

# Anticoagulation in frail and complex patients

Dr Will Lester

**Frailty**





In over 20 years in the UK (2000)  
Over 9 million the number aged >80 years  
Five quadruple aged (>85 years)  
Eightfold increase aged >100 years



**What to do after bleeding?**







- Anticoagulation in the frail
- Restarting anticoagulation after a bleed
- Oral anticoagulants combined with anti-platelet drugs








**Oral anticoagulants and anti-platelet drugs**

ALL combinations are associated with a higher risk of bleeding

**Chronic kidney disease and falls**

**Summary**

- The application of real data to frail patients with multiple comorbidities is a challenge
- Assessing benefits and risks of anticoagulation in patients of high risk of bleeding is complex as the risks of thrombosis is also increased eg. chronic kidney disease
- Co-prescription of oral anticoagulants with anti-platelet agents should be avoided unless essential
- Some forms of oral anticoagulation may be more appropriate in certain circumstances eg. renal failure or bleeding (intermittent bleeding)
- Alternatives to anticoagulation may sometimes be available eg. distal athero-occlusion devices

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Declarations

Speaker:	Boehringer-Ingelheim, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Pfizer, Roche
Advisory board:	Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Pfizer, Roche, Sanofi, Servier
Support to attend scientific meetings:	Boehringer-Ingelheim

Which anticoagulant is more appealing?

Drug A:  
Slightly more effective than warfarin with the same bleeding risk

Drug B:  
As effective as warfarin with a lower risk of bleeding

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# Which anticoagulant is more appealing?

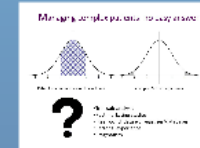
Drug A:

Slightly more effective than warfarin with the same bleeding risk

Drug B:

As effective as warfarin with a lower risk of bleeding

# Frailty



## *In next 30 years in the UK (ONS):*

- Over triple the number aged >90 years
- Over quadruple aged >95 years
- Eightfold increase aged >100 years

**Case 1**

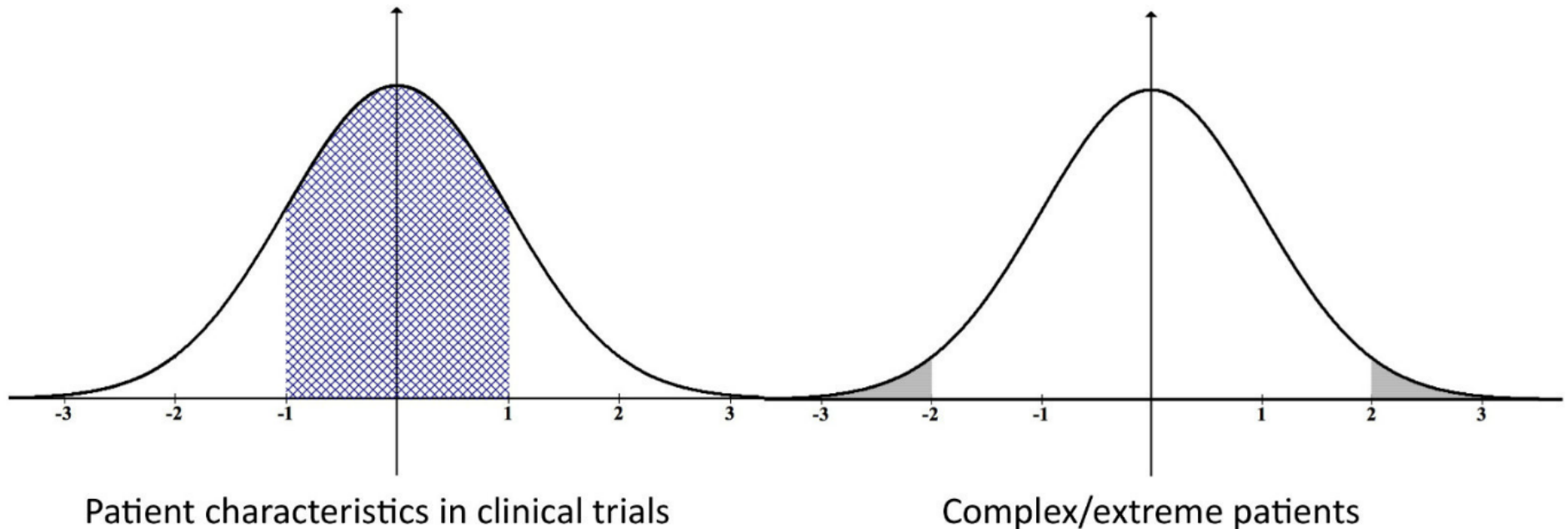
- 86 year old female is admitted with DVA  
- Altered vision  
- acute SOB  
- SOB  
- weakness
- asks symptoms of dementia?  
- Keganis and she had her admission
- States a good response and is transferred to the  
local rehab hospital
- What are you going to do about it response in?

**Issues to explore**

Resident care plans  
Admission with acute respiratory  
Respiratory and health screening

Two small icons are shown below the text: a bar chart icon on the left and a person with a speech bubble icon on the right.

# Managing complex patients: no easy answer



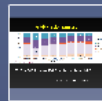
- Trial sub-analysis
- Post marketing studies
- 'Real world' data eg. registries/databases
- Personal experience
- Pragmatism

## Case 1

- 86 year old female is admitted with CVA
  - Hypertension
  - eGFR 41ml/min
  - 49kg
  - Lives alone
  - Early symptoms of dementia?
  - Known AF and is on aspirin on admission
- Makes a good recovery and is transferred to the local rehab hospital
- What are you going to do about anticoagulation?

### Issues to explore

Patient/carer opinion  
Adherence with medicines/dosette box  
Responsibility to wider health economy



# Case 1

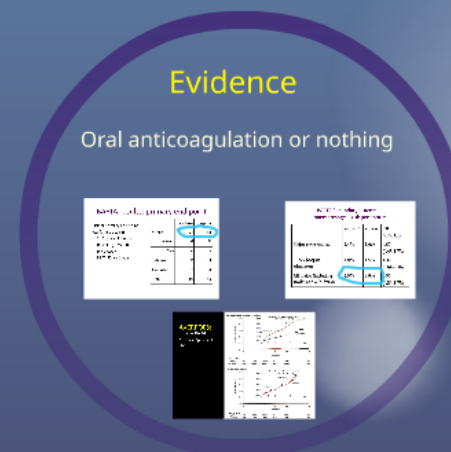
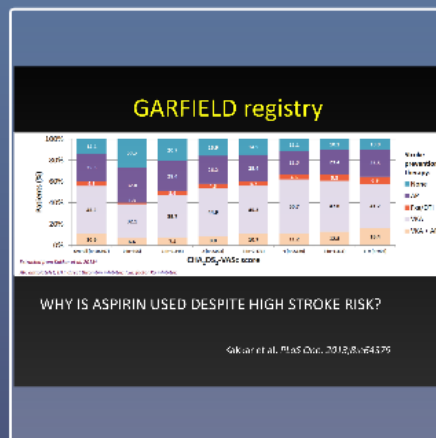
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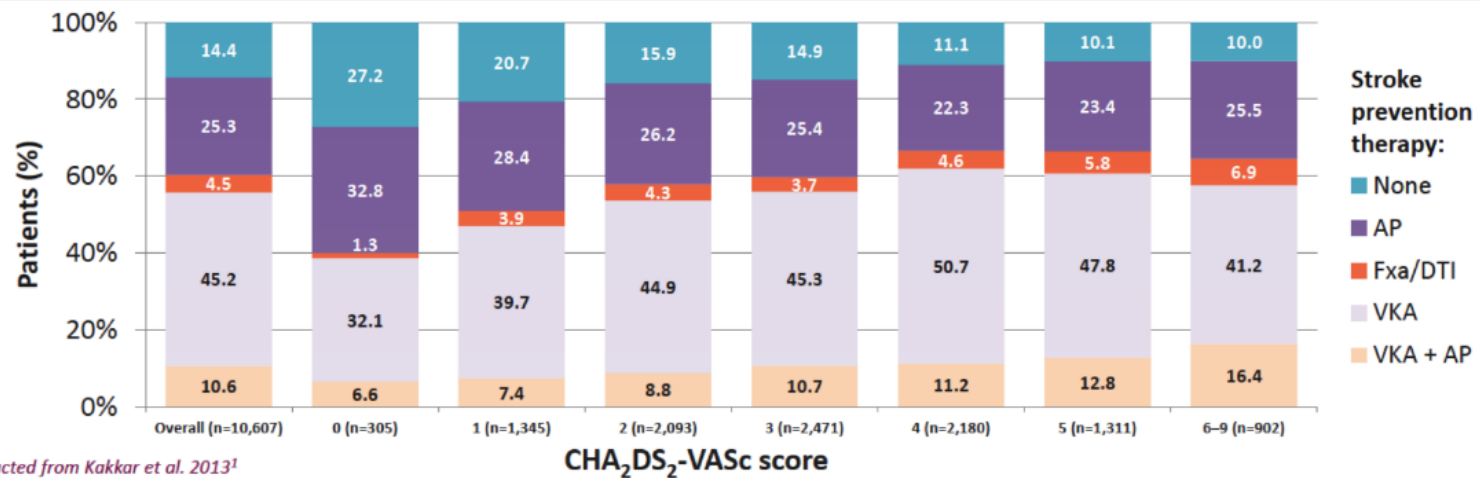
Patient/carer opinion

Adherence with medicines/dosette box

Responsibility to wider health economy



# GARFIELD registry



Extracted from Kakkar et al. 2013<sup>1</sup>

AP: antiplatelet; DTI: direct thrombin inhibitor; Fxa: factor Xa inhibitor.

