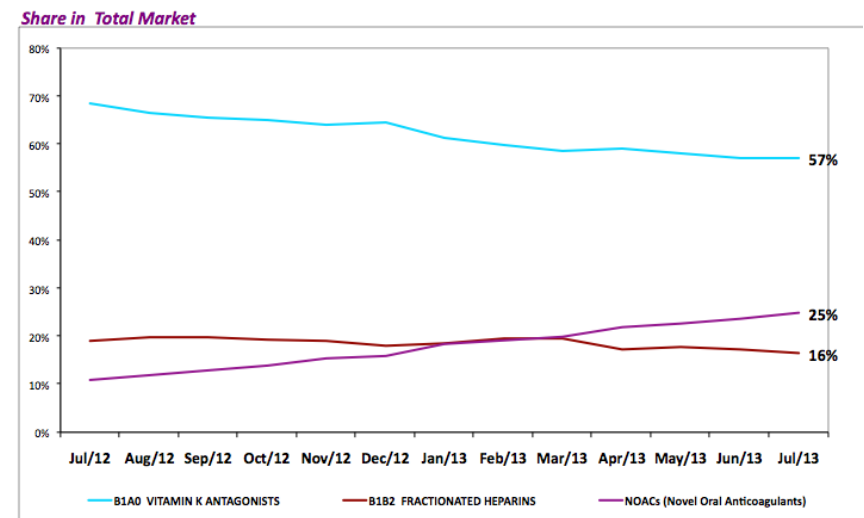
Geography: Netherlands - Treatment Days - September 2013



Geography: Belgium - Treatment Days - September 2013



Geography: Germany - Treatment Days - September 2013



# Why are we staying behind?

- Netherlands are always slow
- Hurdles in clinical practice
  - Logistically challenging
  - Who is in the lead for treatment?
  - Negative publicity in newspapers
  - No reimbursement for VTE indication
  - No antidote
  - Monitoring?
  - Renal failure?

