October 16 - 18
14th EDITION 2015

Pfizer Luncheon Panel

The anticoagulation journey continues: the dilemma of thrombosis versus bleeding

Venice, 16 October 2015

Challenging practical situations

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MY CONFLICTS OF INTEREST ARE:

Lecture fees from

- Bristol-Myers Squibb
- Pfizer
- Bayer Healthcare

Clinical scenario 1

Patient: Elizabeth

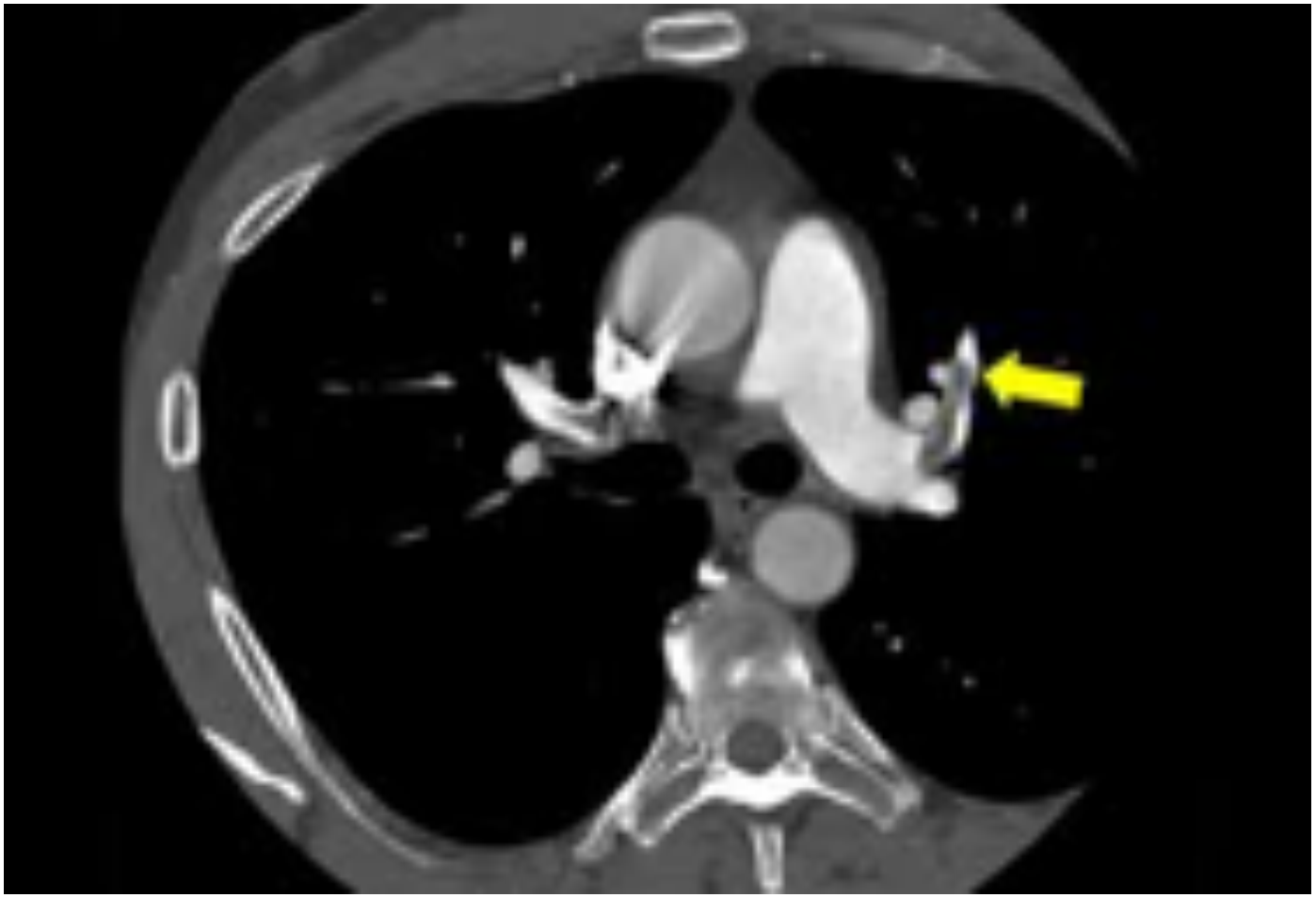
Informazioni personali	
Gender	Female
Age	63 years
Weight	71 kg
Blood pressure	118/78 mmHg
HZ	105 bpm
O_2 saturation	96%
Renal function	eGFR: 90 ml/min

Anamnesis	
Medical History	• Pulmonary embolism 5 years ago (treated with warfarin, but it was interrupted for a low TTR)
Treatment	• Nothing