## WHY IS ASPIRIN USED DESPITE HIGH STROKE RISK?

Kakkar et al. *PLoS One*. 2013;8:e64379



# Evidence

## Oral anticoagulation or nothing

### BAFTA results: primary end point

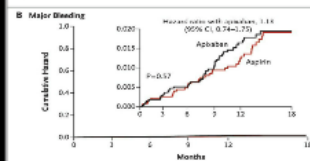
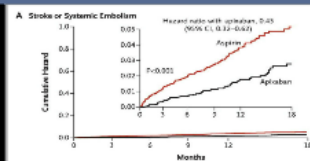
- Risk of primary end point:  
Warfarin v aspirin
- 1.8% p.a v 3.8% p.a
  - RR 0.48 (0.28-0.80)
  - p = 0.0027
  - NNT: 50 for 1 year

	warfarin	aspirin
Stroke	21	44
-ischemic	10	32
-haemorrhagic	6	5
Subdural	2	1
Embolic	1	3
Total	24	48

### BAFTA Secondary outcomes: haemorrhage – risk per annum

	warfarin	aspirin	RR (95% CI)
Major extra-cranial	1.4%	1.6%	0.87 (0.43-1.73)
Other hospital admission	1.8%	1.5%	1.22 (0.64-2.36)
All major (including stroke and sub-dural)	1.9%	2.0%	0.96 (0.53-1.75)

### AVERROES: N Engl J Med 2011; 364:866 Aspirin vs Apixaban in SPAF



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BAFTA Secondary outcomes:  
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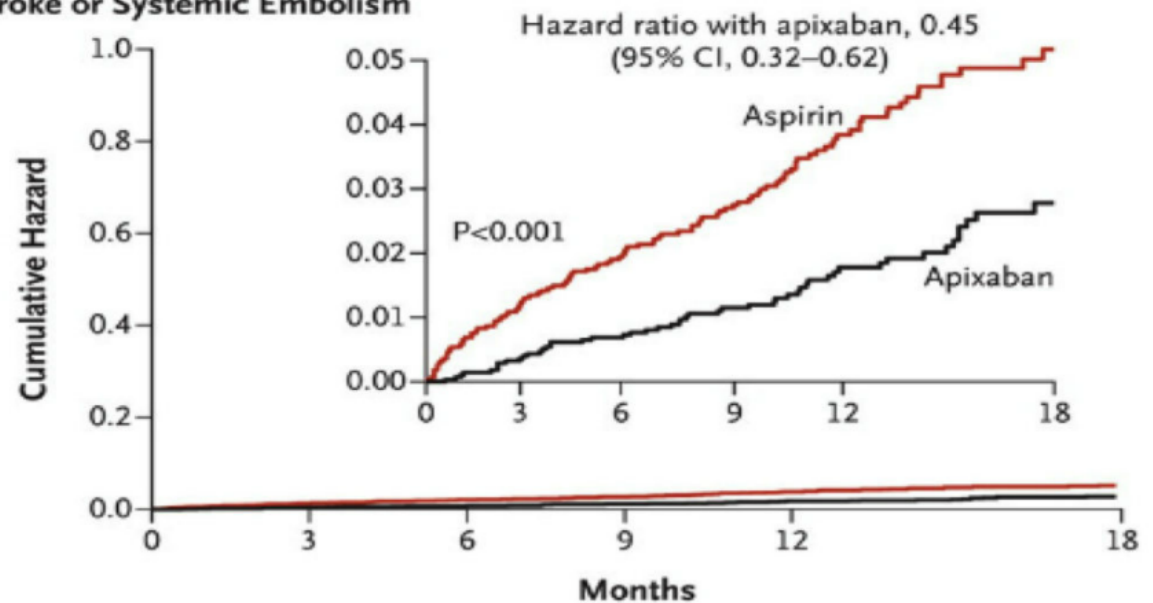
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# AVERROES:

N Engl J Med 2011; 364:806

## Aspirin vs Apixaban in SPAF

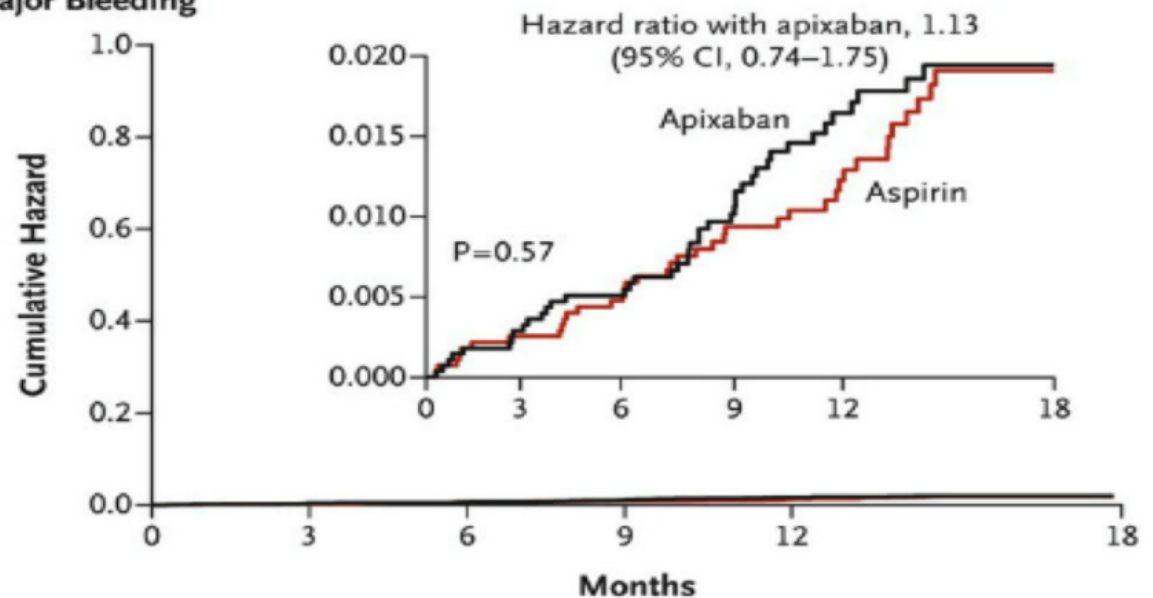
### A Stroke or Systemic Embolism



#### No. at Risk

Aspirin	2791	2716	2530	2112	1543	628
Apixaban	2808	2758	2566	2125	1522	615

### B Major Bleeding



#### No. at Risk

Aspirin	2791	2738	2557	2140	1571	642
Apixaban	2808	2759	2566	2120	1521	622

# Chronic kidney disease and falls

## Falls



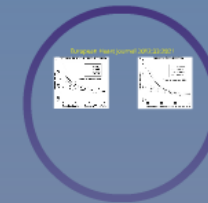
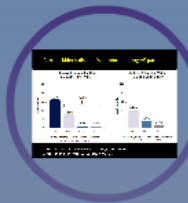
1/3rd patients >65 years fall every year; 10% result in serious injury

### HOWEVER

1. Predictive modeling from literature review: patient with AF and 5% stroke risk would need to fall 295 times a year to lose benefit from anticoagulation
2. Reduction in death/hospitalisation in patients on warfarin with falls greater than the increased risk of intracranial bleeding in retrospective study if CHADS2  $\geq 2$
3. No significant increase in bleeds in falls patients in prospective study

1. Man-Son Hing et al Arch Intern Med. 1999; 159: 677-85
2. Gage et al Am J Med. 2005;118:612-7
3. Donze et al Am J Med. 2012;125:773-8

## Chronic kidney disease



### DOAC dose adjustments for renal disease

- Dabigatran: 110mg bd for GFR 30-50ml/min
- Rivaroxaban: 15mg od for GFR 15-50ml/min
- Apixaban: 2.5mg bd for GFR 15-30ml/min or Creat >133umol/L and either age  $\geq 80$  or weight  $\leq 60$ kg
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# Falls



