

Antikoaguláns kezelés a Kardiológiában

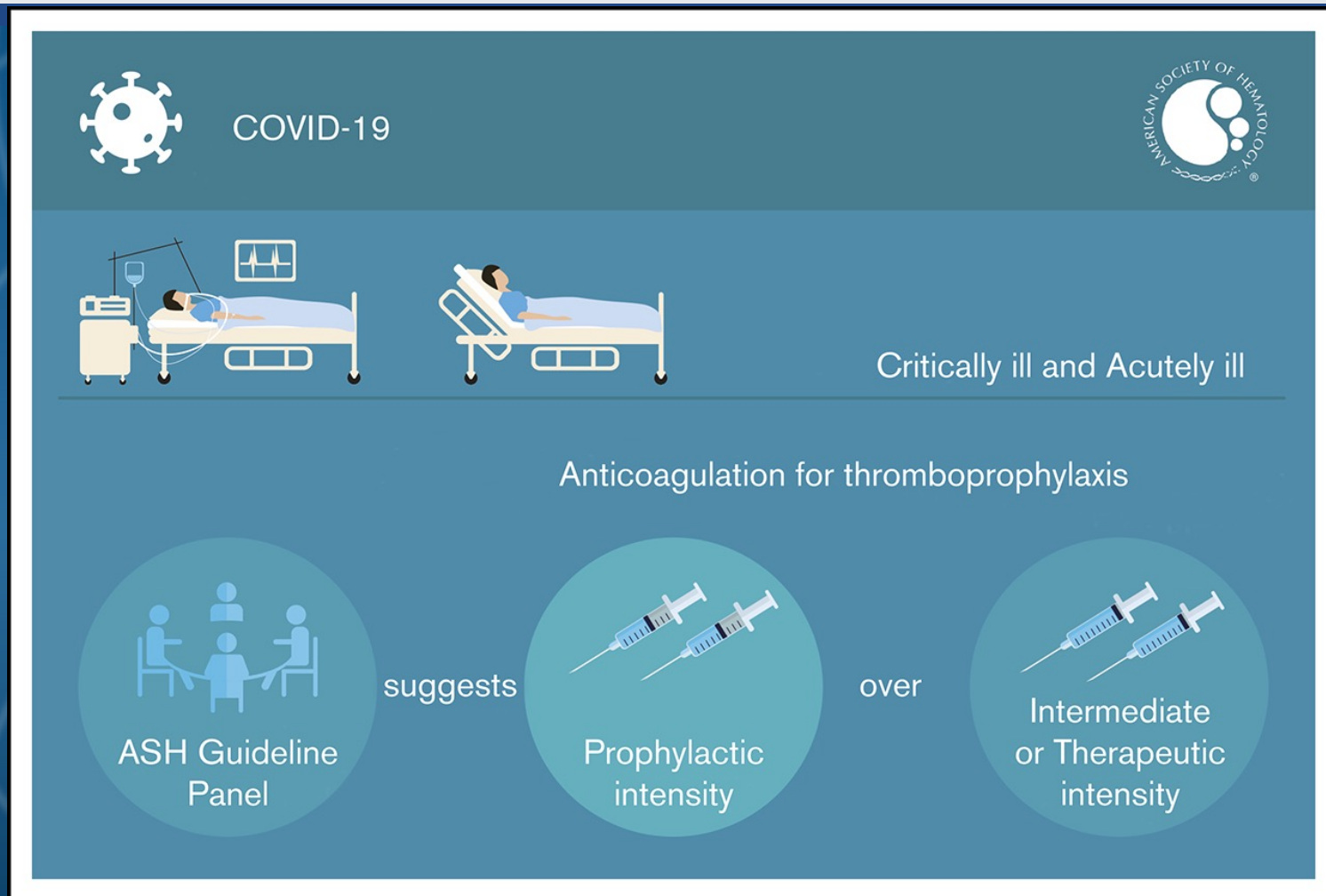
Dr. Habon Tamás
I. sz. Belgyógyászati Klinika



Az anticoaguláns kezelés indikációi

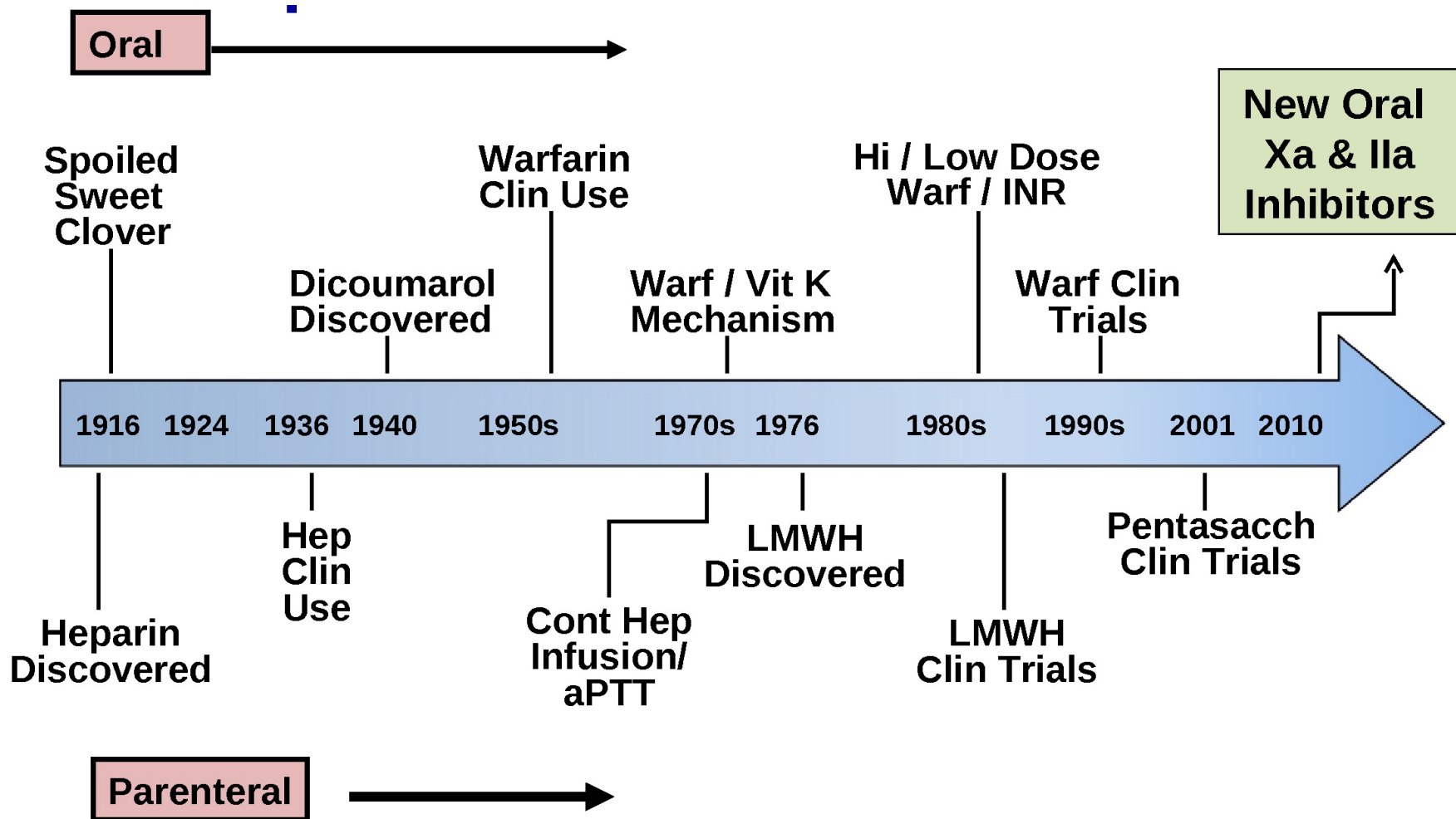
- Thrombophilia
- Antiphospholipid syndrome
- Perifériás érműtétek
- Paroxysmal nocturnal haemoglobinuria
- Daganatos betegségek (LMWH)
- Perioperatív állapotok, immobilizáció
- Neurológiai indikációk
- ACS
- BK falmozgászavar ill. csökkent BKF (AMI, DCM)
- Vénás thromboemboliák
- Műbillentyű, Billentyűbetegségek
- Pitvarfibrillatio (cardioversio)