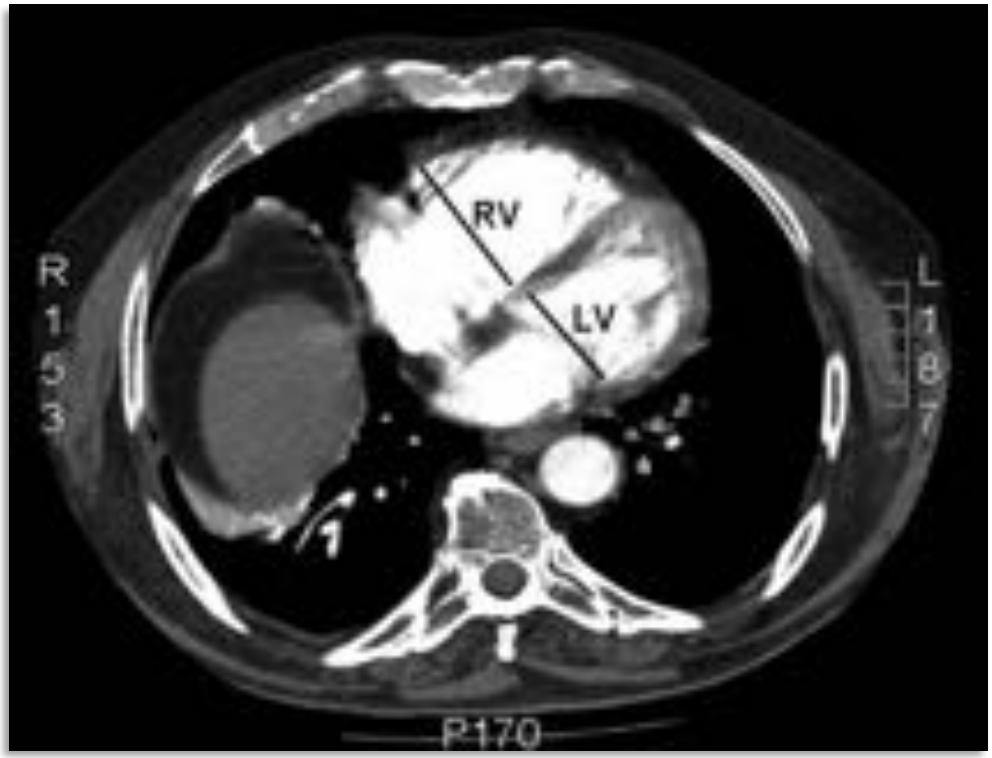
Signs and symptoms

- Sudden onset of breathlessness and chest pain
- Chest Rx: normal
- EKG: normal
- Blood test: troponin and NT-proBNP in the normal range

CTPA



Normal RV/LV ratio (< 0.9)



Konstantinides S. et al Eur Heart J. 2014 Nov 14;35(43):3033-69

ESC guidelines 2014 - recommendations

Early mortality risk		Risk parameters and scores			
		Shock or Hypotension	PESI class III-V or sPESI ≥1[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate-high	-	+	Both positive	
	Intermediate-low	-	+	Either one (or none) positive[e]	
Low		-	-	Assessment optional; if assessed, both negative[e]	

Konstantinides S. et al Eur Heart J. 2014 Nov 14;35(43):3033-69

Question 1

Calculate the PESI score

1. Low risk (class I and II)
2. High risk (class > II)
3. Very high risk
4. Impossible to calculate

Enough information	
Gender	Female
Age	63 years
Weight	71 kg
Blood pressure	118/78 mmHg
HZ	105 bpm
O_2 saturation	96%
Renal function	eGFR: 90 ml/min

PESI

Variable	Points
Age	1/year
Male sex	10
Cancer	30
Heart failure	10
Chronic lung disease	10
Heart rate >110/min	20
Systolic blood pressure <100 mmHg	30
Respiratory rate ≥30/min	20
Body temperature <36°C	20
Disorientation, lethargy, stupor, coma	60
SaO_2 <90%	20

Data are from reference 214.
Risk categories (30-day all-cause mortality, %): class I, <65 points (0%); class II, 66–85 points (1%); class III, 86–105 points (3.1%); class IV, 106–125 points (10.4%); class, V >125 points (24.4%). Low risk = classes I and II (0–1%).
SaO_2 = pulsoximetry.

Aujesky et al; Eur Heart J 2006

Question 1

Calculate the PESI score

1. Low risk (class I and II)
2. High risk (class > II)
3. Very high risk
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Informazioni personali	
Gender	Female
Age	63 years
Weight	71 kg
Blood pressure	118/78 mmHg
HZ	105 bpm
O_2 saturation	96%
Renal function	eGFR: 90 ml/min

Question 2

- Diagnosis of recurrent PE
- Normal blood pressure

….

How to manage Elisabeth ?

1. Primary reperfusion (thrombolysis)
2. Anticoagulant drug based on reperfusion therapy
3. Anticoagulant drug and hospital admission
4. Anticoagulant drug and short hospital stay/complete home treatment