# Who is responsible for the patients with DOACs?

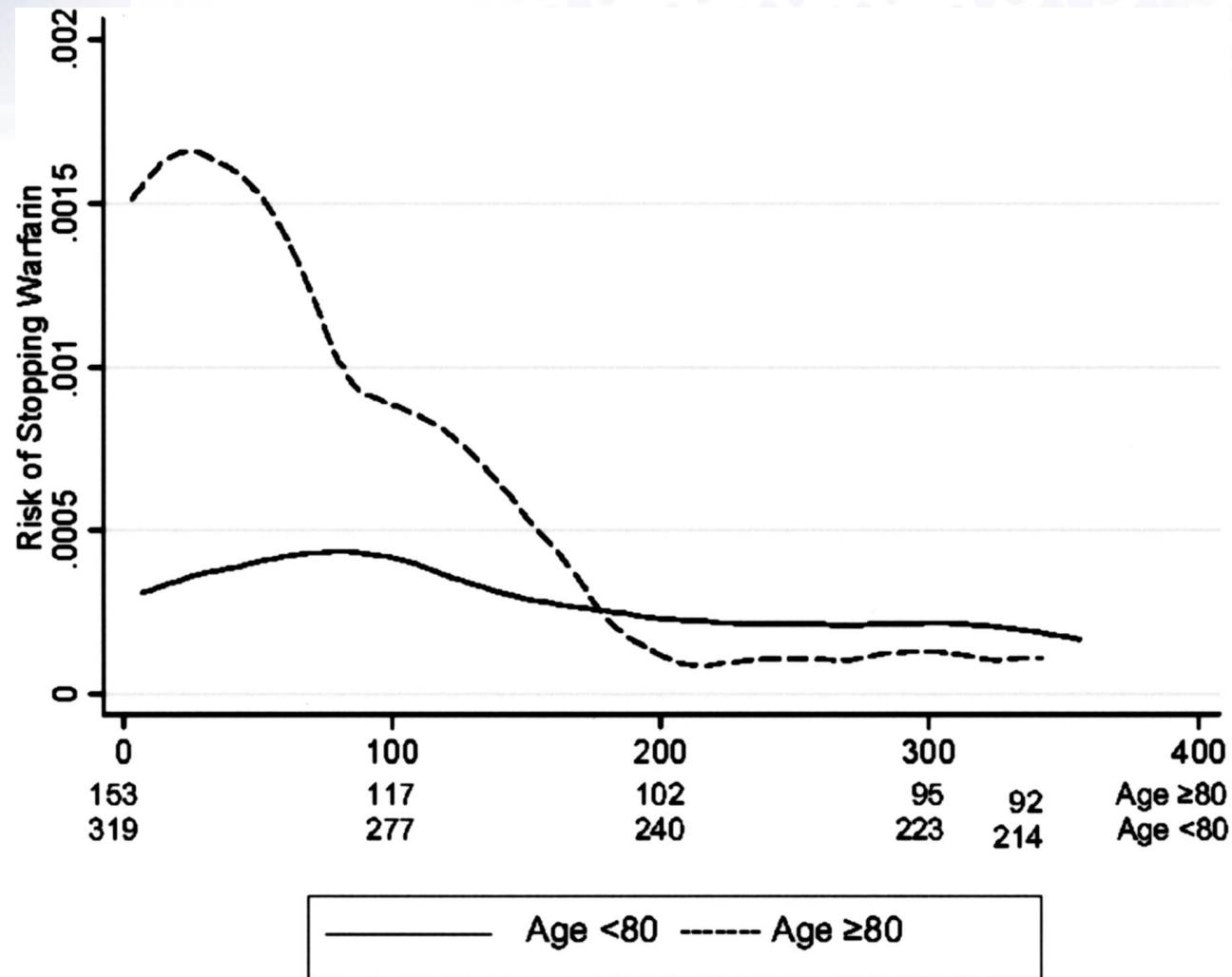




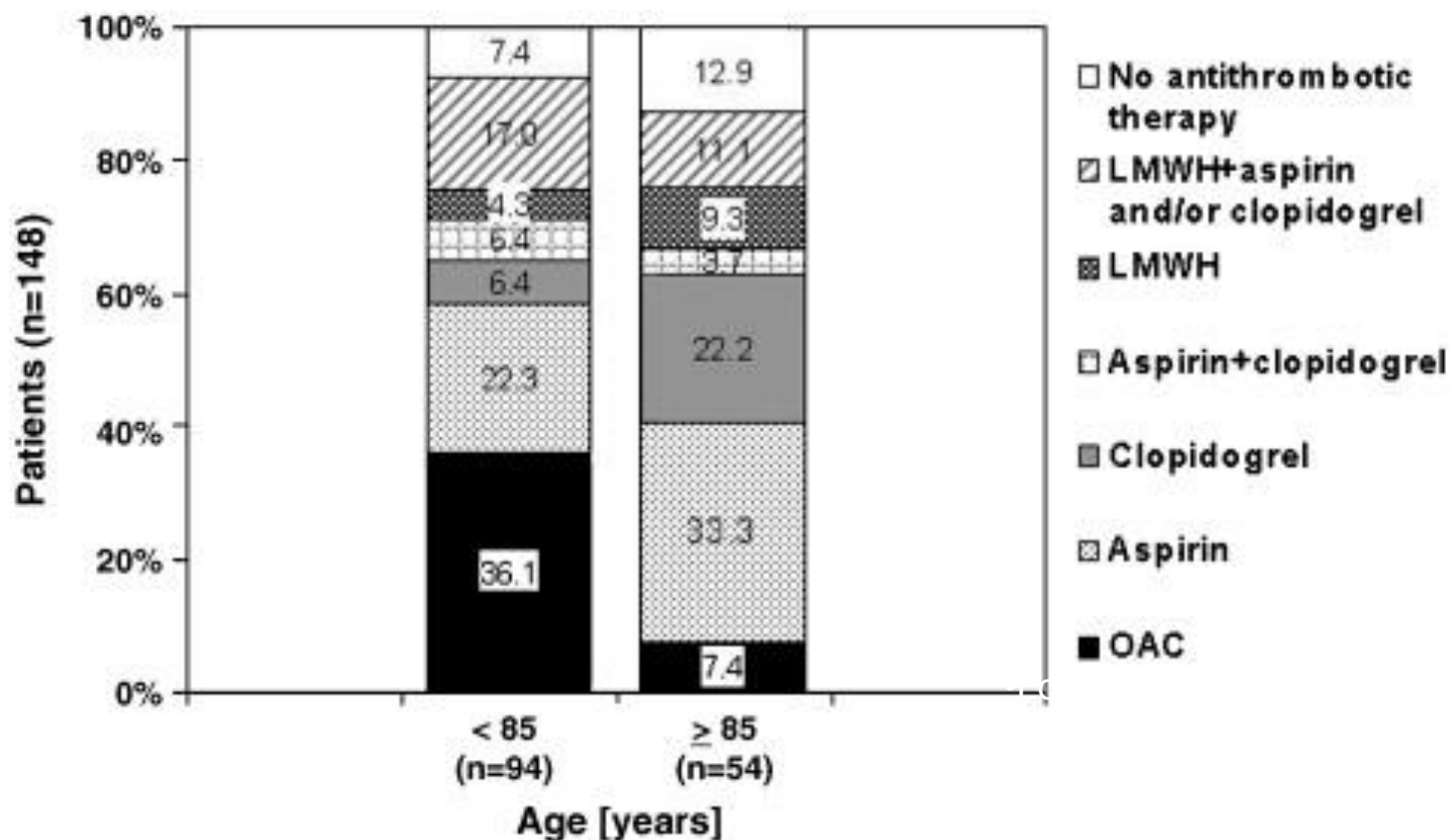
# What about the elderly?