American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19

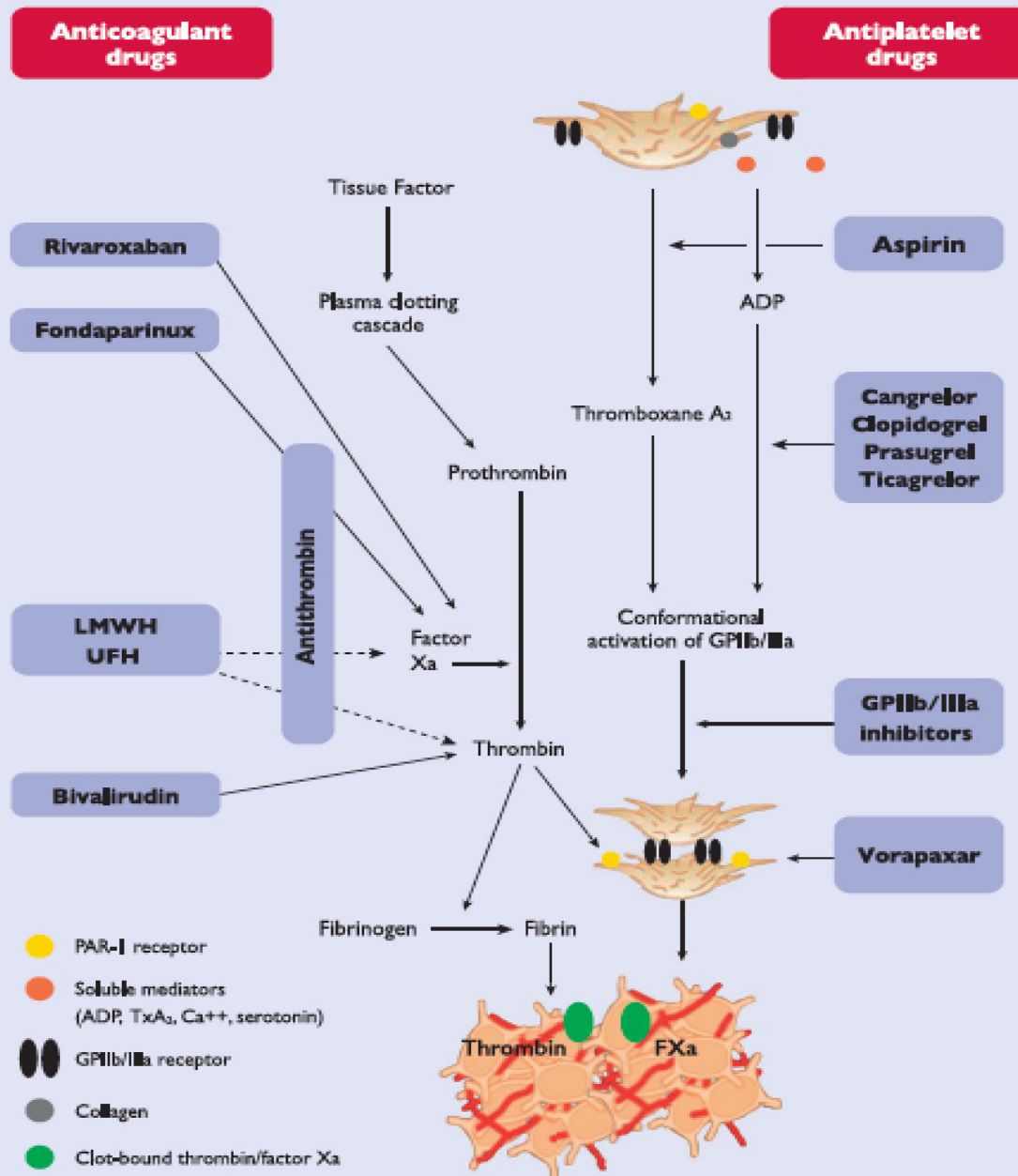


Adam Cuker, Eric K. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19, Blood Adv, 2021,

Antikoaguláns kezelés állomásai



Targets for antithrombotic drugs



ADP = adenosine diphosphate; AT = antithrombin; GP = glycoprotein; LMWH = low molecular weight heparin; Tx = thromboxane; UFH = Unfractionated heparin. Vorapaxar is a protease-activated receptor 1 (PAR1) blocker.

ACS - STEMI

Periprocedural and postprocedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention

Recommendations	Class	Level
Antiplatelet therapy		
A potent P2Y ₁₂ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.	I	A
Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received P2Y ₁₂ receptor inhibitors.	IIb	A

Periprocedural and postprocedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention

Recommendations	Class	Level
Anticoagulant therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.	I	C
Routine use of UFH is recommended.	I	C
In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.	I	C
Routine use of enoxaparin i.v. should be considered.	IIa	A
Routine use of bivalirudin should be considered.	IIa	A
Fondaparinux is not recommended for primary PCI.	III	B

Doses of antiplatelet and anticoagulant co-therapies in primary PCI(*continued*)

Doses of antiplatelet and parenteral anticoagulant co-therapies in primary PCI	
Parenteral anticoagulant therapies	
UFH	70-100 IU/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned 50-70 IU/kg i.v. bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg i.v. bolus.
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/hour for up to 4 hours after the procedure.

Doses of antiplatelet and anticoagulant co-therapies in not reperfused patients

Doses of antiplatelet and parenteral anticoagulant therapies in patients not receiving reperfusion therapy

Antiplatelet therapies

Aspirin	Loading dose of 150-300 mg orally followed by a maintenance dose of 75-100 mg/day.
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day orally.

Parenteral anticoagulant therapies

UFH	Same dose as with fibrinolytic therapy.
Enoxaparin	Same dose as with fibrinolytic therapy.
Fondaparinux	Same dose as with fibrinolytic therapy.

Fibrinolytic therapy

Recommendations	Class	Level
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the prehospital setting.	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, reteplase) is recommended.	I	B
A half-dose of tenecteplase should be considered in patients ≥ 75 years of age.	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Oral or i.v. aspirin is indicated.	I	B
Clopidogrel is indicated in addition to aspirin.	I	A
DAPT (in the form of aspirin plus a P2Y ₁₂ inhibitor) is indicated for up to 1 year in patients undergoing fibrinolysis and subsequent PCI.	I	C

Fibrinolytic therapy (*continued*)

Recommendations	Class	Level
Anticoagulation co-therapy with fibrinolysis		
Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I	A
• Enoxaparin i.v. followed by s.c. (preferred over UFH).	I	A
• UFH given as a weight-adjusted i.v. bolus followed by infusion.	I	B
• In patients treated with streptokinase: fondaparinux i.v. bolus followed by an s.c. dose 24 hours later.	IIa	B
Transfer after fibrinolysis		
Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis.	I	A

Fibrinolytic therapy (*continued*)

Recommendations	Class	Level
Interventions following fibrinolysis		
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock.	I	A
Rescue PCI is indicated immediately when fibrinolysis has failed (< 50% ST-segment resolution at 60-90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia.	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 hours after successful fibrinolysis.	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.	I	B

Doses of fibrinolytic agents and antithrombotic co-therapies

Drug	Initial treatment	Specific contra-indications
Doses of fibrinolytic therapy		
Streptokinase	1.5 million units over 30–60 min i.v.	Previous treatment with streptokinase or anistreplase
Alteplase (tPA)	15 mg i.v. bolus 0.75 mg/kg i.v. over 30 min (up to 50 mg) then 0.5 mg/kg i.v. over 60 min (up to 35 mg)	
Reteplase (rPA)	10 units + 10 units i.v. bolus given 30 min apart	
Tenecteplase (TNK-tPA)	Single i.v. bolus: 30 mg (6000 IU) if <60 kg 35 mg (7000 IU) if 60 to <70 kg 40 mg (8000 IU) if 70 to <80 kg 45 mg (9000 IU) if 80 to <90 kg 50 mg (10000 IU) if ≥90 kg It is recommended to reduce to half-dose in patients ≥75 years of age.	