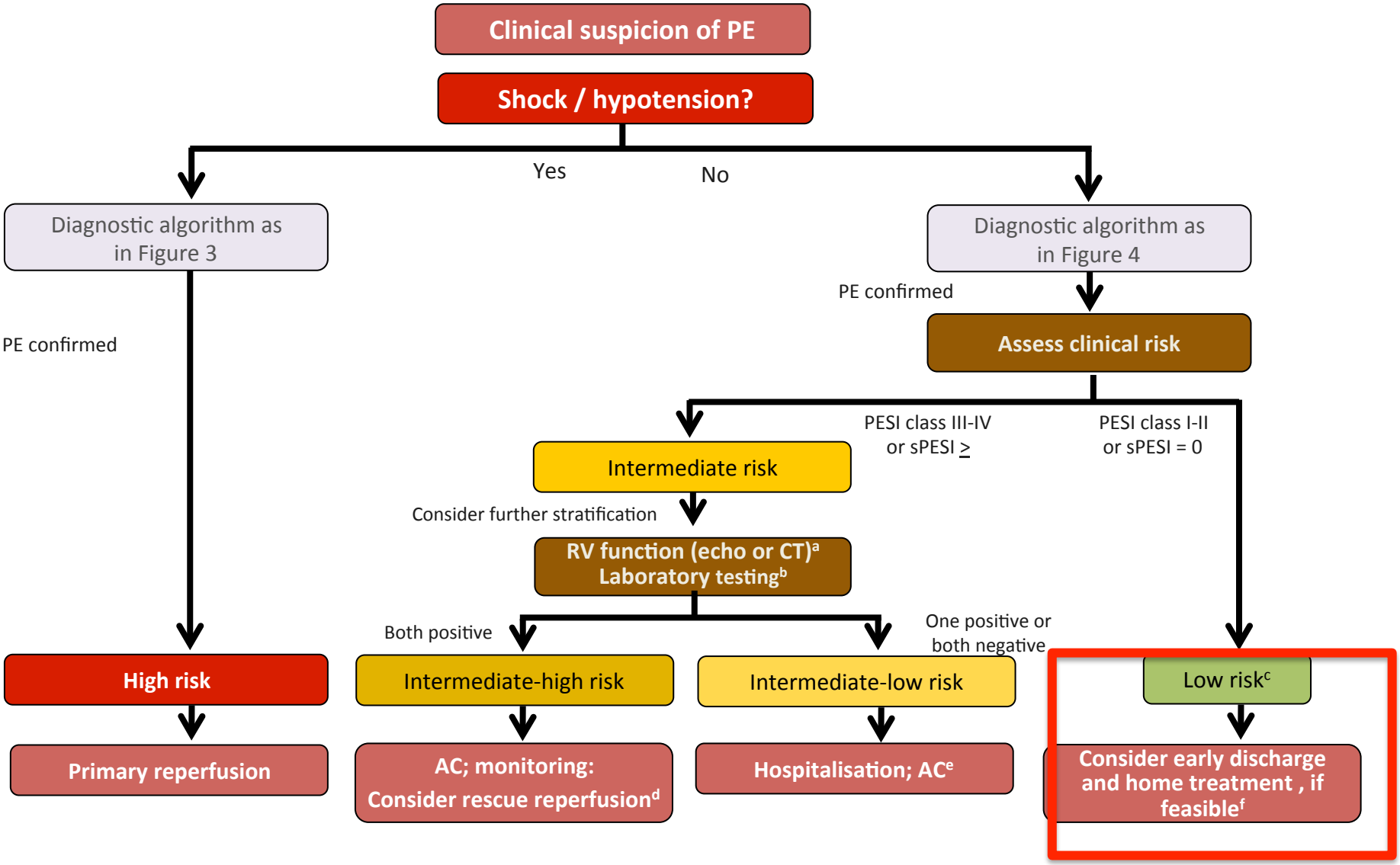
ESC guidelines 2014 recommendations

Recommendations	Class[a]	Level[b]
Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension.	III	B
Close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of 'rescue' reperfusion therapy.	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[c]	IIb	C
Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[c]	IIb	B

[a] Class of recommendation.
[b] Level of evidence.
[c] If appropriate expertise and resources are available on site.

Konstantinides S. et al Eur Heart J. 2014 Nov 14;35(43):3033-69

ESC 2014 - guidelines



Konstantinides S. et al Eur Heart J. 2014 Nov 14;35(43):3033-69

Question 2

- Diagnosis of recurrent PE
- Normal blood pressure

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How to manage Elisabeth ?

1. Primary reperfusion (thrombolysis)
2. Anticoagulant drug based on reperfusion therapy
3. Anticoagulant drug and hospital admission
4. Anticoagulant drug and short hospital stay/complete home treatment

Question 3

Which treatment to select ?

1. LMWH o fondaparinux as monotherapy
2. VKA
3. LMWH/fondaparinux + VKA
4. DOAC

ESC 2014 guidelines
Acute phase

Recommendations	Class[a]	Level[b]
PE without shock or hypotension (intermediate-or low-risk)		
Anticoagulation: combination of parenteral treatment with VKA		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress	I	C
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients	I	A
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0-3.0)	I	B

[a] Class of recommendation
[b] Level of evidence
* CAUTION: Edoxaban is currently subject to regulatory review for the treatment of venous thromboembolism in the European Union.

Konstantinides S. et al Eur Heart J. 2014 Nov 14;35(43):3033-69

Linee guida ESC 2014
Acute phase (cont'd)

Recommendations	Class[a]	Level[b]
PE without shock or hypotension (intermediate-or low-risk)		
Anticoagulation: new oral anticoagulants		
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) is recommended following acute phase parenteral anticoagulation.	I	B
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B
As an alternative to VKA treatment, administration of edoxaban* is recommended following acute-phase parenteral anticoagulation.	I	B

[a] Class of recommendation
[b] Level of evidence
* CAUTION: Edoxaban is currently subject to regulatory review for the treatment of venous thromboembolism in the European Union.

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Question 3

Which treatment to select ?

1. LMWH o fondaparinux as monotherapy
2. VKA
3. LMWH/fondaparinux + VKA
4. DOAC

Question 4

If your choice is a DOACs, which one ?

- Apixaban
- Dabigatran 110
- Dabigatran 150
- Rivaroxaban

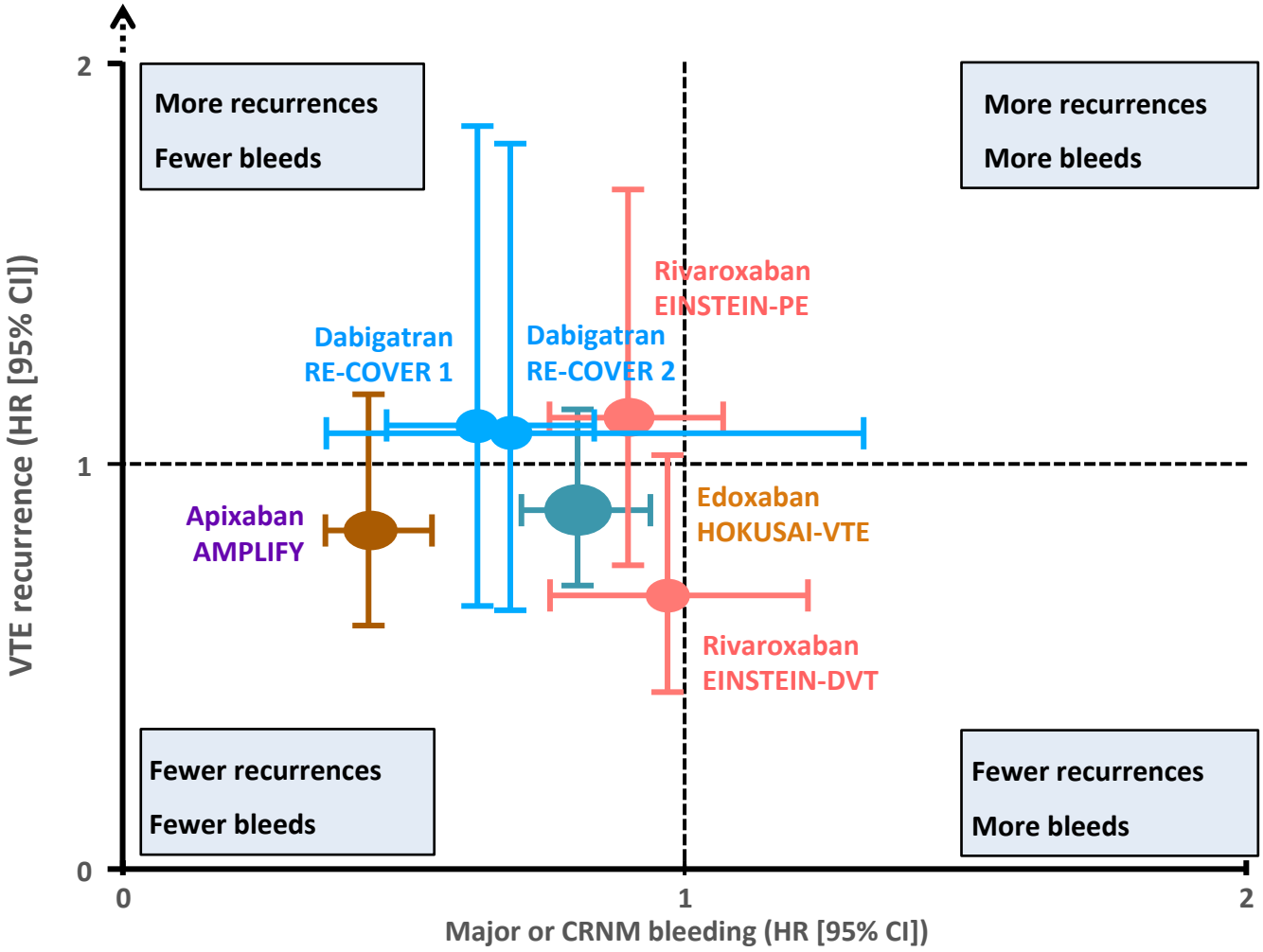
ESC 2014
Duration of secondary prevention