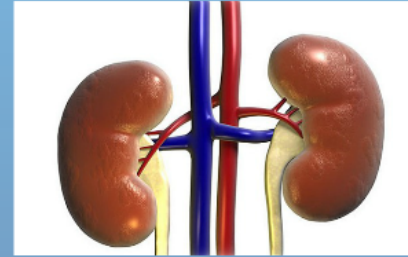
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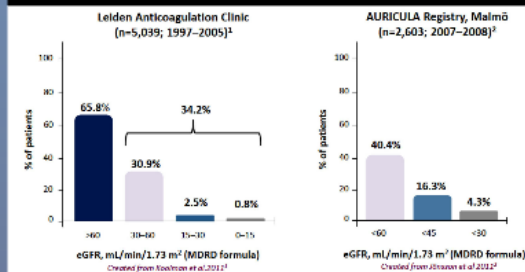
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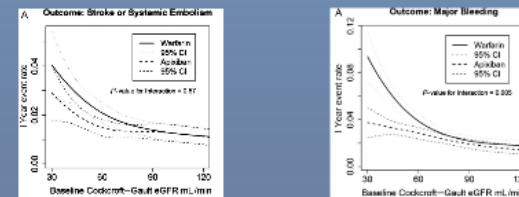


## Chronic kidney disease is common among AF patients



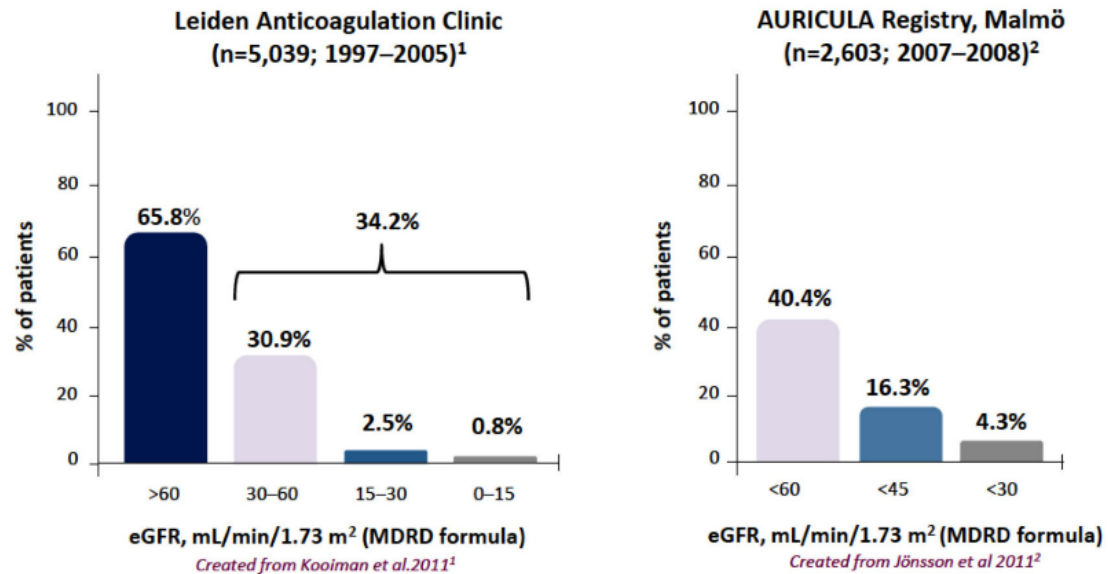
1. Kooimein et al. *J Thromb Haemost.* 2011;9:1652-1653.
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## European Heart Journal 2012;33:2821





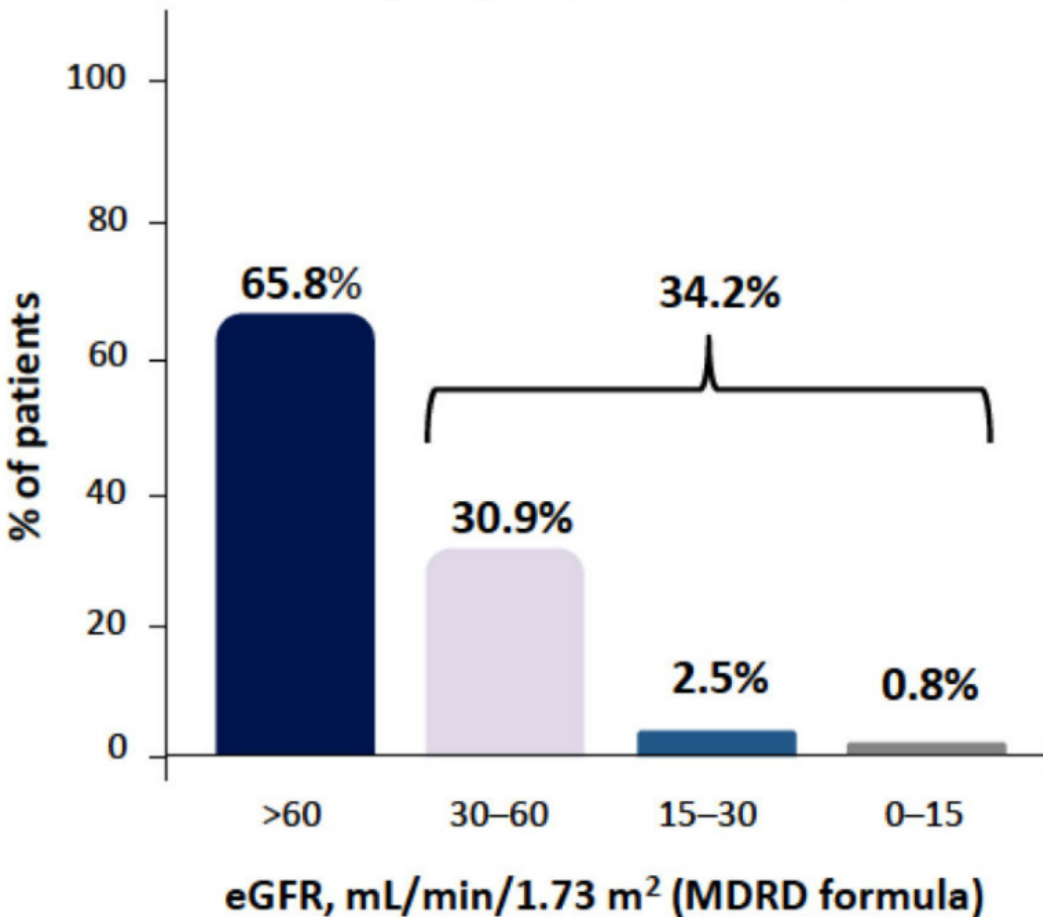
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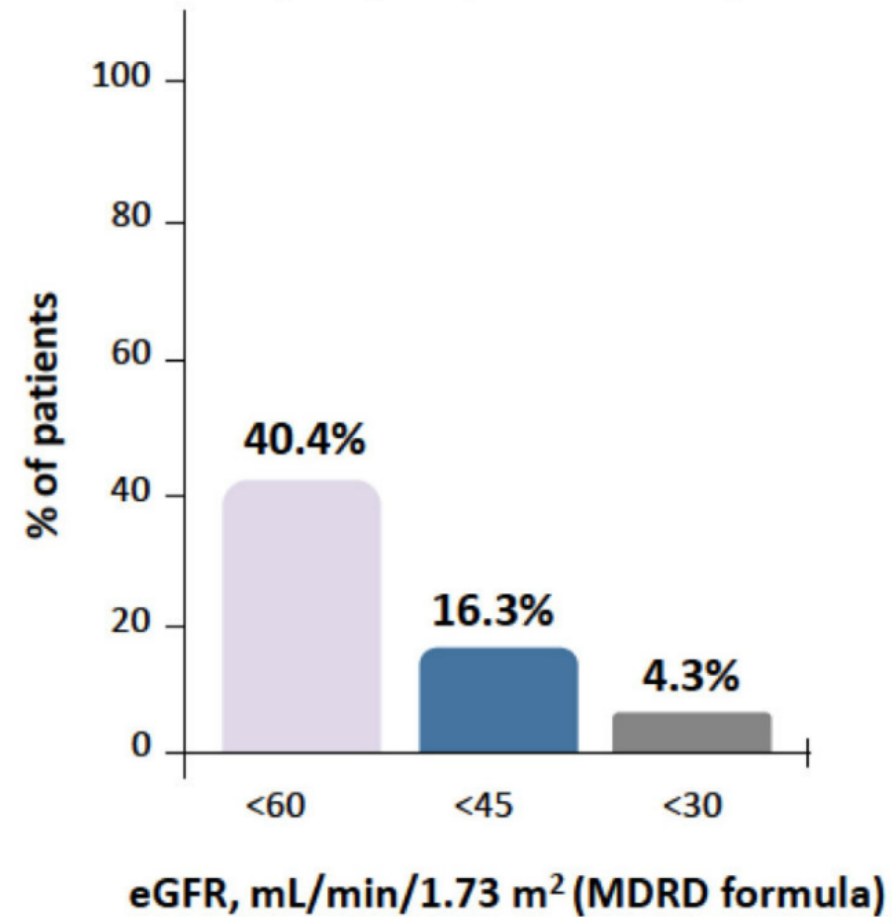
# Chronic kidney disease is common among AF patients