Doses of fibrinolytic agents and antithrombotic co-therapies (*continued*)

Drug	Initial treatment	Specific contra-indications
Doses of anticoagulant co-therapies		
Enoxaparin	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 hours until revascularization or hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg per injection.	
	In patients ≥75 years of age: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg per injection for the first two s.c. doses. In patients with eGFR <30 mL/min/1.73 m ² , regardless of age, the s.c. doses are given once every 24 hours.	

Doses of fibrinolytic agents and antithrombotic co-therapies (*continued*)

Drug	Initial treatment	Specific contra-indications
UFH	60 IU/kg i.v. bolus with a maximum of 4000 IU followed by an i.v. infusion of 12 IU/kg with a maximum of 1000 IU/ hour for 24-48 hours. Target aPTT: 50-70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 hours.	
Fondaparinux (only with streptokinase)	2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge.	

Contra-indications to fibrinolytic therapy

Absolute

Previous intracranial haemorrhage or stroke of unknown origin at anytime.

Ischaemic stroke in the preceding 6 months.

Central nervous system damage or neoplasms or arteriovenous malformation.

Recent major trauma/surgery/head injury (within the preceding month).

Gastrointestinal bleeding within the past month.

Known bleeding disorder (excluding menses).

Aortic dissection.

Non-compressible punctures in the past 24 hours (e.g. liver biopsy, lumbar puncture).

Contra-indications to fibrinolytic therapy

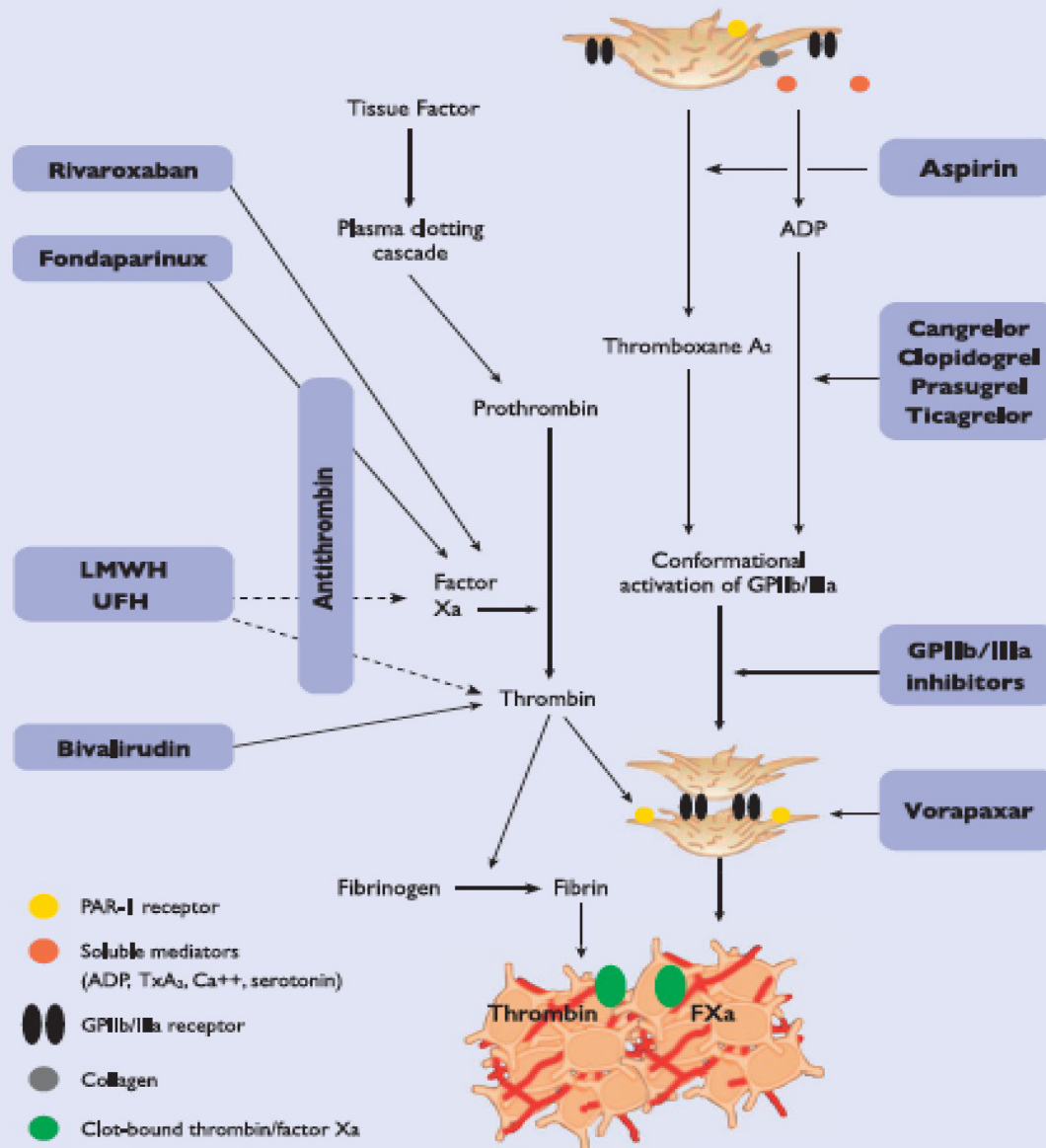
Relative
Transient ischaemic attack in the preceding 6 months.
Oral anticoagulant therapy.
Pregnancy or within 1 week postpartum.
Refractory hypertension (SBP >180 mmHg and/or DBP >110 mmHg).
Advanced liver disease.
Infective endocarditis.
Active peptic ulcer.
Prolonged or traumatic resuscitation.

ACS - NSTEMI

Targets for antithrombotic drugs

Anticoagulant drugs

Antiplatelet drugs



ADP = adenosine diphosphate; AT = antithrombin; GP = glycoprotein; LMWH = low molecular weight heparin; Tx = thromboxane; UFH = Unfractionated heparin. Vorapaxar is a protease-activated receptor 1 (PAR1) blocker.

Table 12 Suggested strategies to reduce bleeding risk related to PCI

- | |
|--|
| <ul style="list-style-type: none">• Anticoagulant doses adjusted to bodyweight and renal function, especially in women and elderly patients. |
| <ul style="list-style-type: none">• Radial approach preferred. |
| <ul style="list-style-type: none">• Proton pump inhibitors in patients on DAPT at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAIDs/corticosteroid use, or two or more among age ≥ 65 years, dyspepsia, gastrooesophageal reflux disease, <i>Helicobacter pylori</i> infection, and chronic alcohol use). |
| <ul style="list-style-type: none">• In patients on OAC<ul style="list-style-type: none">○ PCI performed without interruption of VKAs or NOACs.○ In patients on VKAs, do not administer UFH if INR value >2.5.○ In patients on NOACs, regardless of the timing of the last administration of NOACs, add additional low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg).○ Aspirin indicated but avoid pretreatment with P2Y₁₂ inhibitors.○ GPIIb/IIIa inhibitors only for bailout of periprocedural complications. |

Anticoagulation in NSTEMI-ACS

Recommendations	Class	Level
Parenteral anticoagulation is recommended at the time of diagnosis according to both ischaemic and bleeding risks.	I	B
Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favourable efficacy-safety profile regardless of the management strategy.	I	B
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) is recommended as alternative to UFH plus GPIIb/IIIa inhibitors during PCI.	I	A
UFH 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors) is recommended in patients undergoing PCI who did not receive any anticoagulant.	I	B
In patients on fondaparinux (2.5 mg s.c. daily.) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure.	I	B
Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available.	I	B
Crossover between UFH and LMWH is not recommended.	III	B
In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B