Recommendations	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.	I	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B
Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary).[c]	IIa	B[d]

[a] Class of recommendation.
[b] Level of evidence.
[c] Long-term data on patients taking new oral anticoagulants for secondary PE prophylaxis are not yet available.
[d] B refers to the evidence available for each drug separately.

Konstantinides S. et al Eur Heart J. 2014 Nov 14;35(43):3033-69

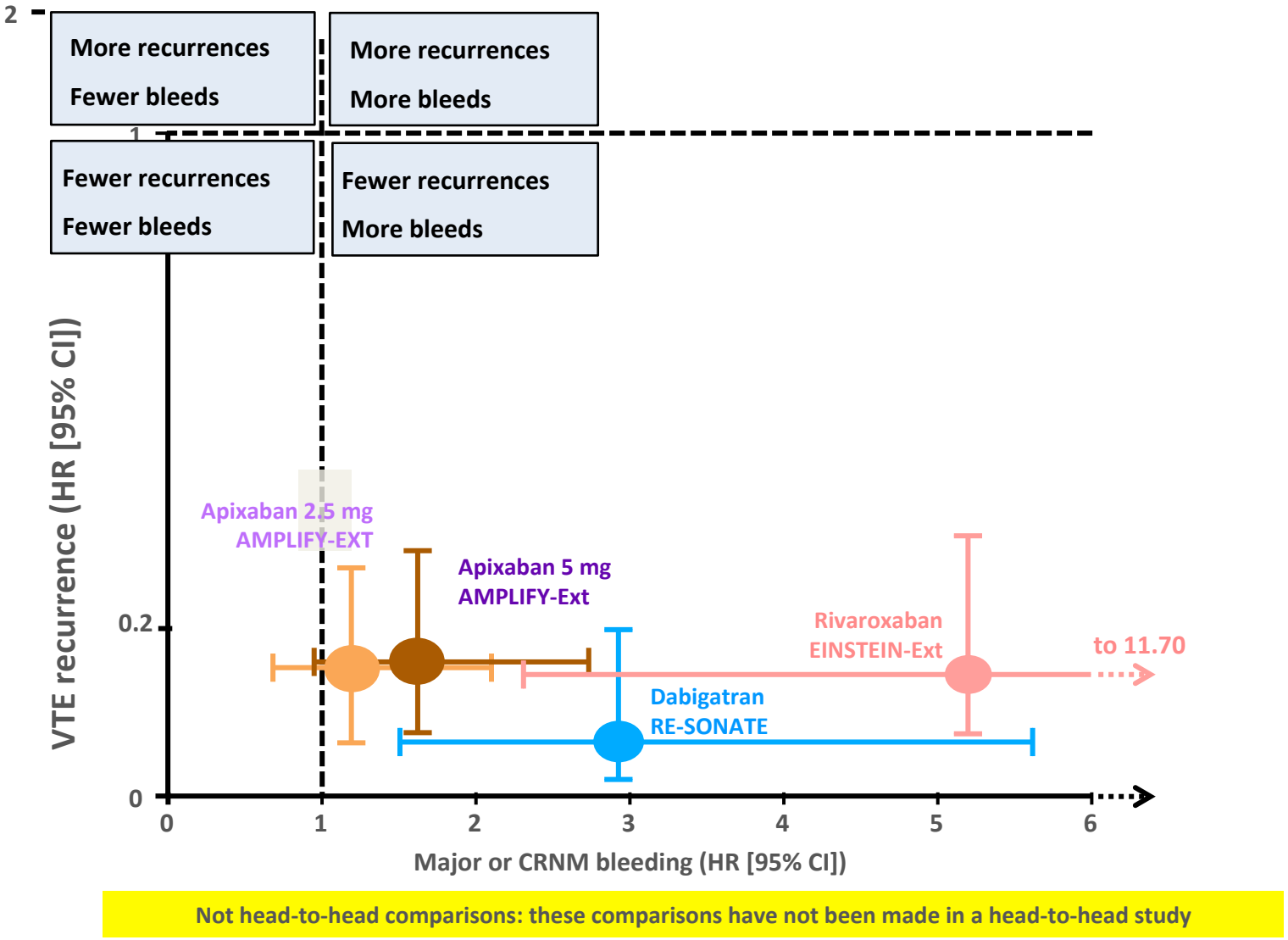
Efficacy and safety of NOACs vs. comparator in acute VTE



Not head-to-head comparisons: these comparisons have not been made in a head-to-head study

Cohen *et al.* Adv Ther 2014;31:473-93

Efficacy and safety of NOACs vs. placebo in extended VTE



Not head-to-head comparisons: these comparisons have not been made in a head-to-head study