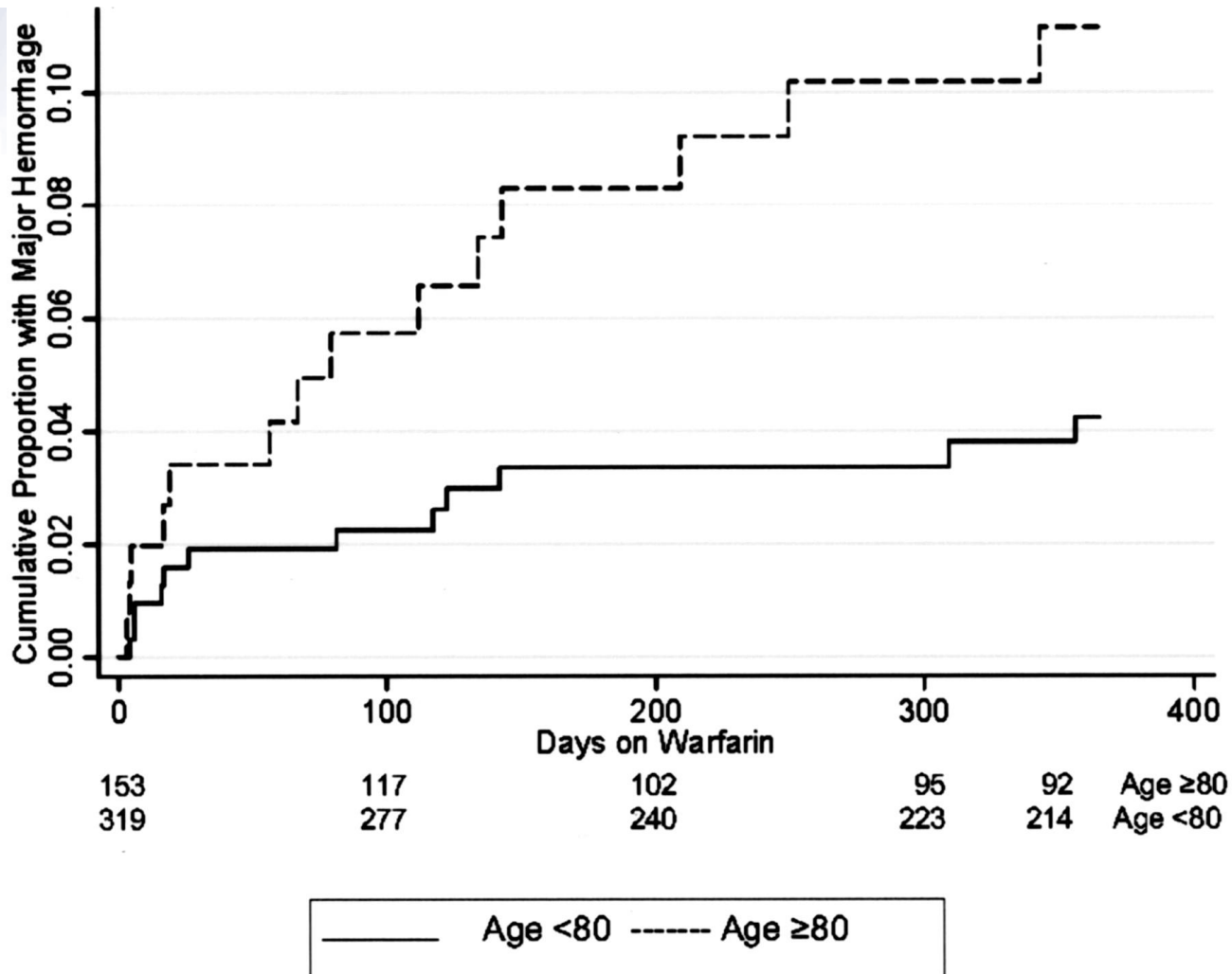
# Risk of stopping warfarin in the first year on the basis of perceived safety concerns by age