Antiplatelet therapy in NSTEMI-ACS patients requiring CABG (1)

Recommendations	Class	Level
Irrespective of the revascularization strategy, a P2Y ₁₂ inhibitor is recommended in addition to aspirin and maintained over 12 months unless there are contraindications such as excessive risk of bleeding events.	I	A
It is recommended that the Heart Team estimate the individual bleeding and ischaemic risks and guide the timing of CABG as well as management of DAPT.	I	C
It is recommended to perform CABG without delay in patients with haemodynamic instability, ongoing myocardial ischaemia or very-high-risk coronary anatomy, regardless of antiplatelet treatment.	I	C

Combining antiplatelet agents and anticoagulants in NSTEMI-ACS patients requiring chronic oral anticoagulation and undergoing stenting (1)

Recommendations	Class	Level
Anticoagulation		
During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all NOACs and if INR is <2.5 in VKA-treated patients.	I	C
Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase.	IIa	C

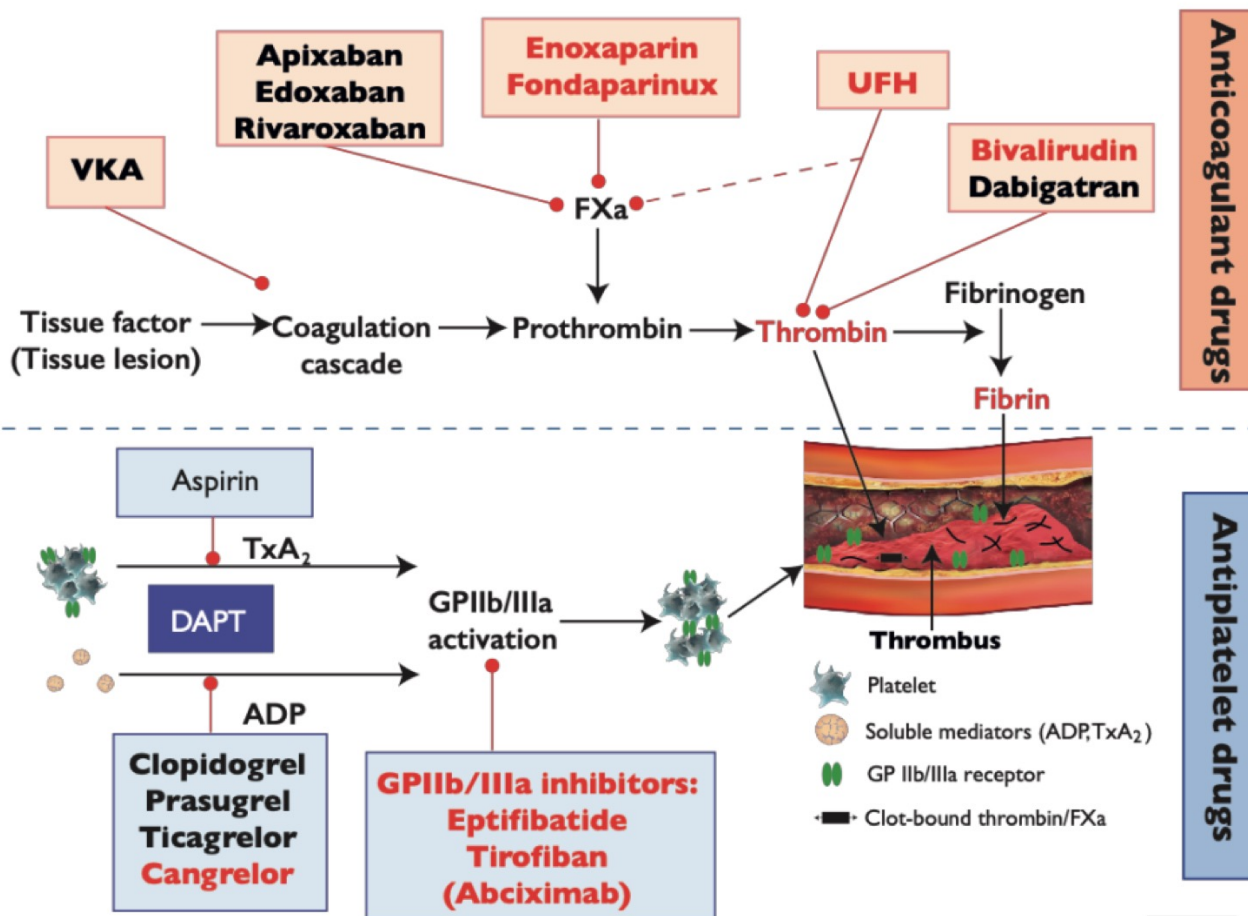
PCI = percutaneous coronary intervention; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.

Combining antiplatelet agents and anticoagulants in NSTEMI-ACS patients requiring chronic oral anticoagulation and undergoing stenting (2)

Recommendations	Class	Level
If at low bleeding risk (HAS-BLED ≤ 2), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day should be considered for 6 months, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C
If at high bleeding risk (HAS-BLED ≥ 3), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 1 month, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months irrespective of the stent type (BMS or new-generation DES).	IIa	C
Following coronary stenting, DAPT including new P2Y ₁₂ inhibitors should be considered as an alternative to triple therapy for patients with NSTEMI-ACS and atrial fibrillation with a CHA ₂ DS ₂ -VASc score of 1 (in males) or 2 (in females).	IIa	C
Dual therapy with OAC and clopidogrel 75 mg/day may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥ 3 and low risk of stent thrombosis).	IIb	B
The use of ticagrelor or prasugrel as part of triple therapy is not recommended.	III	C

ESC 2020 NSTEMI Guideline

Figure 6
Antithrombotic
treatments in non-ST-
segment elevation acute
coronary syndrome
patients: pharmacological
targets. Drugs with oral
administration are shown
in black letters and drugs
with preferred parenteral
administration in red.
Abciximab (in brackets) is
not supplied anymore.