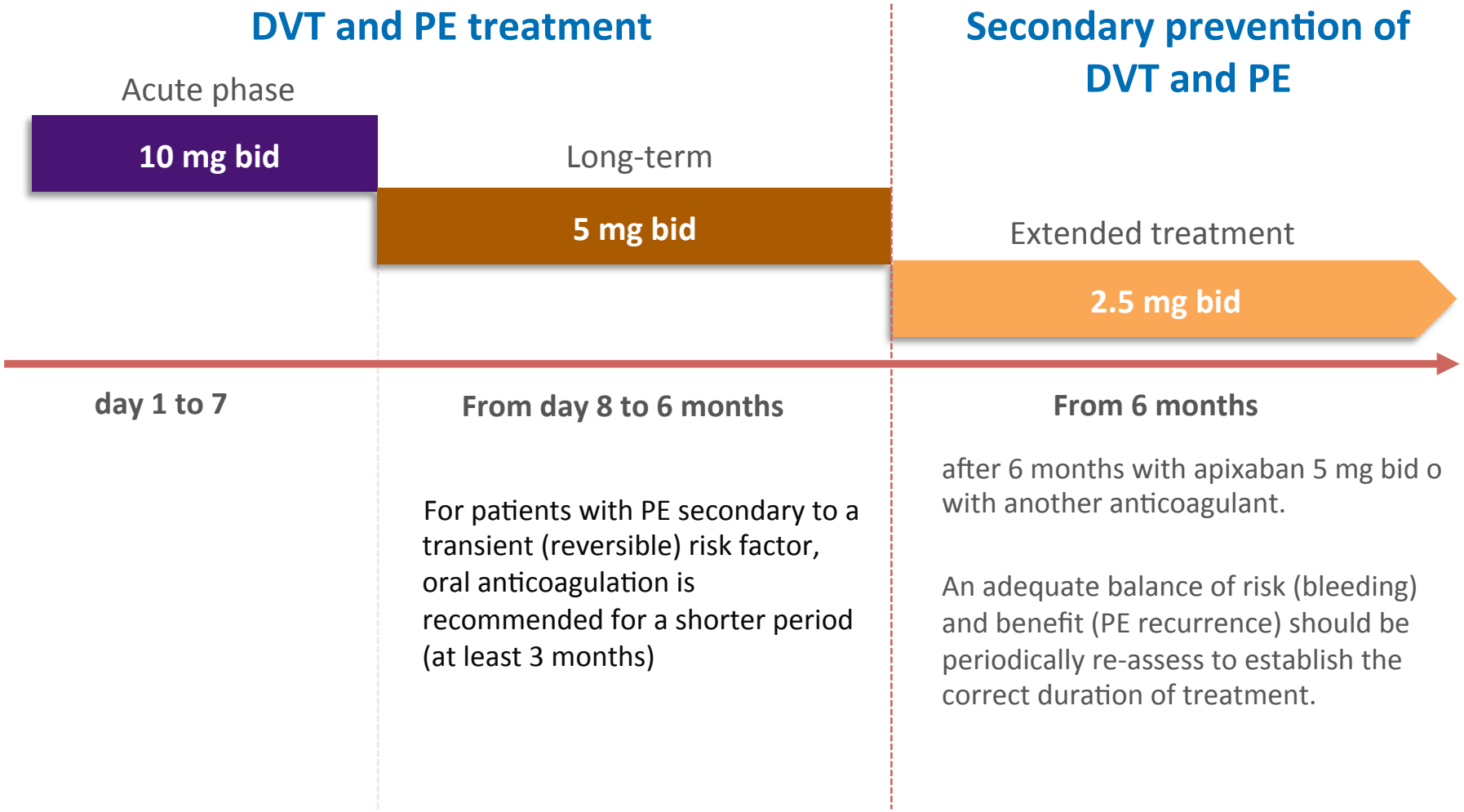
Cohen *et al.* Adv Ther 2014;31:473-93

Question 4

If your choice is a DOACs, which one ?

- Apixaban
- Dabigatran 110
- Dabigatran 150
- Rivaroxaban

Apixaban



Apixaban SmPC July 2014

major bleeding compared to warfarin [65]. Fatal haemorrhagic complications have been reported in elderly patients with low body weight and impaired renal function treated with dabigatran [66]. In patients with renal dysfunction (eGFR of 30–50 mL min^{-1}) enrolled in the ROCKET-AF trial, there were no significant differences between the primary end-point of stroke and systemic embolism, and rates of the principal safety end-point of major and clinically relevant nonmajor bleeding, between warfarin- and rivaroxaban-treated patients, although fatal bleeding occurred significantly less often in the rivaroxaban-treated group [67].

Apixaban is principally excreted via the biliary route. Subgroup analysis of the ARISTOTLE trial based on renal function demonstrated that apixaban was more effective than warfarin in the

patients regardless of renal fun
greatest relative risk reduction of
rhage was found in patients v
<50 mL min^{-1} [68]. This finding
apixaban may be a favourable ch
with renal impairment. Approxi
edoxaban is excreted renally. A fo
analysis of the ENGAGE AF-TIMI 4
renal function has yet to be publis

Elderly patients

The prevalence of AF rises with
epidemiological studies, the preva
estimated to be between 10.0%
patients over the age of 85 [69, 7
for stroke including hypertension
previous transient ischaemic attac
significantly more likely in elderly p

Clinical scenario: 2

Patient: Simon

Characteristics	
Gender	Man
Age	66 age
Weight	59 kg
Blood pressure	142/88 mmHg
HR	74 bpm
Creatinine	1,6 mg/dl
Creatinine clearance	38 ml/min

Anamnesis	
	• Hypertension on treatment for 10 years • Hypercholesterolemia on treatment for 4 years • **Parossistic NVAF (3-4 episodes in the last 2 years), on treatment with ASA** • **Dyspepsia for 6 months with diagnosis of jatal hernia, GE reflux with mild esophagitis**
Therapy	• Aspirin • Irbesartan/Idroclortiazide • Atorvastatin • Omeprazol

$CHADS_2$ and CHA_2DS_2-VASc

$CHADS_2$[1]	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	**6**

Created from Gage et al. JAMA.2001;285:2864–2870

CHA_2DS_2-VASc[2]	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Aged 65-74 years	1
Sex category (i.e. female gender)	1
Maximum score	**9**