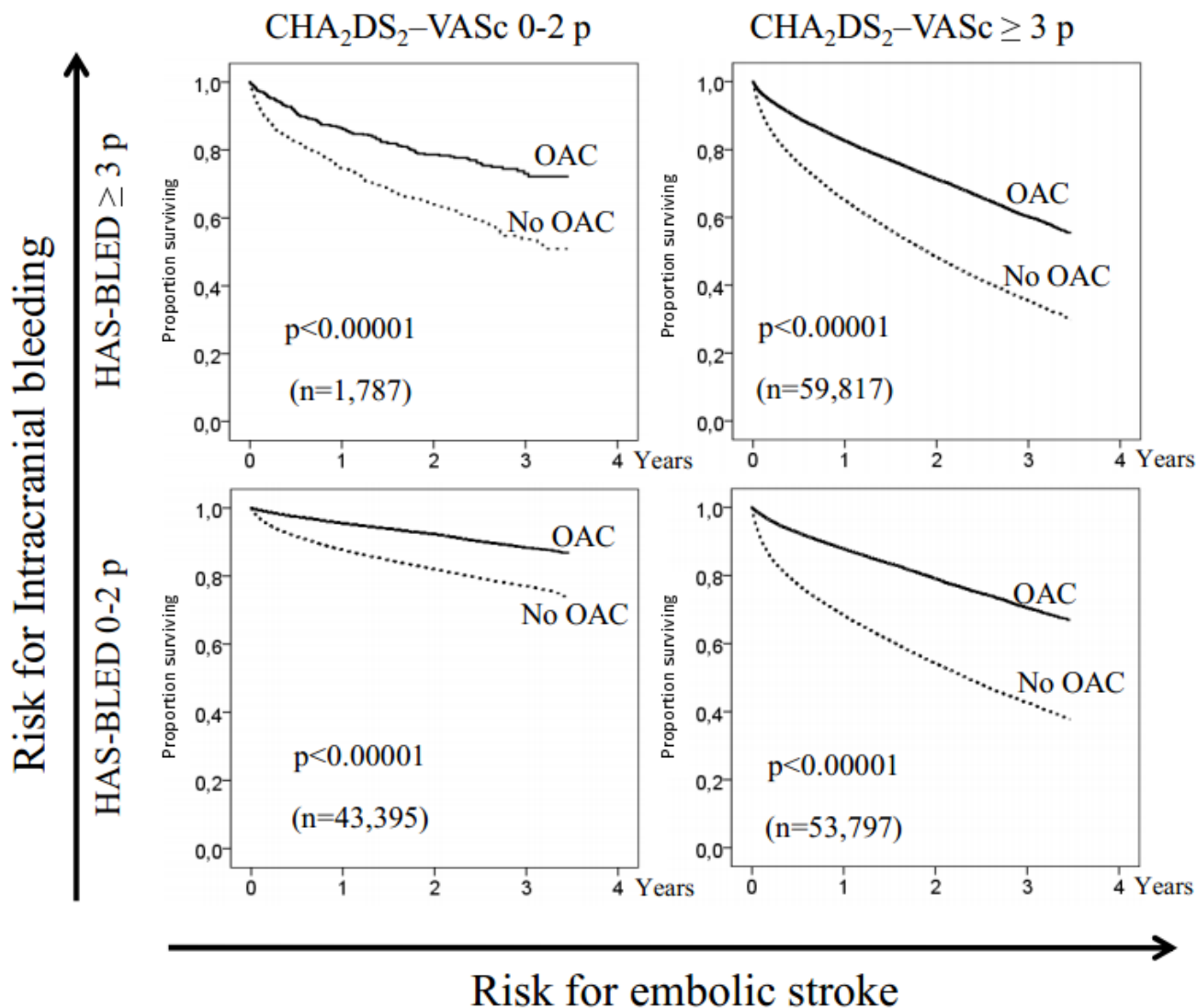
## VKA in elderly underused!