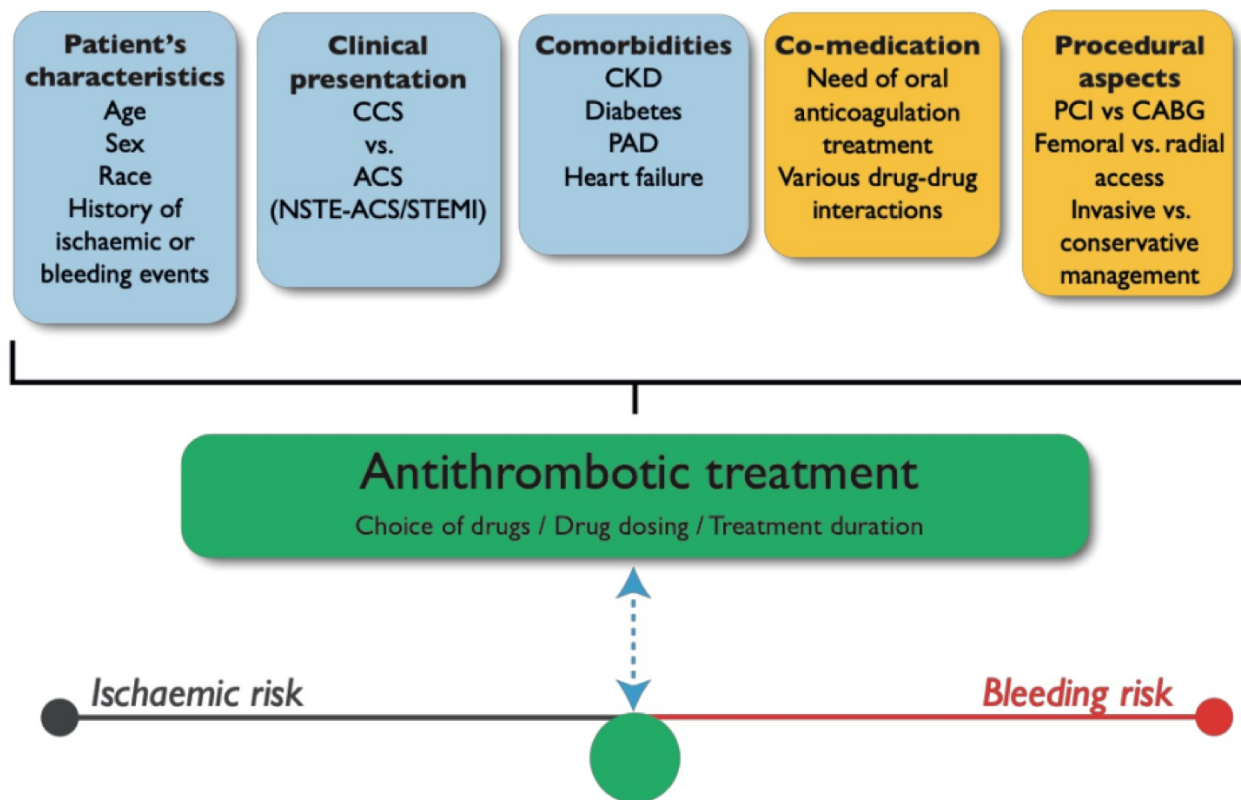


Figure 5
Determinants of antithrombotic treatment in coronary artery disease.

Intrinsic (in blue: patient's characteristics, clinical presentation & comorbidities) and extrinsic (in yellow: co-medication & procedural aspects) variables influencing the choice, dosing, and duration of antithrombotic treatment.

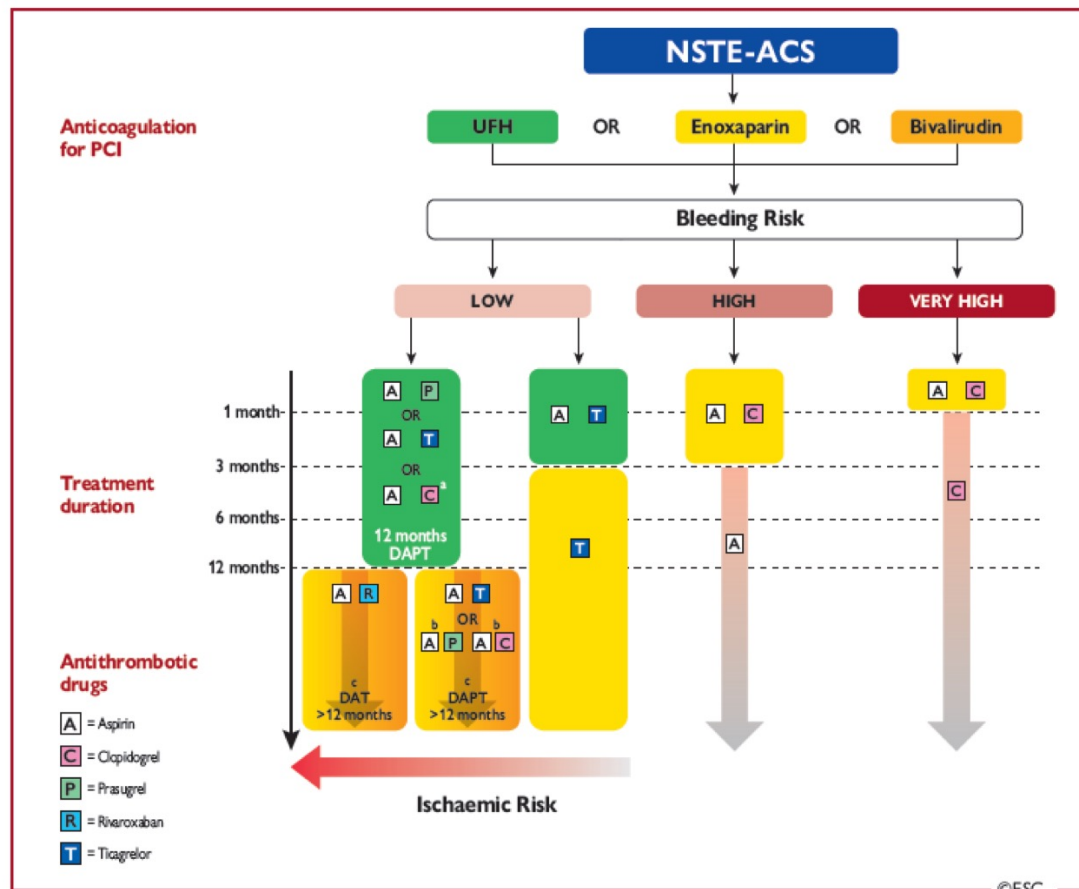


Figure 7 (1)
Algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients without atrial fibrillation undergoing percutaneous coronary intervention.

Table 6 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients^a (1)

I. Antiplatelet drugs

Aspirin	LD of 150–300 mg orally or 75–250 mg i.v. if oral ingestion is not possible, followed by oral MD of 75–100 mg o.d.
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P2Y₁₂ receptor inhibitors (oral or i.v.)

Clopidogrel	LD of 300–600 mg orally, followed by a MD of 75 mg o.d., no specific dose adjustment in CKD patients.
Prasugrel	LD of 60 mg orally, followed by a MD of 10 mg o.d. In patients with body weight <60 kg, a MD of 5 mg o.d. is recommended. In patients aged ≥75 years, prasugrel should be used with caution, but a dose of 5 mg o.d. should be used if treatment is deemed necessary. No specific dose adjustment in CKD patients. Prior stroke is a contraindication for prasugrel.

^aAll dosing regimens refer to doses given for the respective drugs for protection against thrombosis within the arterial system.

Table 6 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients^a (2)

I. Antiplatelet drugs

P2Y₁₂ receptor inhibitors (oral or i.v.) (continued)

Ticagrelor	LD of 180 mg orally, followed by a MD of 90 mg b.i.d., no specific dose adjustment in CKD patients.
Cangrelor	Bolus of 30 µg/kg i.v. followed by 4 µg/kg/min infusion for at least 2 h or the duration of the procedure (whichever is longer).

GP IIb/IIIa receptor inhibitors (i.v.)

Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 h (drug is not supplied anymore).
Eptifibatide	Double bolus of 180 µg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 µg/kg/min for up to 18 h.

^aAll dosing regimens refer to doses given for the respective drugs for protection against thrombosis within the arterial system.

Table 6 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients^a (3)

I. Antiplatelet drugs

GP IIb/IIIa receptor inhibitors (i.v.) (continued)

Tirofiban	Bolus of 25 µg/kg i.v. over 3 min, followed by an infusion of 0.15 µg/kg/min for up to 18 h.
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II. Anticoagulant drugs (for use before and during PCI)

UFH	70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned followed up by an IV infusion until the invasive procedure. 50–70 U/kg i.v. bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg i.v. bolus.
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted.

^aAll dosing regimens refer to doses given for the respective drugs for protection against thrombosis within the arterial system.

Table 6 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients^a (4)

II. Anticoagulant drugs (for use before and during PCI)

Fondaparinux	2.5 mg/d subcutaneously (only before PCI).
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III. Oral anticoagulant drugs^b

Rivaroxaban	Very low MD of 2.5 mg b.i.d. (in combination with aspirin) for long-term extended antithrombotic treatment in a secondary prevention setting of CAD patients.
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^aAll dosing regimens refer to doses given for the respective drugs for protection against thrombosis within the arterial system.