1. Gage et al. *JAMA*.2001;285:2864–2870.
2. Lip et al. *CHEST*. 2010;137:263–272.

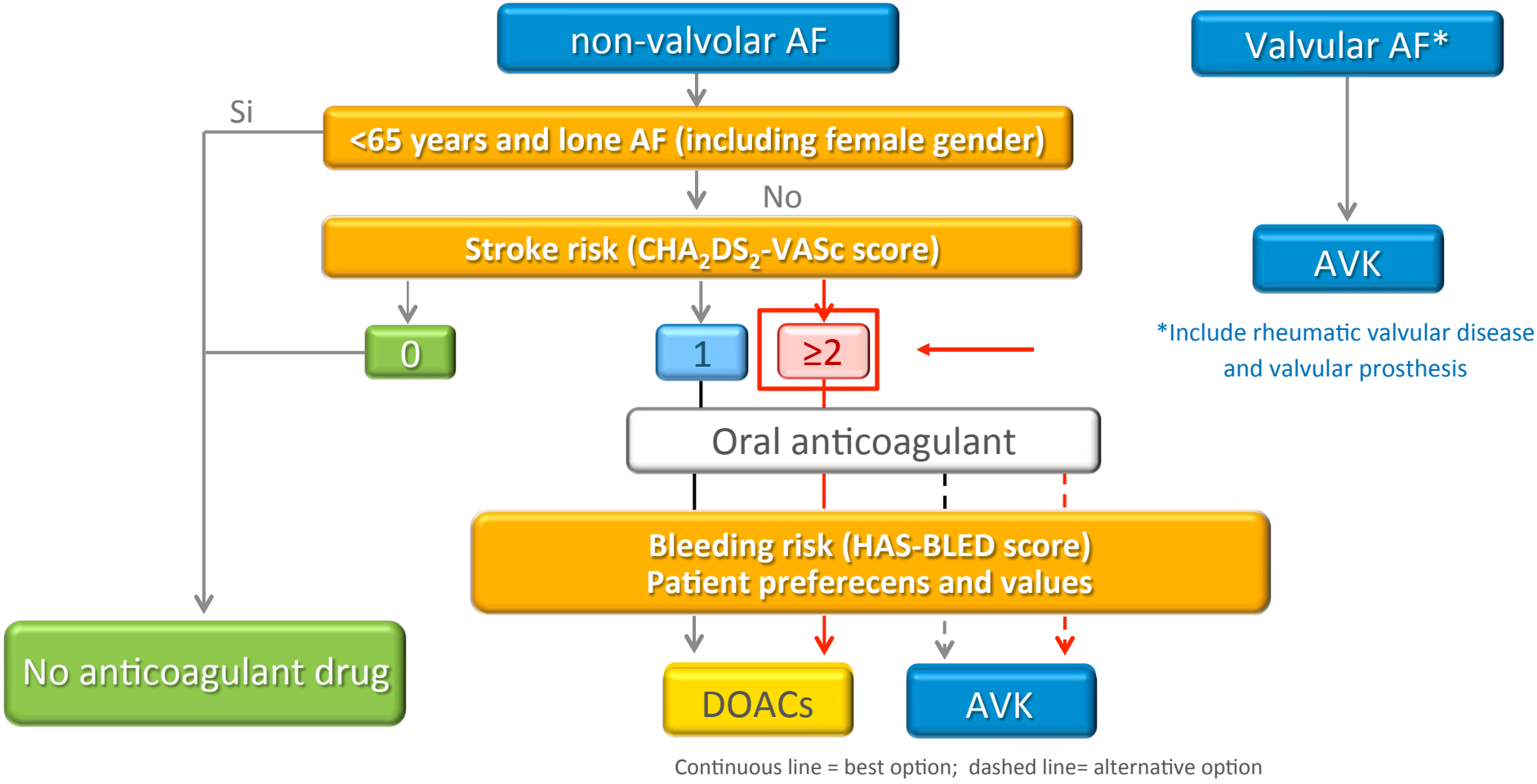
Outpatient Cardiology Clinic

The Cardiologist decides, according to recent ESC guidelines to start an oral anticoagulant instead of aspirin …

… which oral anticoagulant do you prefer to prescribe?

1. AVK
2. DOAC
3. I do not agree (ASA is better)

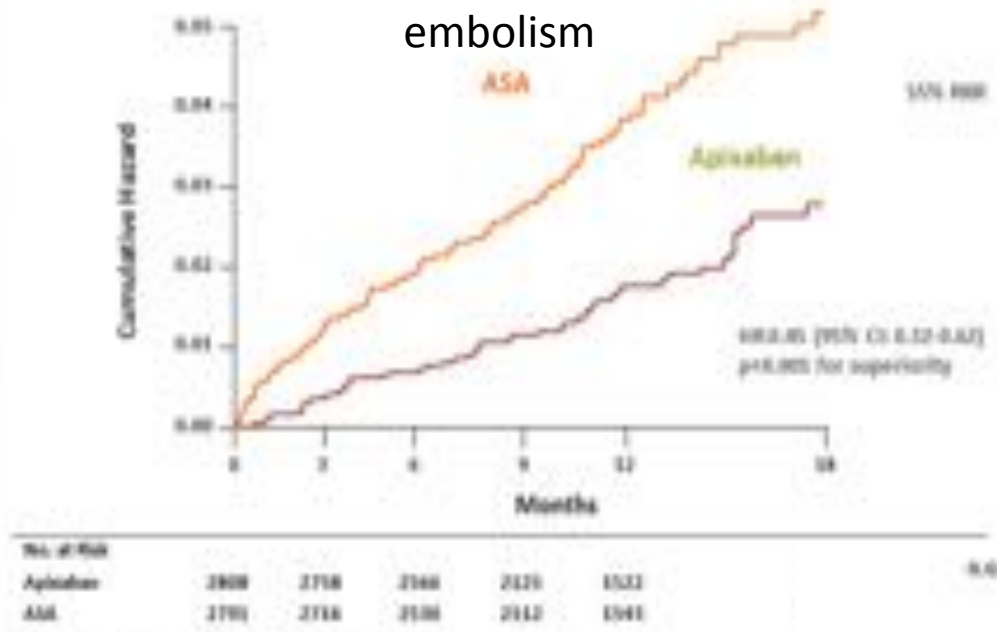
ESC 2012 – oral anticoagulant !