Leiden Anticoagulation Clinic  
(n=5,039; 1997–2005)<sup>1</sup>



Created from Kooiman et al. 2011<sup>1</sup>

AURICULA Registry, Malmö  
(n=2,603; 2007–2008)<sup>2</sup>

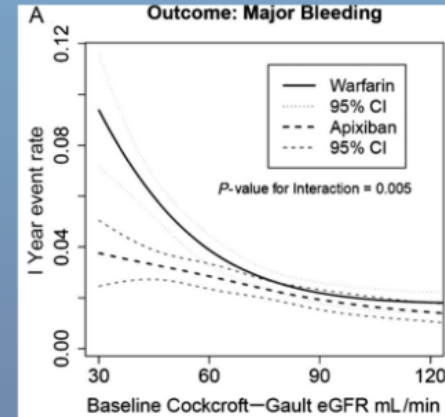
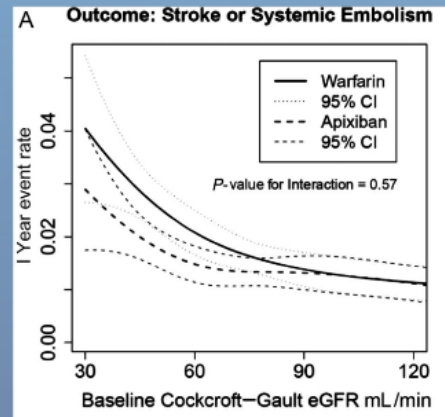


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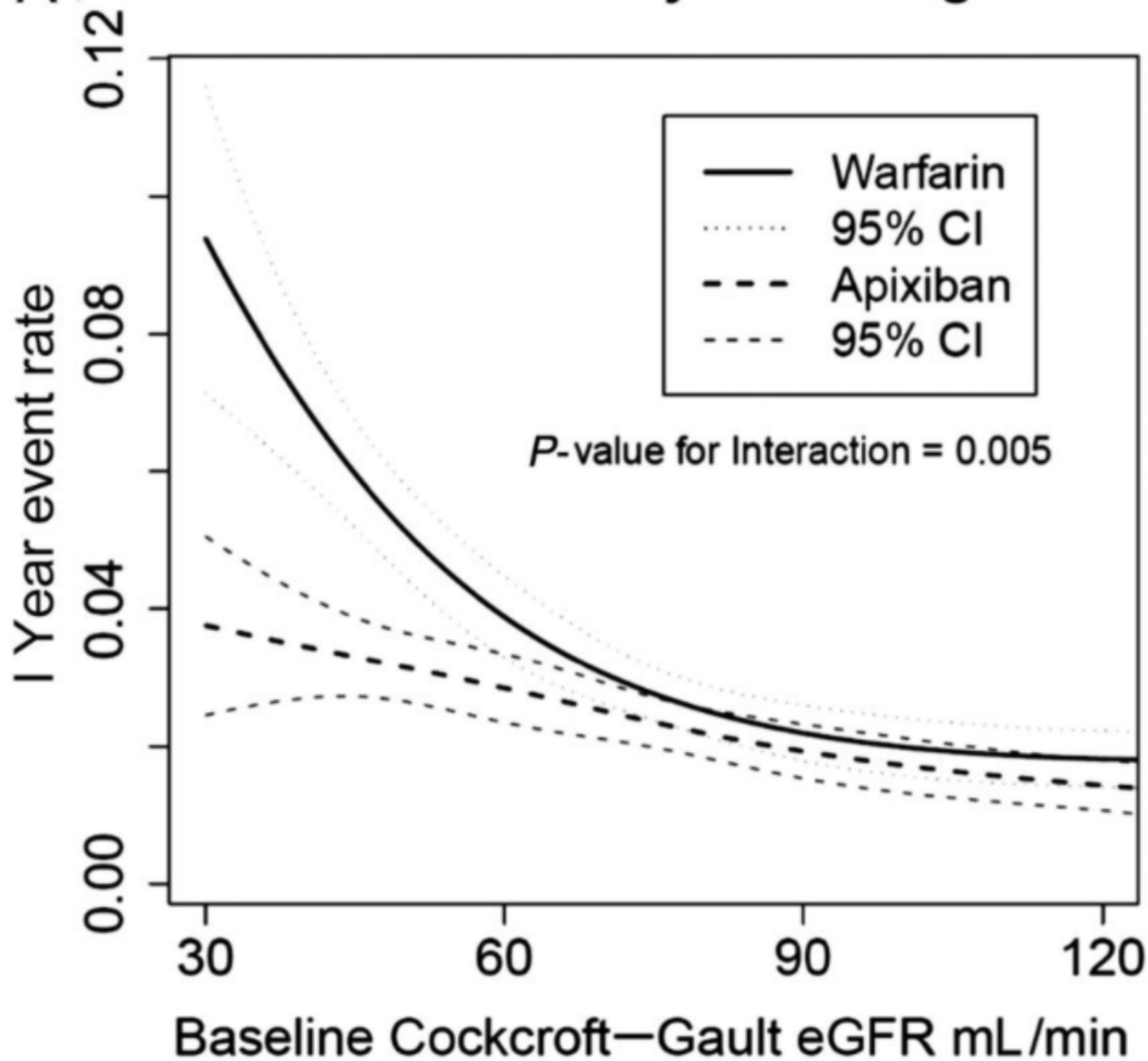
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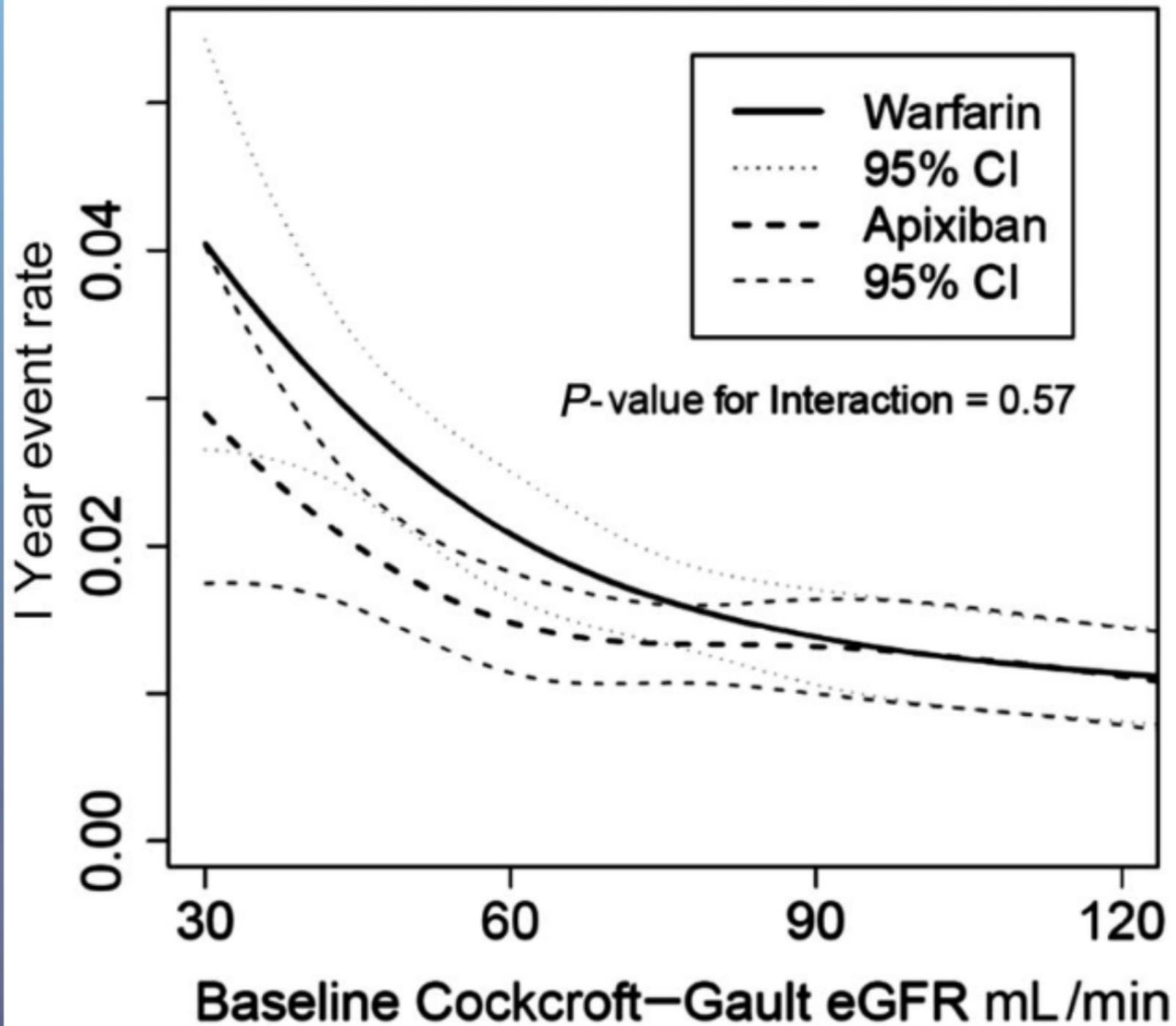
## European Heart Journal 2012;33:2821