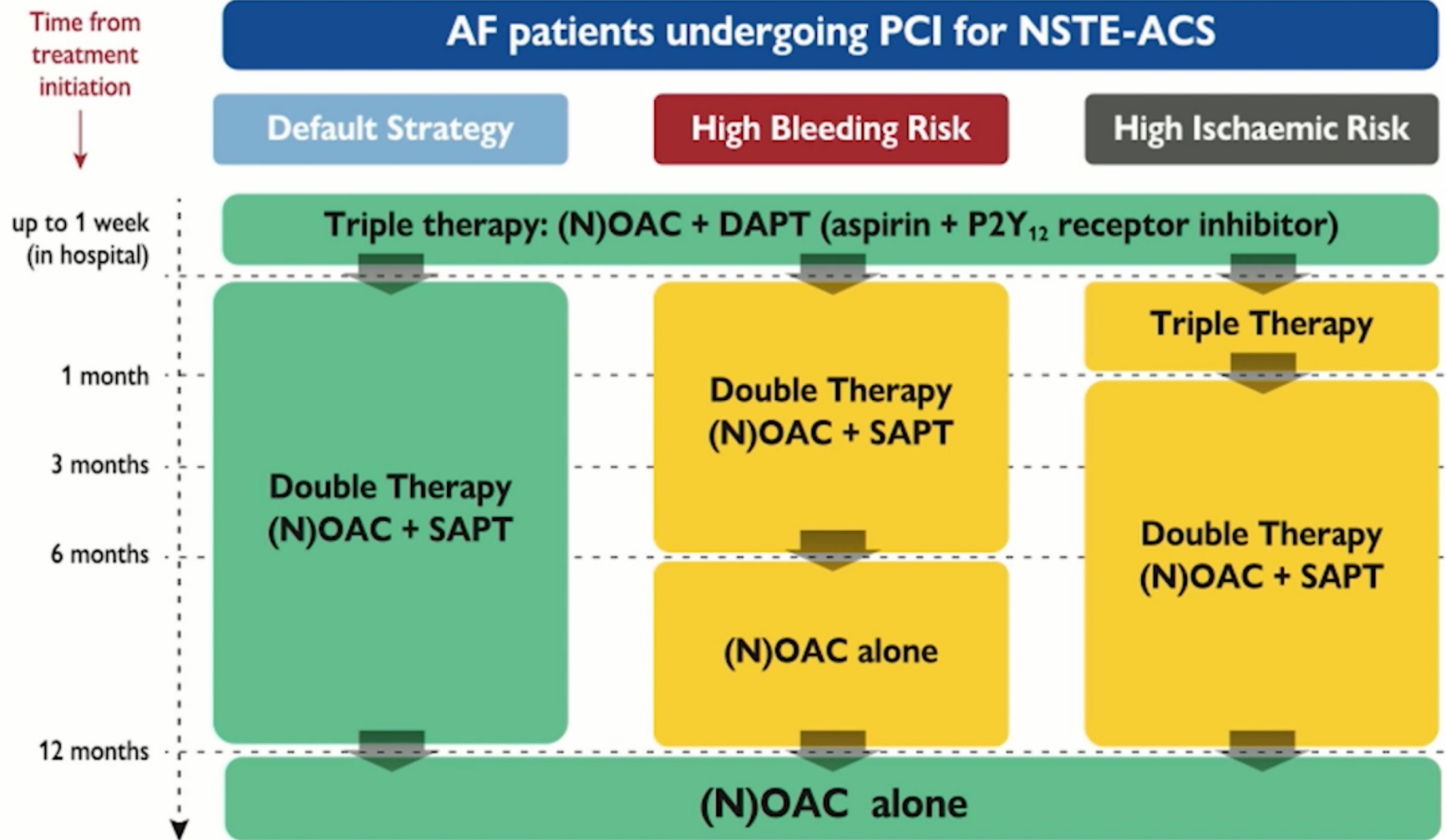
^bSection III lists the dosing for rivaroxaban in a secondary prevention setting in CAD patients. For a comprehensive summary on dosing of OACs (NOACs and VKAs) in a setting of full-dose anticoagulation please see: The 2018 European Heart Rhythm Association Practical Guide on the use of NOACs in patients with AF.

AF patients undergoing PCI for NSTEMI-ACS

Default Strategy

High Bleeding Risk

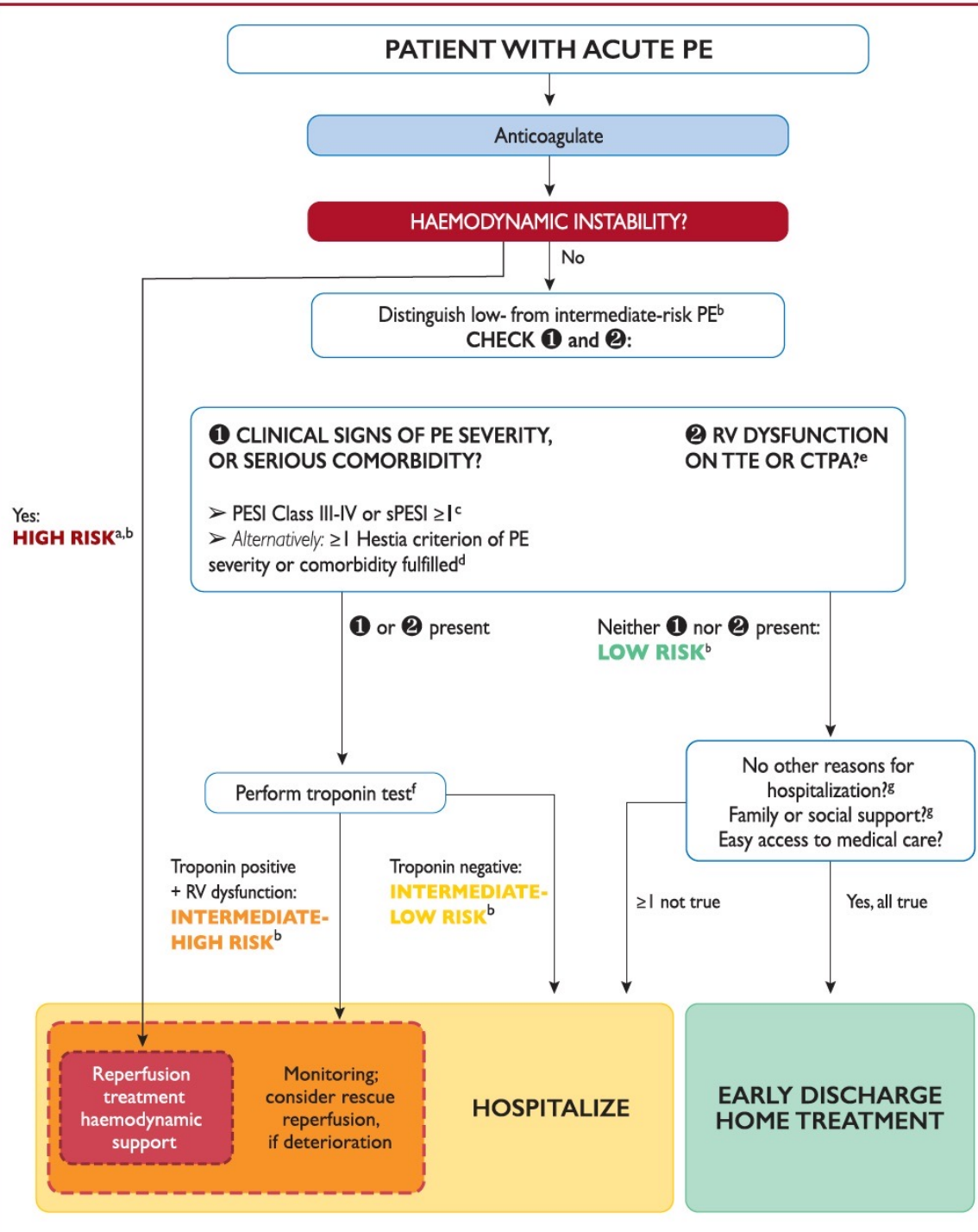
High Ischaemic Risk



Pulm. Emb.