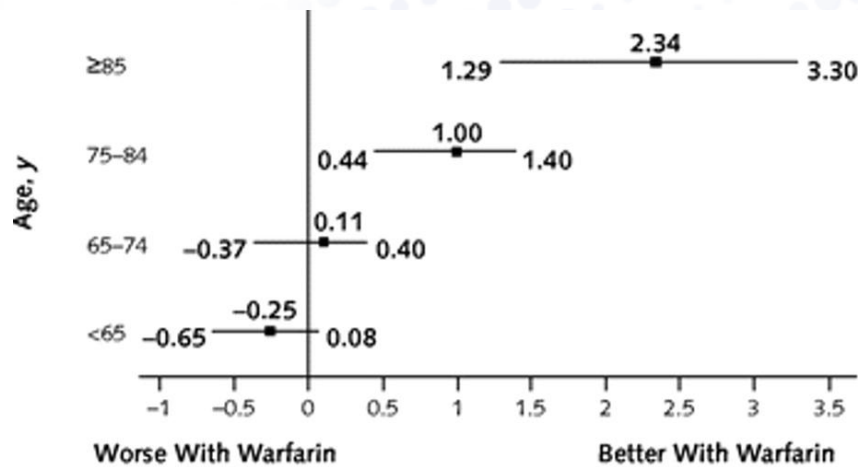


# Cumulative incidence of major bleeding among patients aged $\geq 80$ years and $<80$ years (n=472)

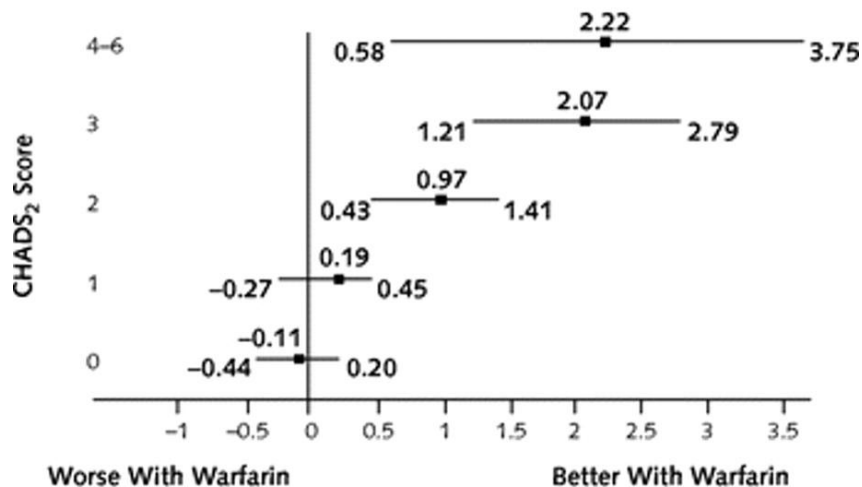








Net Clinical Benefit, Events Prevented per 100 Person-Years



Net Clinical Benefit, Events Prevented per 100 Person-Years

# Major bleeding in elderly AF patients with anticoagulation

	>75 years		<75 years	
	DOAC	VKA	DOAC	VKA
Dabigatran 150 mg	5.10%	4.37%	2.12%	3.04%
Dabigatran 110 mg	4.44%	4.37%	1.89%	3.04%
Rivaroxaban 20 mg	2.67%	4.03%	2.68%	2.97%
Apixaban 5 mg	3.3%	5.2%	2.0%	2.8%
Edoxaban 60 mg	4.01%	4.83%	2.02%	2.62%
Edoxaban 30 mg	2.02%	4.83%	1.23%	2.62%

No clear difference in efficacy between younger and older patients

# Renal impairment and DOACs

**Table 2** Dose-adjustment Requirements of Newer Oral Anticoagulants According to Creatinine Clearance Levels

	Creatinine Clearance			
	≥50 mL/min	30-49 mL/min	15-29 mL/min	<15 mL/min
Dabigatran <sup>46</sup>	150 mg, twice daily	150 mg, twice daily	75 mg/d, twice daily	Contraindicated
Rivaroxaban <sup>47</sup>	20 mg, once daily	15 mg, once daily	15 mg, once daily	Contraindicated
Apixaban <sup>55</sup>	2.5 mg, twice daily	2.5 mg, twice daily	2.5 mg, twice daily*	Contraindicated

mg = milligrams; min = minutes; mL = milliliters.