A

# Outcome: Major Bleeding



**A****Outcome: Stroke or Systemic Embolism**

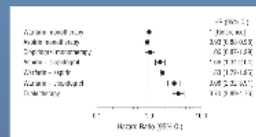
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# Oral anticoagulants and anti-platelet drugs

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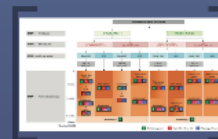
Arch Intern Med 2010;170:1433



## HAS-BLED

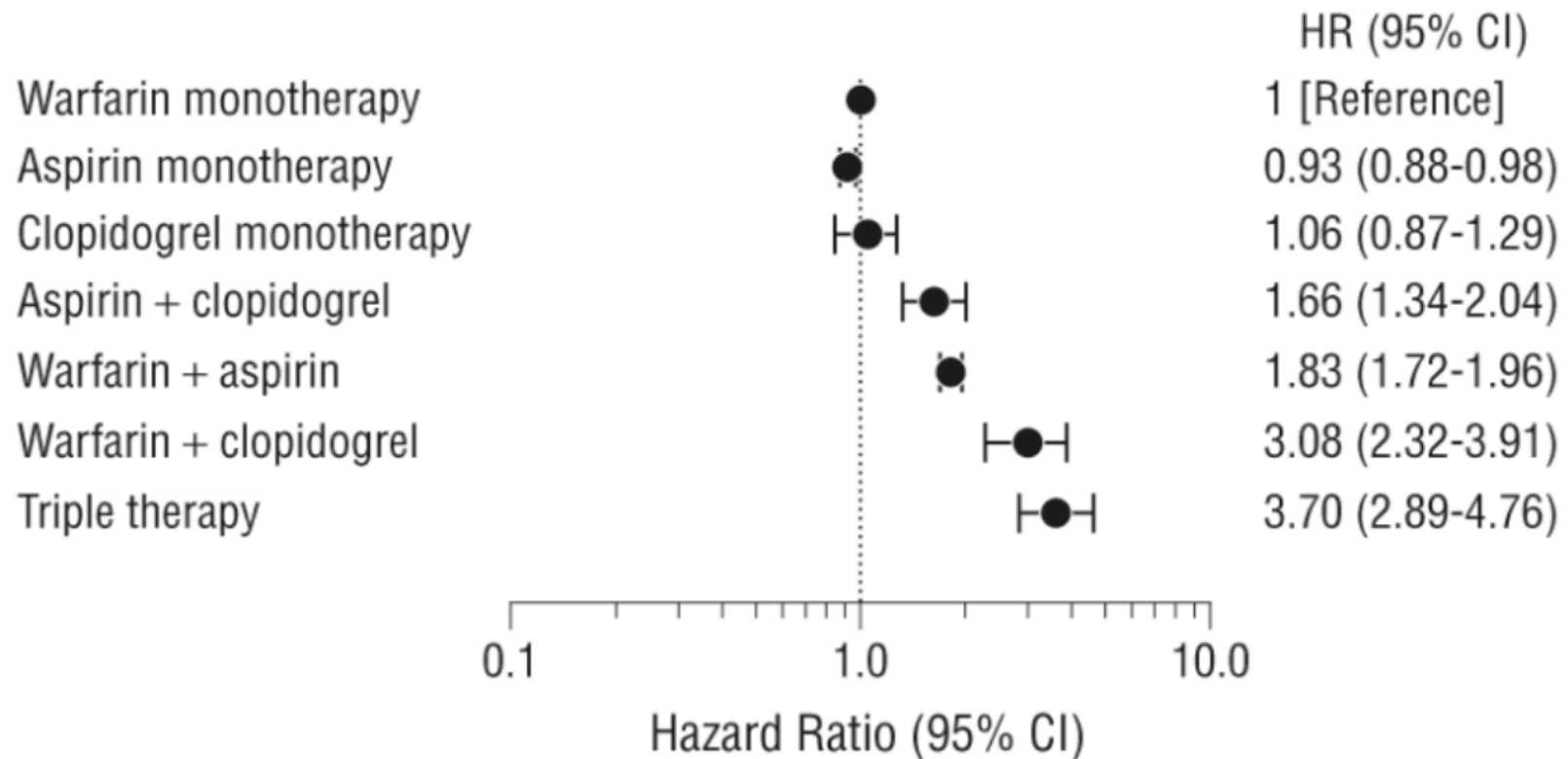
	Condition	Points
<b>H</b>	Hypertension: (uncontrolled, $\geq 160$ mmHg systolic)	1
	Abnormal renal function: Dialysis, transplant, Cr $> 2.6$ mg/dL or $> 200$ $\mu$ mol/L	1
<b>A</b>	Abnormal liver function: Cirrhosis or Bilirubin $> 2 \times$ Normal or AST/ALT/AP $> 3 \times$ Normal	1
<b>S</b>	Stroke: Prior history of stroke	1
<b>B</b>	Bleeding: Prior Major Bleeding or Predisposition to Bleeding	1
<b>L</b>	Labile INR: (Unstable/high INRs), Time in Therapeutic Range $< 60\%$	1
	Elderly: Age $> 65$ years	1
<b>E</b>	Medication Usage Predisposing to Bleeding: (Antiplatelet agents, NSAIDs)	1
<b>D</b>	Prior Alcohol or Drug Usage History	1

Management of AF patients with Acute Coronary Syndrome or Percutaneous coronary Intervention  
European Heart Journal  
doi:10.1093/eurheartj/ehu298





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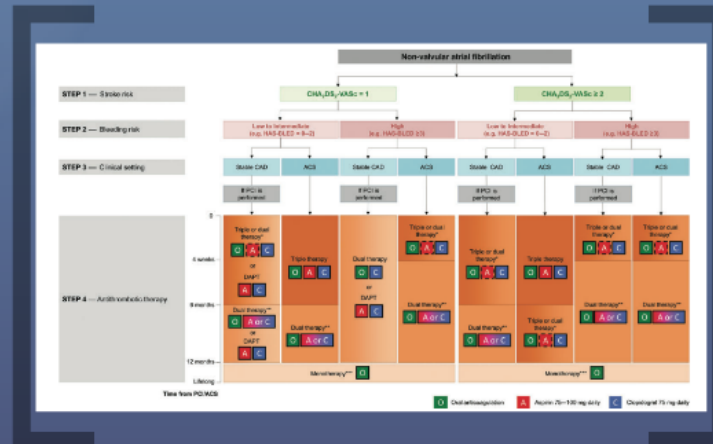