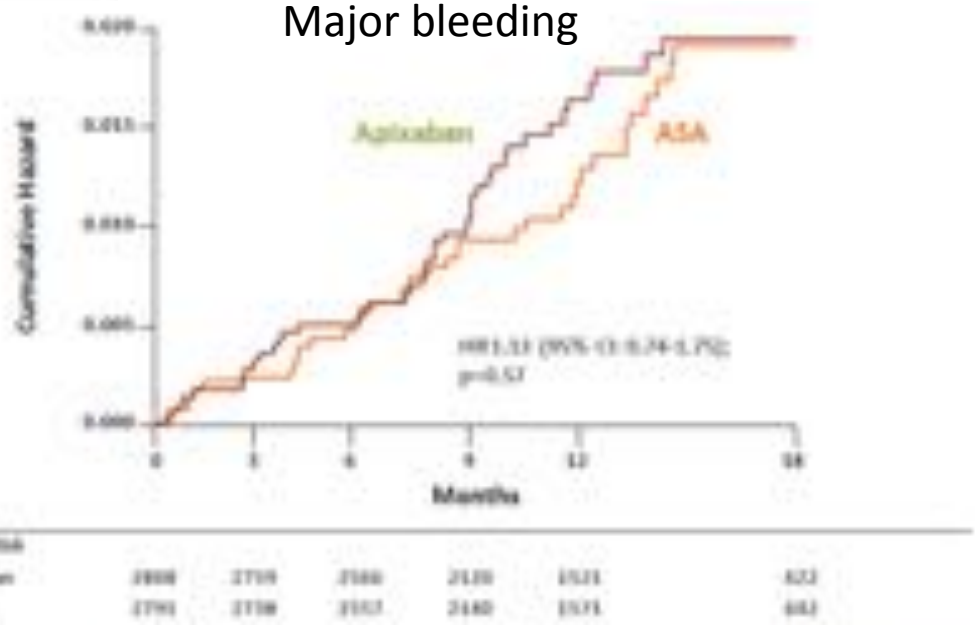
Camm et al. *Europace* 2012;14:1385–1413.

AVERROES: main results

Stroke or systemic embolism



Major bleeding

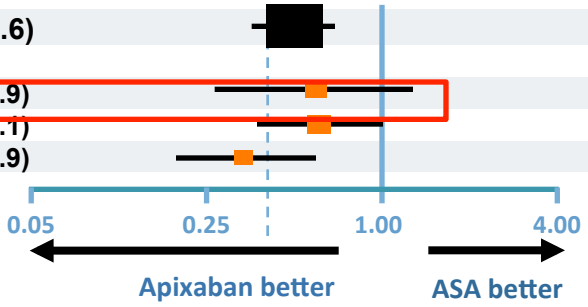


Connolly SJ et al. *N Engl J Med* 2011;364:806–817

AVERROES: main outcomes according to CHADS2 score

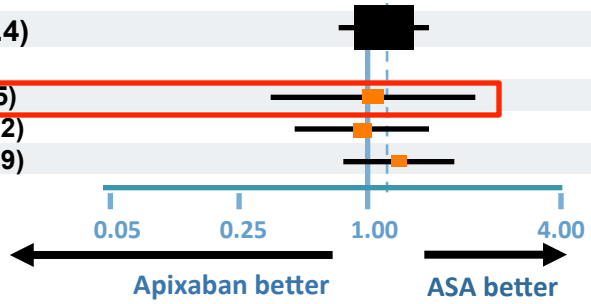
A. Stroke and Systemic Embolism

Characteristic	No. of patients	ASA	Apixaban	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
Overall	5599	113 (3.7)	51 (1.6)		
$CHADS_2$ score					0.23
0-1	2026	18 (1.6)	10 (0.9)		
2	1999	40 (3.7)	25 (2.1)		
≥ 3	1570	55 (6.3)	16 (1.9)		



B. Major Bleeding

Characteristic	No. of patients	ASA	Apixaban	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
Overall	5599	39 (1.2)	44 (1.4)		
$CHADS_2$ score					0.70
0-1	2026	6 (0.5)	6 (0.5)		
2	1999	14 (1.3)	14 (1.2)		
≥ 3	1570	19 (2.1)	24 (2.9)		



Adapted from Connolly et al. N Engl J Med 2011;364:806-17.

Editorial

"R" for "Renal" and for "Risk"

Refining Risk Stratification for Stroke in Atrial Fibrillation

Impaired renal function contributes to increased risk of stroke via procoagulant and inflammatory pathways and changes in arterial compliance/stiffness.

Camm J et al. Circulation 2013; 127:169-71

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Danish national registries

All patients discharged with NVAF between 1997 and 2008.

No Renal Disease (N=127,884)	Non–End-Stage Chronic Kidney Disease (N=3587)	Disease Requiring Renal-Replacement Therapy (N=901)

Stroke or systemic thromboembolism and bleeding associated with non–end-stage CKD and with end-stage chronic kidney disease

Olesen JB et al. NEJM 2012; 367:625-35

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Bleeding

Event	No. of Person-yr	No. of Events	Event Rate per 100 Person-yr (95% CI)
Bleeding			
No renal disease	457,605	16,195	3.54 (3.48–3.59)
Non–end-stage CKD	12,515	1,097	8.77 (8.26–9.30)
Disease requiring renal-replacement therapy	2,734	243	8.89 (7.84–10.08)

Olesen JB et al. NEJM 2012; 367:625-35

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Stroke or thromboembolism

Event	No. of Person-yr	No. of Events	Event Rate per 100 Person-yr (95% CI)
Stroke or thromboembolism			
No renal disease	461,734	16,648	3.61 (3.55–3.66)
Non–end-stage CKD	13,078	842	6.44 (6.02–6.89)
Disease requiring renal-replacement therapy	2,922	164	5.61 (4.82–6.54)

Olesen JB et al. NEJM 2012; 367:625-35

Predictor of **Stroke or thromboembolism** in **atrial fibrillation**

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

GFR < 60 ml/min **2**

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

Renal Dysfunction as a Predictor of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation: Validation of the R2CHADS2 Index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) Study Cohorts

R_2CHADS_2 Score	Overall (All Patients)	
	n	Rate at 3 y†
0	6826	0.425
1	8317	1.274
2	6361	2.201
3	5331	2.288
4	4346	3.313
5	2615	4.857
6	1002	4.992
7	324	6.167
8	63	7.913

R_2CHADS_2 score
in
ATRIA Study Cohort

Piccini JP et al. Circulation 2013; 127:224-232

Outpatient Cardiology Clinic

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… which oral anticoagulant do you prefer to prescribe?