2019 ESC, ERS Guidelines on the diagnosis and management of acute pulmonary embolism

**2016 ACCP Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report**



6.6 Recommendations for acute-phase treatment of high-risk pulmonary embolism^a

Recommendations	Class ^b	Level ^c
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.	I	C
Systemic thrombolytic therapy is recommended for high-risk PE. ²⁸²	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed. ^{d 281}	I	C
Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed. ^d	IIa	C

6.7 Recommendations for acute-phase treatment of intermediate- or low-risk pulmonary embolism

Recommendations	Class ^a	Level ^b
Initiation of anticoagulation		
Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE, ^c while diagnostic workup is in progress.	I	C
If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients. ^{262,309–311}	I	A
When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA. ^{260,261,312–314}	I	A
When patients are treated with a VKA, overlapping with parenteral anticoagulation is recommended until an INR of 2.5 (range 2.0–3.0) is reached. ^{315,316}	I	A
NOACs are not recommended in patients with severe renal impairment, ^d during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome. ^{260,261,312–314}	III	C

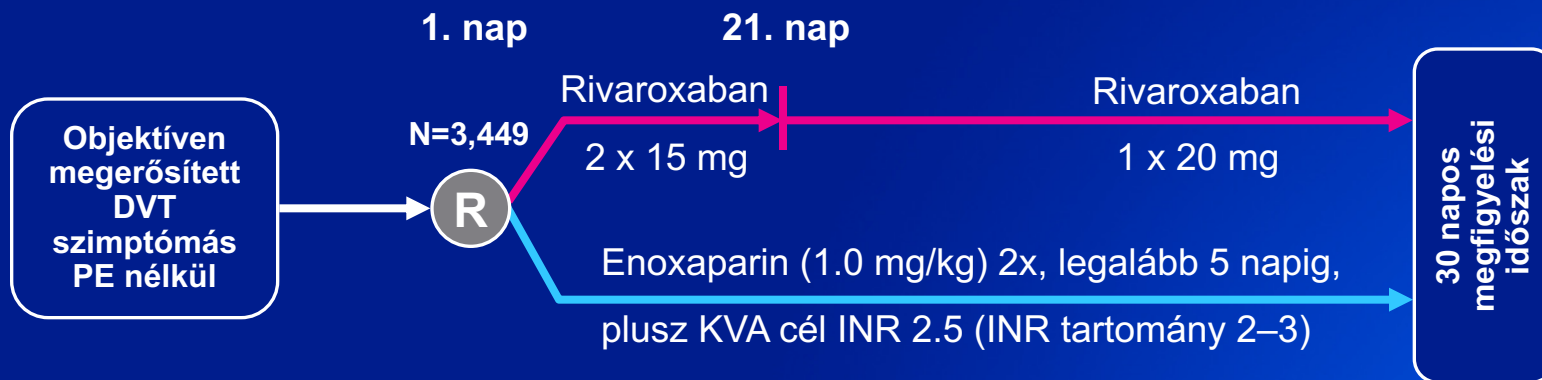
Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER ²⁹³	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.) ^a vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II ²⁹⁴	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.) ^a vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin
Rivaroxaban	EINSTEIN-DVT ²⁹⁵	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	3449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding: 8.1% under rivaroxaban vs. 8.1% under warfarin
	EINSTEIN-PE ²⁹⁶	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	4832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin
Apixaban	AMPLIFY ²⁹⁷	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin
Edoxaban	Hokusai-VTE ²⁹⁸	Double-blind, double-dummy	LMWH/edoxaban (60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 ml/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 months	8240 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 3.2% under edoxaban vs. 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs. 10.3% under warfarin

EINSTEIN DVT: a vizsgálat felépítése

Randomizált, nyílt, esemény-vezérelt, non-inferiority vizsgálat

- ◆ 48 óráig heparins/fondaparinux kezelés megengedett volt a vizsgálatba való belépés előtt
- ◆ szükséges eseményszám: 88 elsődleges hatékonysági végpont

Kezelési időtartam: 3, 6 v. 12 hónap



A kezelési időtartam hosszát (3, 6 v. 12 hónap) a vizsgáló választotta meg a randomizáció előtt, a beteg kockázati profiljának és a helyi irányelveknek megfelelően.

Table 11 **Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term**

Estimated risk for long-term recurrence ^a	Risk factor category for index PE ^b	Examples ^b
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	<ul style="list-style-type: none"> • Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only “bathroom privileges”) for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	<ul style="list-style-type: none"> • Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	<ul style="list-style-type: none"> • Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		<ul style="list-style-type: none"> • Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

8.4 Recommendations for the regimen and duration of anticoagulation after pulmonary embolism in patients without cancer

Recommendations	Class ^a	Level ^b
Therapeutic anticoagulation for ≥ 3 months is recommended for all patients with PE. ³⁴⁷	I	A
Patients in whom discontinuation of anticoagulation after 3 months is recommended		
For patients with first PE/VTE secondary to a major transient/reversible risk factor, discontinuation of therapeutic oral anticoagulation is recommended after 3 months. ^{331,340,341}	I	B
Patients in whom extension of anticoagulation beyond 3 months is recommended		
Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with recurrent VTE (that is, with at least one previous episode of PE or DVT) not related to a major transient or reversible risk factor. ³⁵⁸	I	B
Oral anticoagulant treatment with a VKA for an indefinite period is recommended for patients with antiphospholipid antibody syndrome. ³⁵⁹	I	B
Patients in whom extension of anticoagulation beyond 3 months should be considered^{c,d}		
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor. ^{330,331,347,351–353}	IIa	A
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than antiphospholipid antibody syndrome. ^{330,352,353}	IIa	C
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor. ^{330,331,352}	IIa	C
NOAC dose in extended anticoagulation^e		
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg b.i.d.) or rivaroxaban (10 mg o.d.) should be considered after 6 months of therapeutic anticoagulation. ^{352,353}	IIa	A
Extended treatment with alternative antithrombotic agents		
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis. ^{355–357}	IIb	B
Follow-up of the patient under anticoagulation		
In patients who receive extended anticoagulation, it is recommended that their drug tolerance and adherence, hepatic and renal ^f function, and bleeding risk be reassessed at regular intervals. ²⁵⁹	I	C