# HAS-BLED

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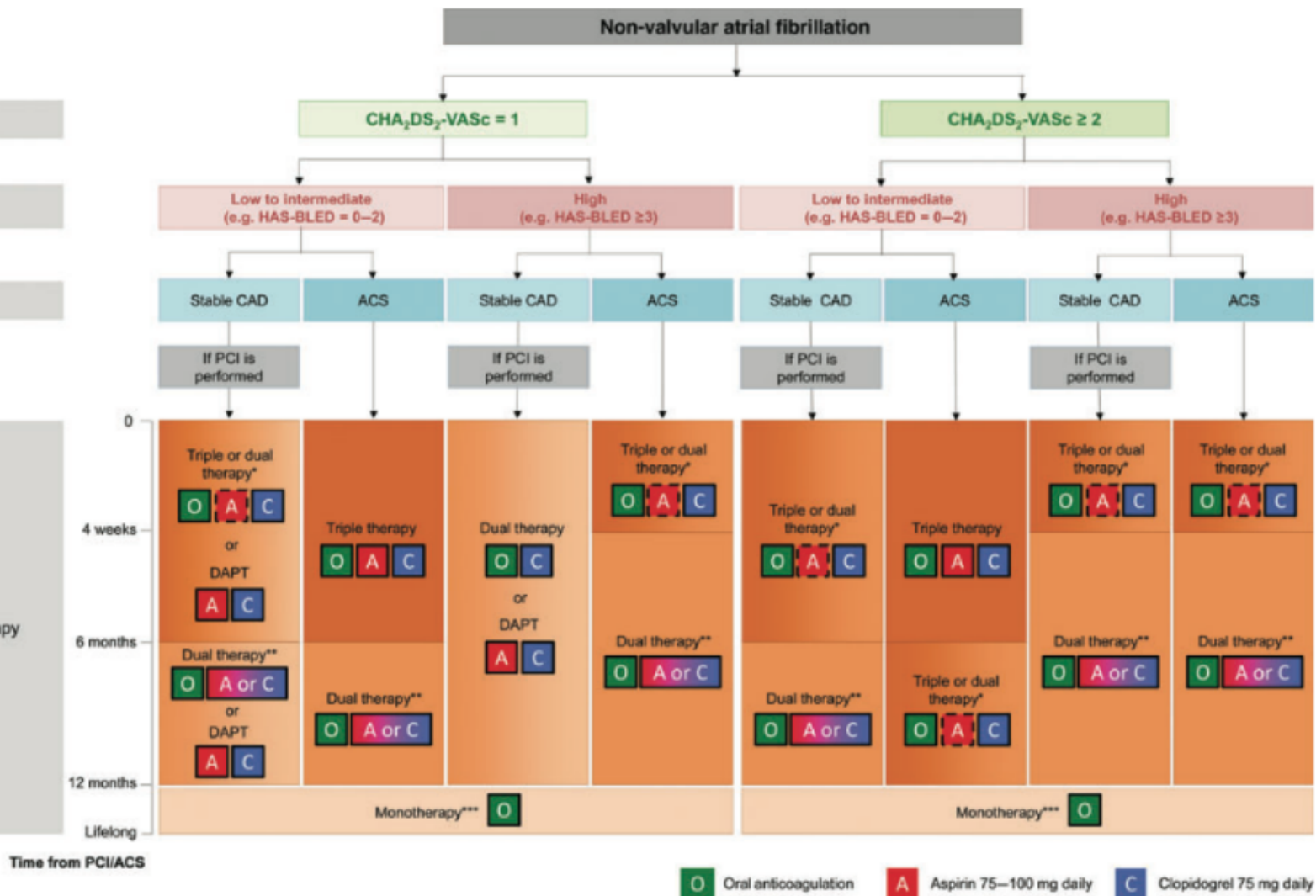


STEP 1 — Stroke risk

STEP 2 — Bleeding risk

STEP 3 — Clinical setting

STEP 4 — Antithrombotic therapy



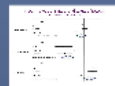
# What to do after bleeding?



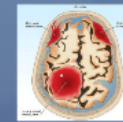
## Gastrointestinal bleeding



- If on VKA, was the INR high?
- Is it a treatable lesion eg. ulcer?
- NSAIDs or antiplatelet use?
- Risk of thrombosis off anticoagulation vs risk bleeding if continued



## Intra-cranial bleeding

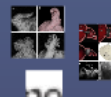


*Up to 43% of patients presenting with chronic subdural haematoma are on anticoagulants*

Considerations:  
ICH in deep location - 2% annual recurrence  
Lobar ICH - 4% annual recurrence

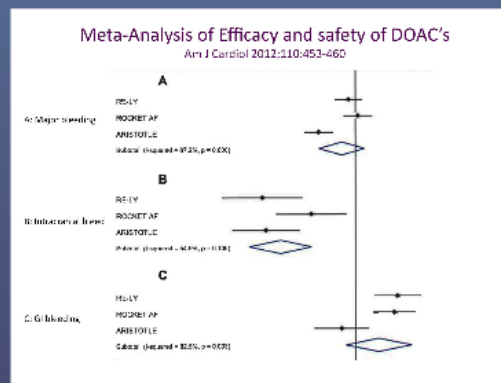


## Alternatives to anticoagulation



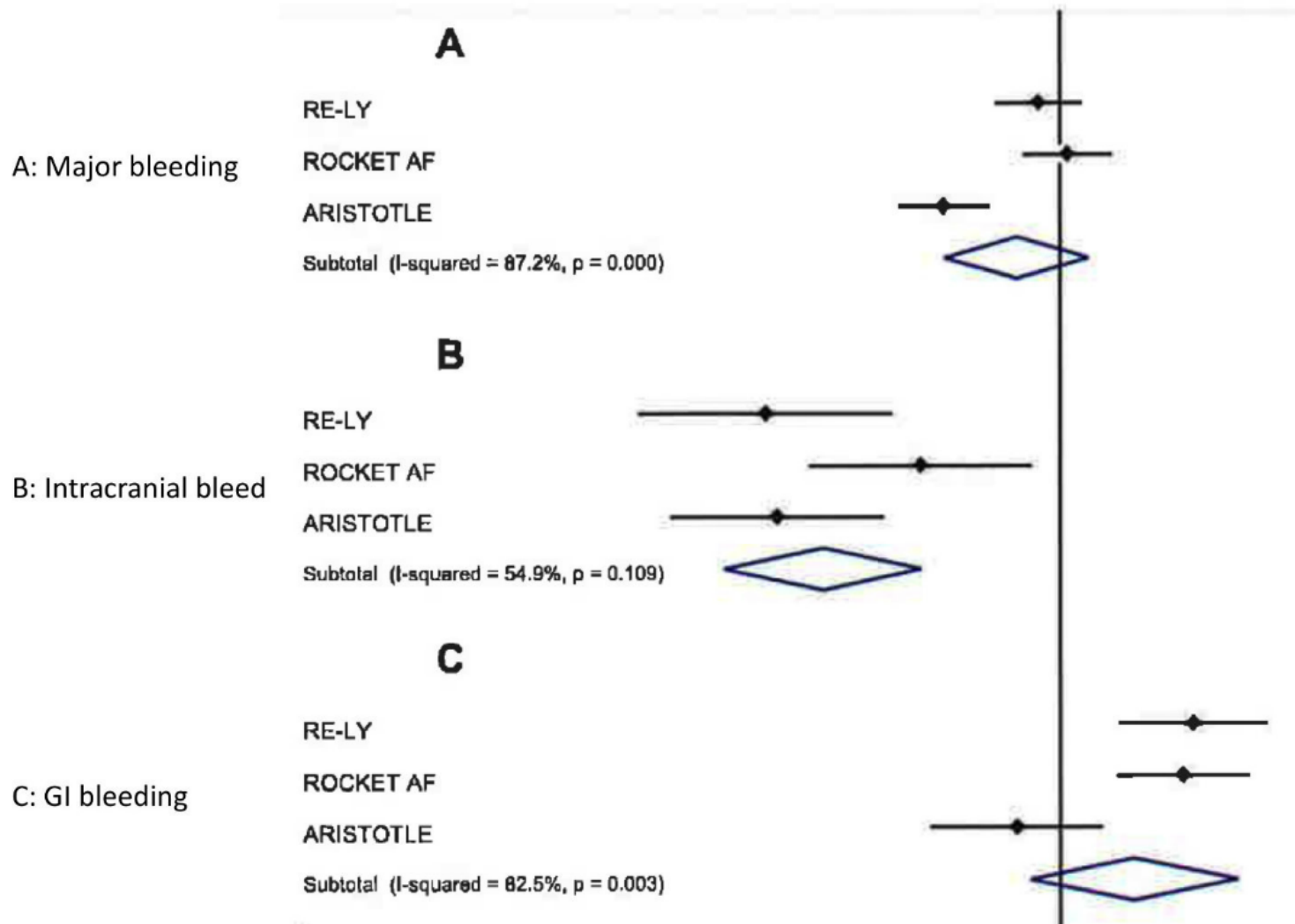
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# Meta-Analysis of Efficacy and safety of DOAC's

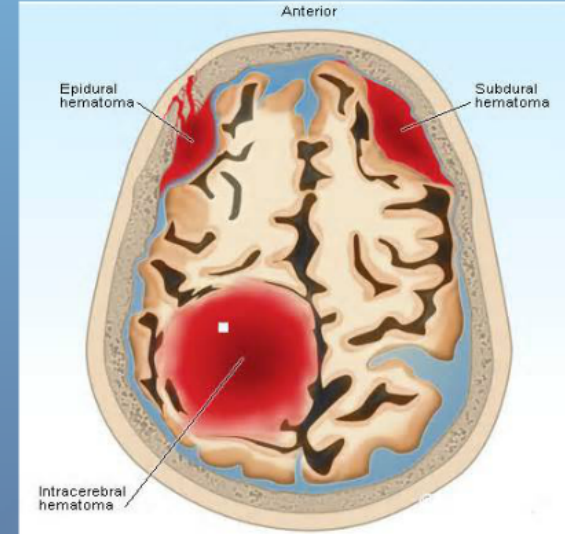
Am J Cardiol 2012;110:453-460





# Intra-cranial bleeding

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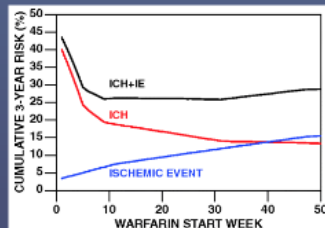