1. AVK
2. DOAC
3. I do not agree (ASA is better)

Outpatient Cardiology Clinic

If you select Apixaban, at which dose ?

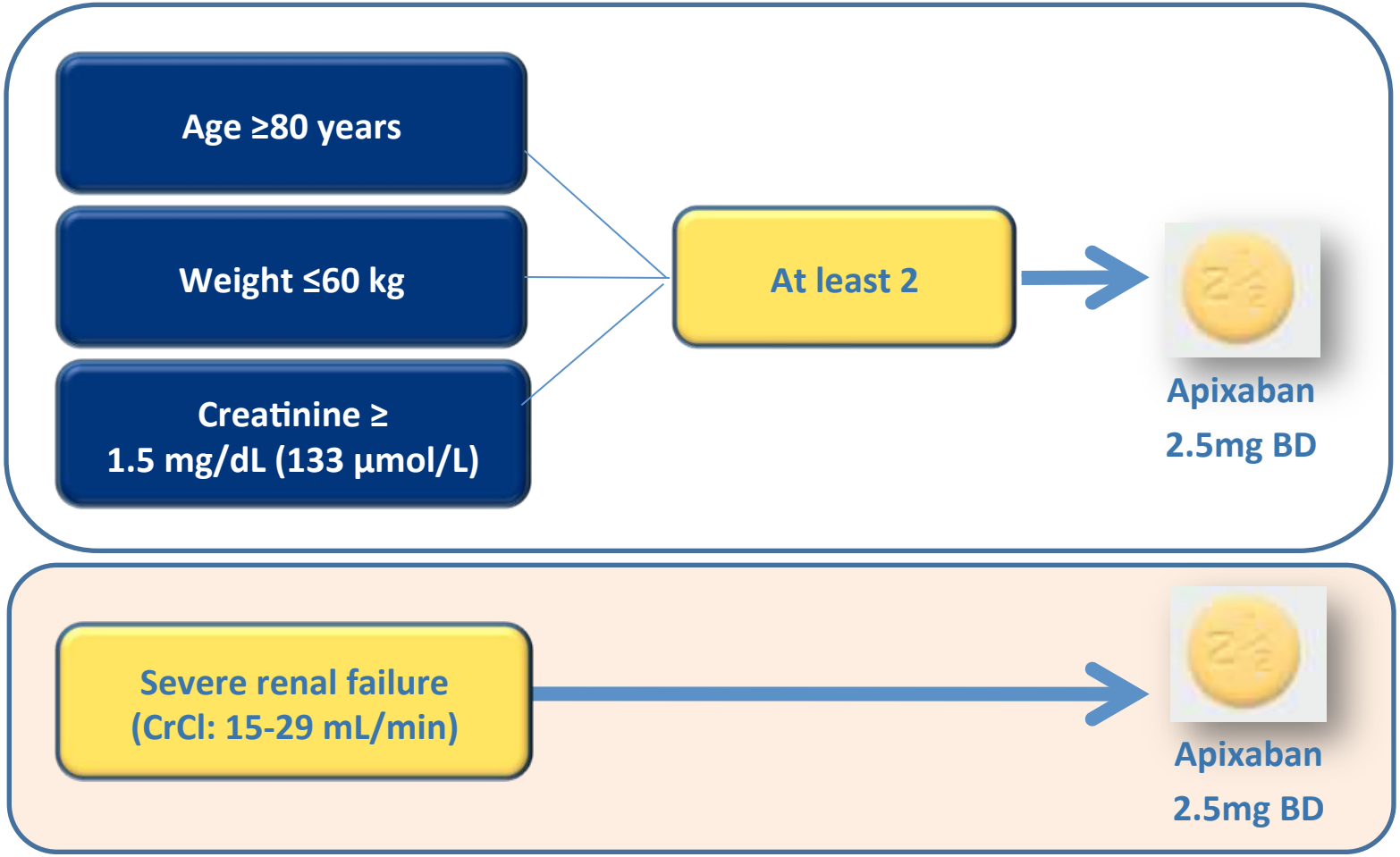
1. 5 mg bid
2. 2.5 mg bid
3. 5 mg once daily
4. 2.5 mg once daily

Funzione renale

of absorbed dose				
Bioavailability	3–7%	50%	62%[51]	66% witho Almost 10 food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ . . .	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/r
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 no adju (i.e. 20 mg
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when C 15–49
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 1

Red: contra-indicated/not recommended. **Orange**: reduce dose as per label. **Yellow**: consider dose reduction if two or more 'yellow' factors are present (see als
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.
[a]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine >1.5 mg/dL.
[b]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients wi
after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.
[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the Euro
for AF indication.

Dose reduction of Apixaban for NVAF



Apixaban RCP 2014

Outpatient Cardiology Clinic

At which dose shall we prescribe Apixaban?

1. 5 mg bid
2. 2.5 mg bid
3. 5 mg once daily
4. 2.5 mg once daily

major bleeding compared to warfarin [65]. Fatal haemorrhagic complications have been reported in elderly patients with low body weight and impaired renal function treated with dabigatran [66]. In patients with renal dysfunction (eGFR of 30–50 mL min^{-1}) enrolled in the ROCKET-AF trial, there were no significant differences between the primary end-point of stroke and systemic embolism, and rates of the principal safety end-point of major and clinically relevant nonmajor bleeding, between warfarin- and rivaroxaban-treated patients, although fatal bleeding occurred significantly less often in the rivaroxaban-treated group [67].

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Elderly patients

The prevalence of AF rises with
epidemiological studies, the preva
estimated to be between 10.0%
patients over the age of 85 [69, 7
for stroke including hypertension
previous transient ischaemic attac
significantly more likely in elderly p