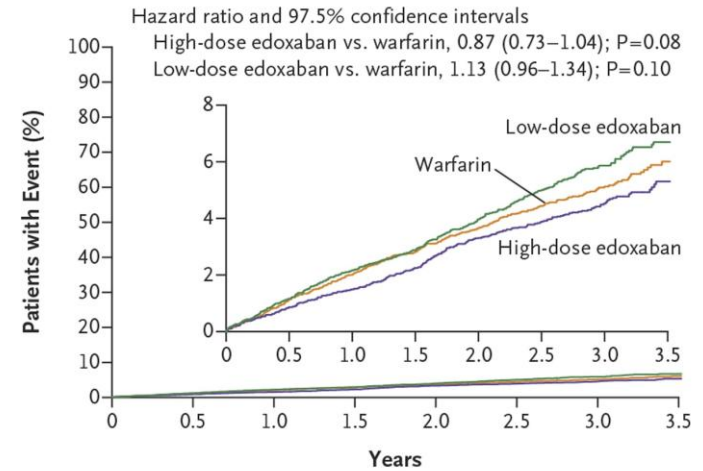
\*Limited clinical data; apixaban should be used with caution.

FDA recommendation 2013

# Major bleeding in AF patients with renal impairment

	eGFR 30-50		eGFR>50	
	DOAC	VKA	DOAC	VKA
Dabigatran 150 mg	6.06%	5.06%	1.78%	3.01%
Dabigatran 110 mg	5.13%	5.06%	1.25%	3.01%
Rivaroxaban 15-20 mg	4.49%	4.7%	3.39%	3.17%
Apixaban 2.5-5 mg	3.2%	6.4%	1.5%	1.8%
Edoxaban 30-60 mg	1.61%	3.63%	2.75%	3.63%

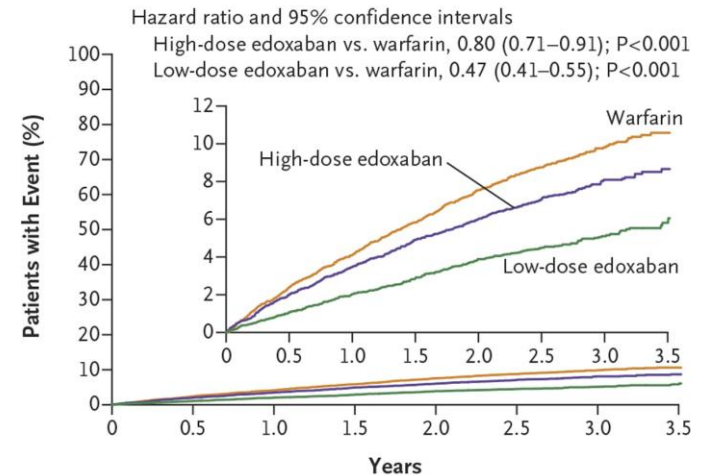
## A Stroke or Systemic Embolic Event



### No. at Risk

Warfarin	7036	6798	6615	6406	6225	4593	2333	536
High-dose edoxaban	7035	6816	6650	6480	6283	4659	2401	551
Low-dose edoxaban	7034	6815	6631	6461	6277	4608	2358	534

## B Major Bleeding



### No. at Risk

Warfarin	7012	6116	5630	5278	4941	3446	1687	370
High-dose edoxaban	7012	6039	5594	5232	4910	3471	1706	345
Low-dose edoxaban	7002	6218	5791	5437	5110	3635	1793	386

# Which patients could preferably use DOACs?

- New AF or new VTE
- Labile INR despite good compliance
- eGFR >50 ml/min
- Elderly patients with good renal function



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Thank you for your attention