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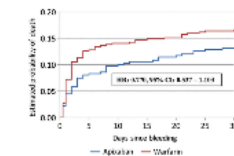
Stroke. 2010;41:2860-2866

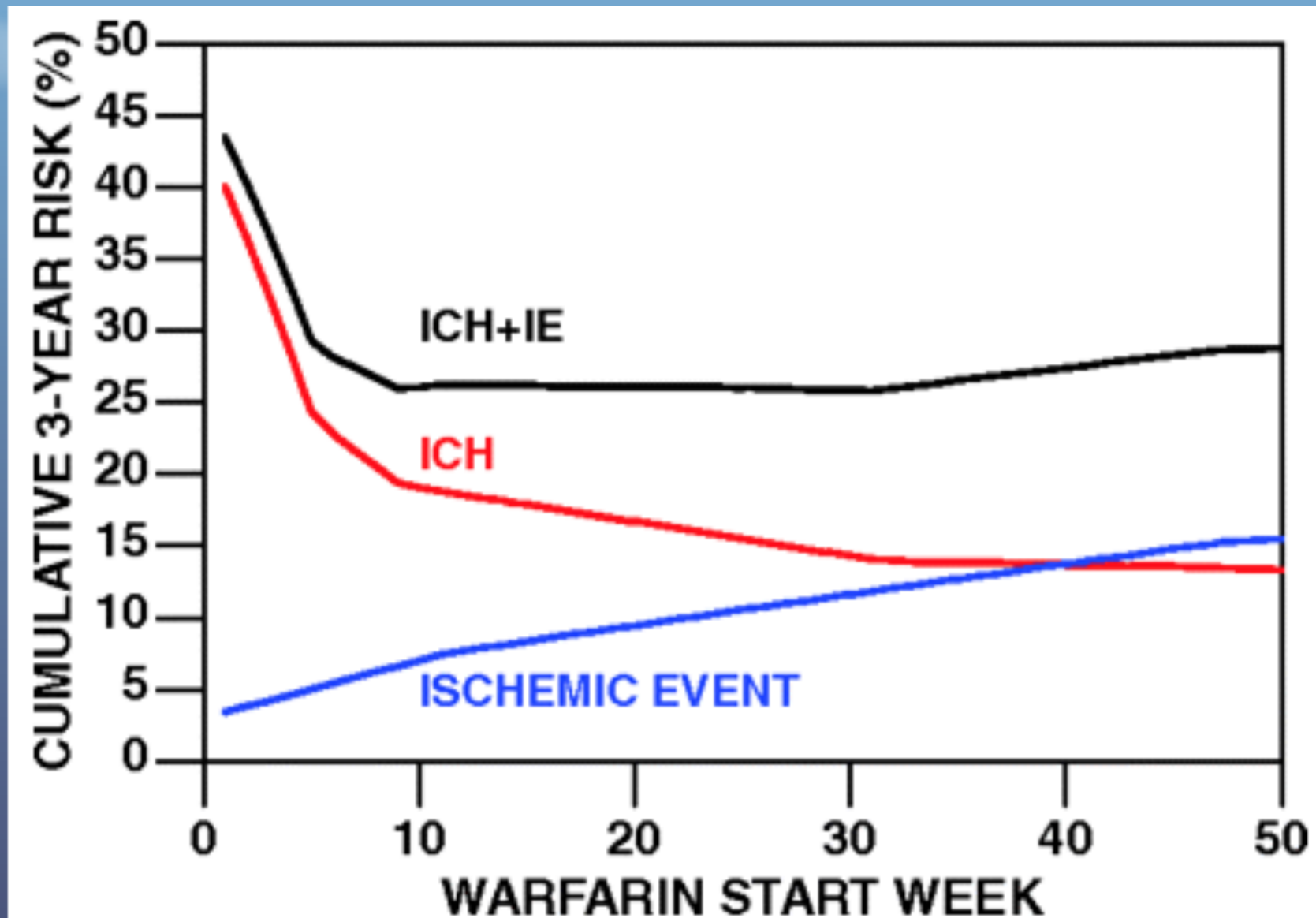


## Outcome of bleeding on DOAC vs VKA

A cause death after major bleeding in Atrial Fibrillation: a comparison of DOACs and VKAs

Stroke. 2015;46:1000-1005



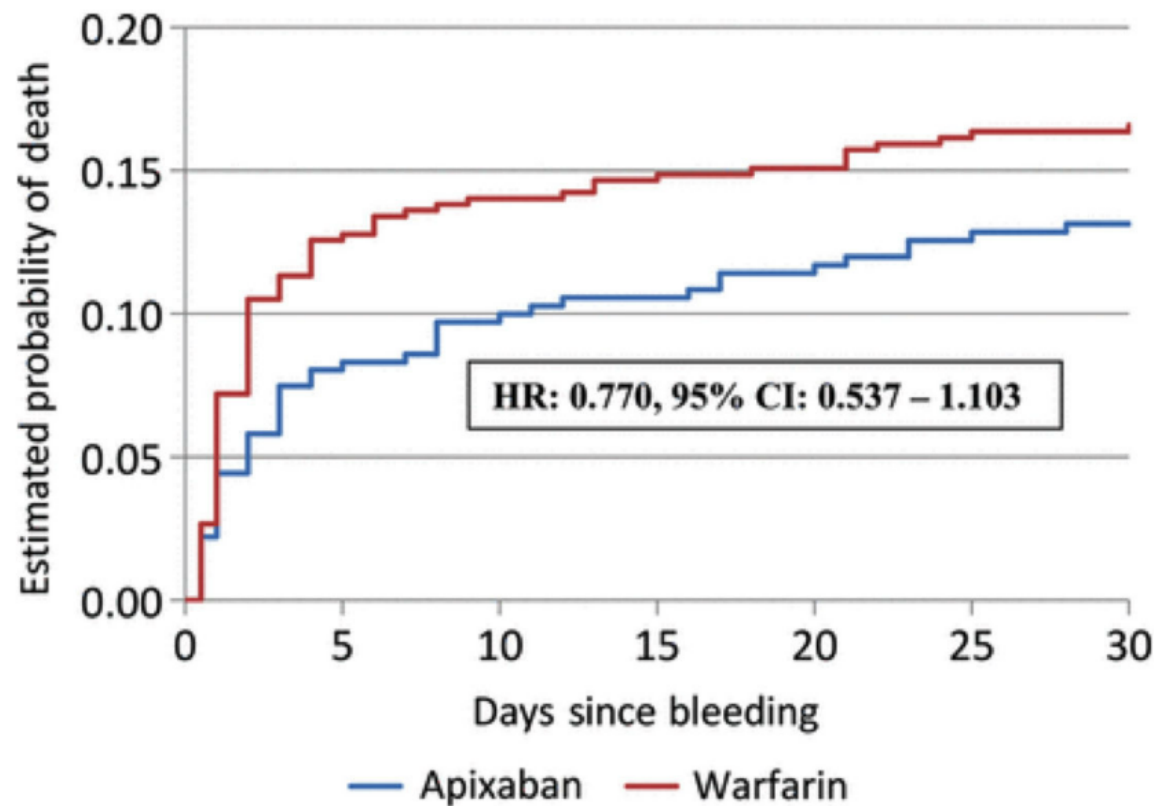


# Outcome of bleeding on DOAC vs VKA

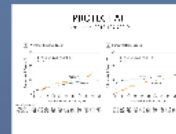
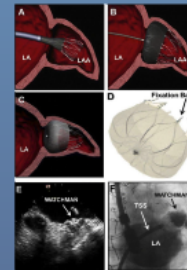
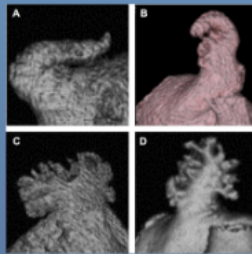
All cause death after major bleeding in ARISTOTLE trial

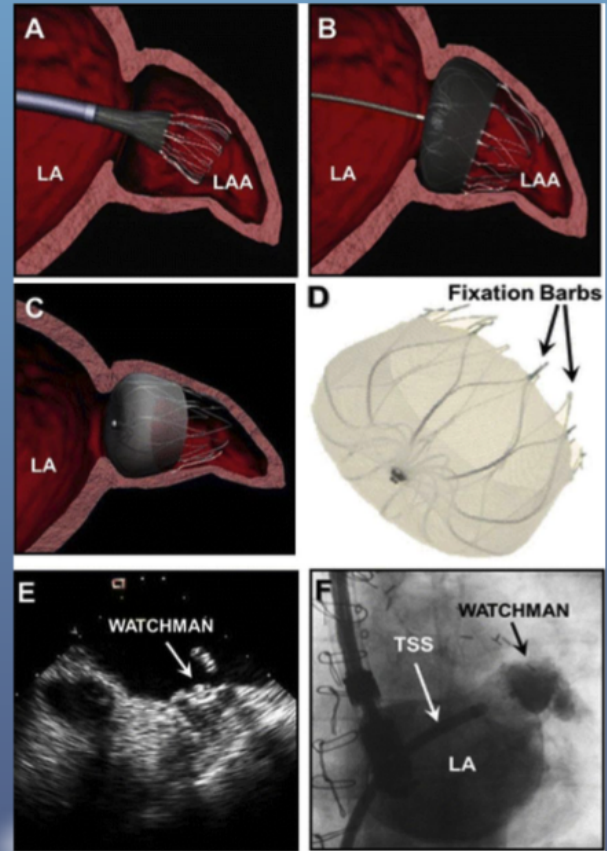
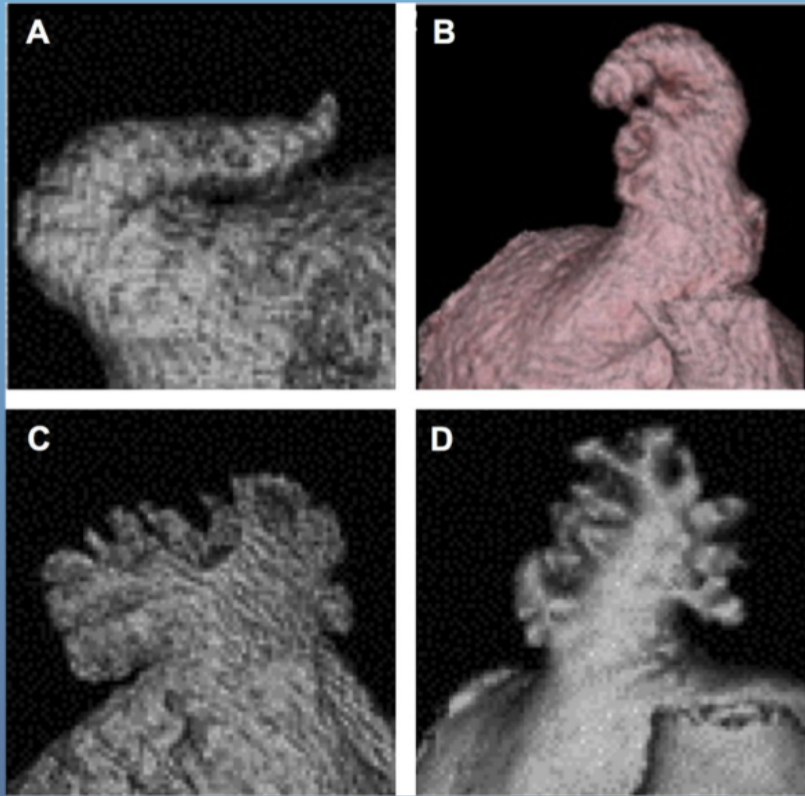
Held et al 2014 European Heart Journal

<http://dx.doi.org.ezproxye.bham.ac.uk/10.1093/eurheartj/ehu463>



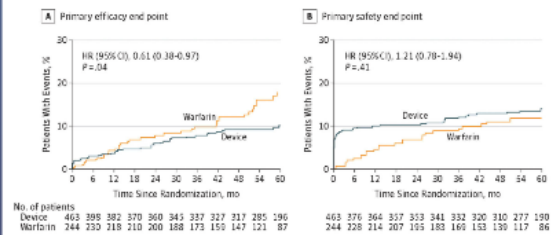
# Alternatives to anticoagulation





## PROTECT AF

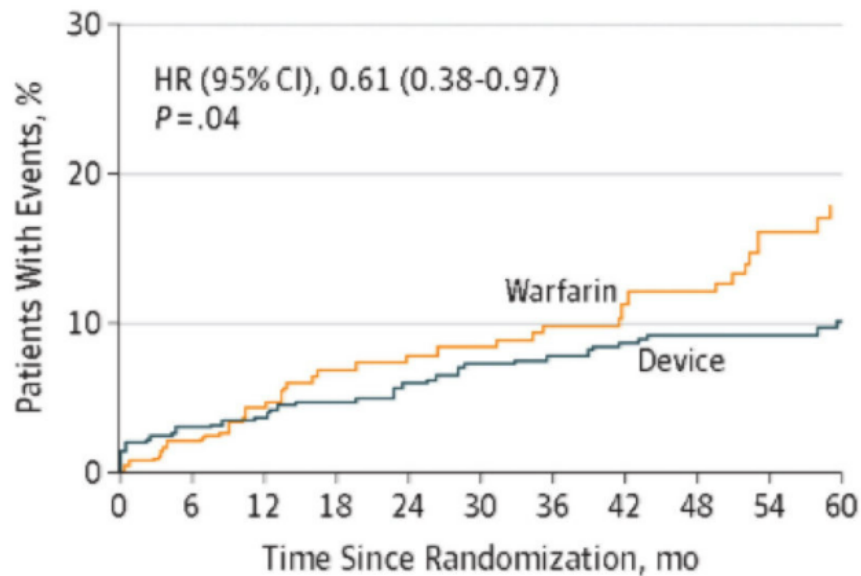
Circulation. 2013;127:720-9



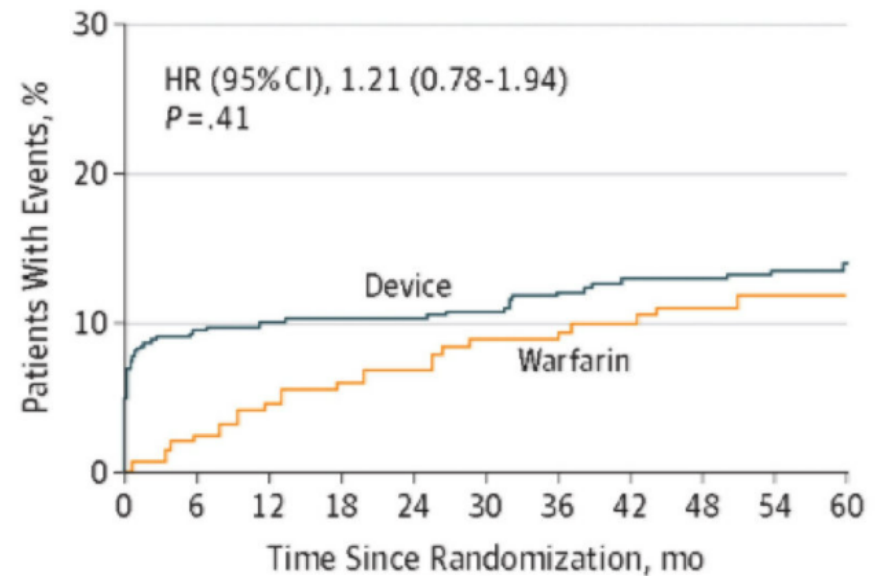
# PROTECT AF

Circulation. 2013;127:720-9

**A** Primary efficacy end point



**B** Primary safety end point



No. of patients

Device	463	398	382	370	360	345	337	327	317	285	196
Warfarin	244	230	218	210	200	188	173	159	147	121	87

Device	463	376	364	357	353	341	332	320	310	277	190
Warfarin	244	228	214	207	195	183	169	153	139	117	86

# Summary

- The application of trial data to frail patients with multiple co-morbidities is a conundrum
- Assessing benefits and risks of anticoagulation in patients at high risk of bleeding is complex as the risks of thrombosis is also increased eg. chronic kidney disease
- Co-prescription of oral anticoagulants with anti-platelet agents should be avoided unless essential
- Some forms of oral anticoagulation may be more appropriate in certain circumstances eg. renal failure, GI bleeding, intracranial bleeding
- Alternatives to anticoagulation may sometimes be available eg. atrial appendage occlusion devices



# Anticoagulation in frail and complex patients

Dr Will Lester

**Frailty**





In over 20 years in the UK (2000)  
Over 9 million the number aged >80 years  
Five quadruple aged >85 years  
Eightfold increase aged >100 years



**What to do after bleeding?**






- Anticoagulation in the frail
- Restarting anticoagulation after a bleed
- Oral anticoagulants combined with anti-platelet drugs





**Oral anticoagulants and anti-platelet drugs**

ALL combinations are associated with a higher risk of bleeding





**Chronic kidney disease and falls**

**Summary**

- The application of real data to frail patients with multiple comorbidities is a challenge
- Assessing benefits and risks of anticoagulation in patients at high risk of bleeding is complex as the risks of thrombosis is also increased eg. chronic kidney disease
- Co-prescription of oral anticoagulants with anti-platelet agents should be avoided unless essential
- Some forms of oral anticoagulation may be more appropriate in certain circumstances eg. renal failure or bleeding (intermittent bleeding)
- Alternatives to anticoagulation may sometimes be available eg. distal athero-occlusion devices