Table 13 Clinical trials on extended treatment of venous thromboembolism

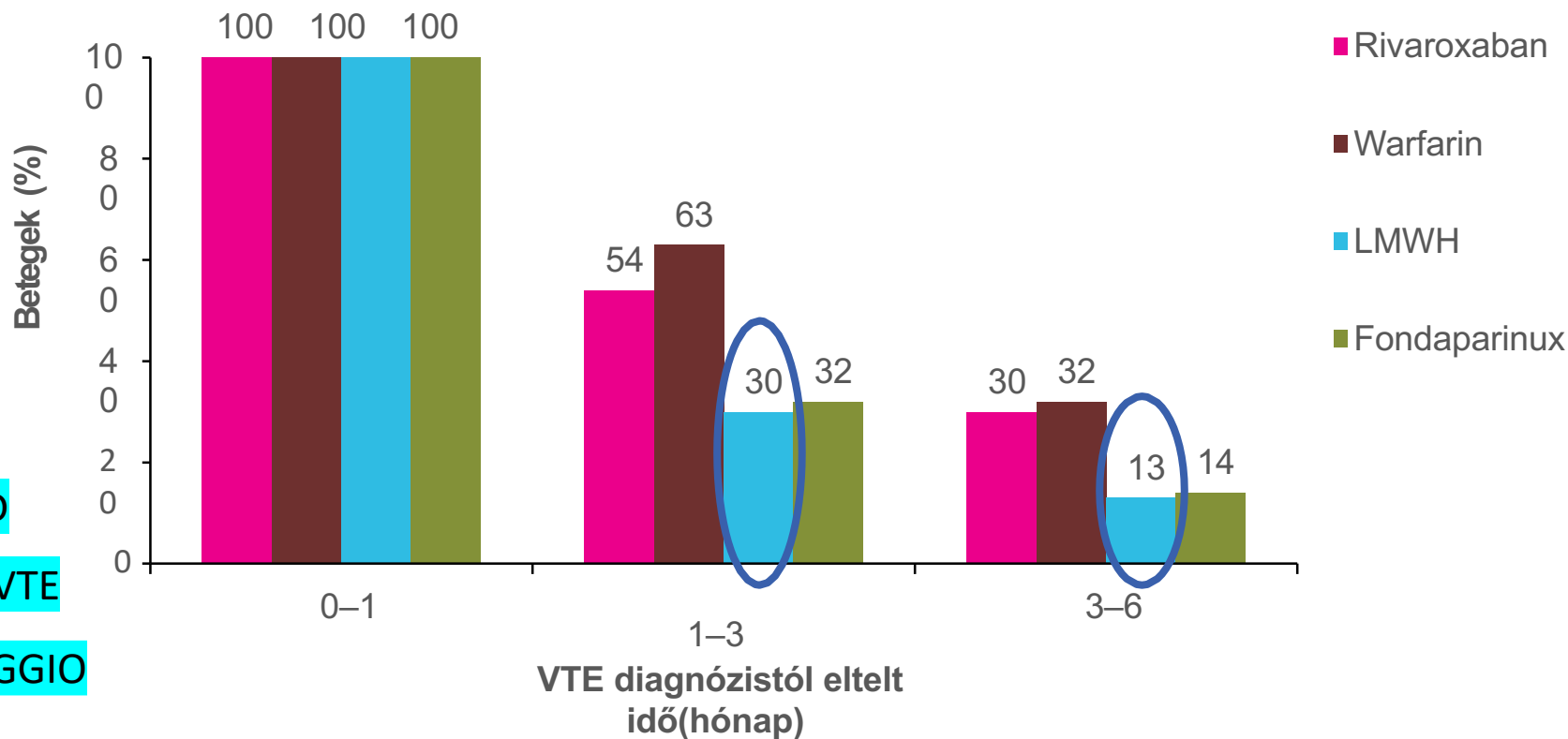
Study	Active ^a	Comparator	Design	Expected reduction	Treatment duration	No. Patients enrolled	VTE rate in control group	Risk reduction for recurrent VTE	Major or CRNM bleeding in active ^a group
RE-SONATE ³⁷⁰	Dabigatran 150 mg b.i.d. ^c	Placebo	Superiority	70%	6 months	1343	5.6%	92%	5.3%
RE-MEDY ³⁷⁰	Dabigatran 150 mg b.i.d. ^c	Warfarin (INR 2–3)	Non-inferiority	Absolute increase, <2.8	18–36 months	2856	1.3%	Risk difference, 0.38% vs.VKA	5.6% (vs. 10.2% in warfarin arm)
EINSTEIN Ext ²⁹⁵	Rivaroxaban 20 mg daily	Placebo	Superiority	70%	6–12 months	1196	7.1%	82%	6.0%
AMPLIFY Ext ³⁷¹	Apixaban 5.0 mg b.i.d.	Placebo	Superiority	41%	12 months	2486	8.8%	80%	4.2%
	Apixaban 2.5 mg b.i.d. ^d							81%	3.0%
WARFASA ³⁶⁸	Aspirin	Placebo	Superiority	40%	≥24 months	402	11.2% ^b	40%	1.0% ^b
ASPIRE ³⁶⁹	Aspirin	Placebo	Superiority	30%	4 years (actual, 27 months)	822	6.5% ^b	26%	1.7% ^b

8.6 Recommendations for the regimen and the duration of anticoagulation after pulmonary embolism in patients with active cancer

Recommendations	Class ^a	Level ^b
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs. ^{360–363}	Ila	A
Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer. ³⁶⁶	Ila	B
Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer. ³⁶⁷	Ila	C
For patients with PE and cancer, extended anticoagulation (beyond the first 6 months) ^c should be considered for an indefinite period or until the cancer is cured. ³⁷⁸	Ila	B
In patients with cancer, management of incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT. ^{376,377}	Ila	B

Nagy kihívást jelentő klinikai kép : a daganathoz társuló thromboembolia

Daganatos betegek , akik az idő elteltével antikoaguláns terápián maradnak
(USA, 2009-2014)



SELECT-D

OKUSAI VTE

CARAVAGGIO

CASSINI

N=52,911 malignus betegségben szenvedő VTE beteg

Khorana AA, et al, *Throm Res*
2016;145:51-53

Műbillentyű

Indications for antithrombotic therapy after valvular surgery

	Class	Level
Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis.	I	B
Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation.	I	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease.	IIa	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis after thromboembolism despite adequate INR.	IIa	C
Oral anticoagulation should be considered for the first 3 months after implantation of a mitral or tricuspid bioprosthesis.	IIa	C
Oral anticoagulation should be considered for the first 3 months after mitral valve repair.	IIa	C
Low-dose aspirin should be considered for the first 3 months after implantation of an aortic bioprosthesis.	IIa	C
Oral anticoagulation may be considered for the first 3 months after implantation of an aortic bioprosthesis.	IIb	C

Risk factors for thromboembolism

- **Prosthesis thrombogenicity**

- Low
 - Carbomedics (aortic position), Medtronic Hall, St.Jude Medical, ON-X.
- Medium
 - Other bileaflet valves.
- High
 - Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley, other tilting-disc valves.

- **Patient-related risk factors**

- Mitral, tricuspid, or pulmonary valve replacement.
- Previous thromboembolism.
- Atrial fibrillation.
- Mitral stenosis of any degree.
- Left ventricular ejection fraction < 35%.

Target international normalized ratio (INR) for mechanical prostheses

Prosthesis thrombogenicity	Patient-related risk factors	
	No risk factor	≥ 1 risk factor
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs109 &
European Journal of Cardio-Thoracic Surgery 2012 -
doi:10.1093/ejcts/ezs455).

Management after valve replacement

- **Complete baseline assessment**
 - 6 to 12 weeks after surgery.
 - Clinical assessment, chest X-ray, ECG, TTE, blood testing.
- **Antithrombotic therapy**
 - Adapted to prostheses- and patient-related risk factors.
 - Lifelong for all mechanical prostheses.
 - During the first 3 post-operative months for mitral and tricuspid bioprostheses.
- **Detection of complications**
 - Prosthetic thrombosis.
 - Bioprosthetic failure.
 - Haemolysis and paravalvular leak.
 - Heart failure.

Műbillentyű thrombosis

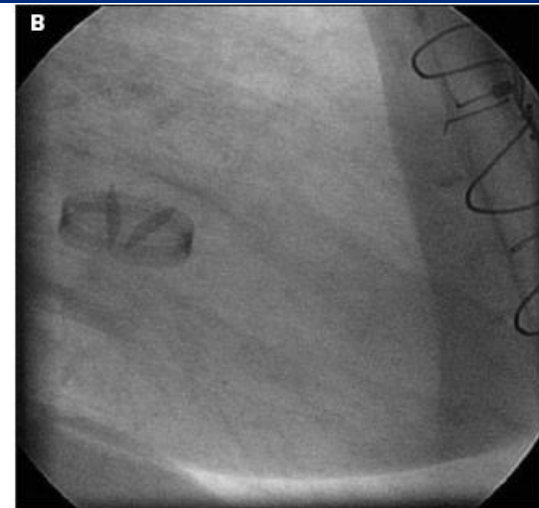
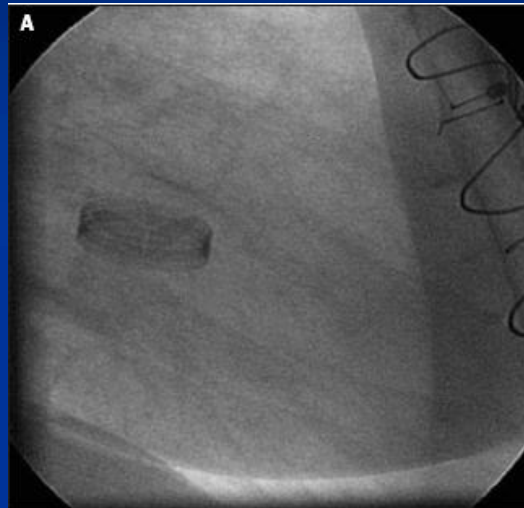
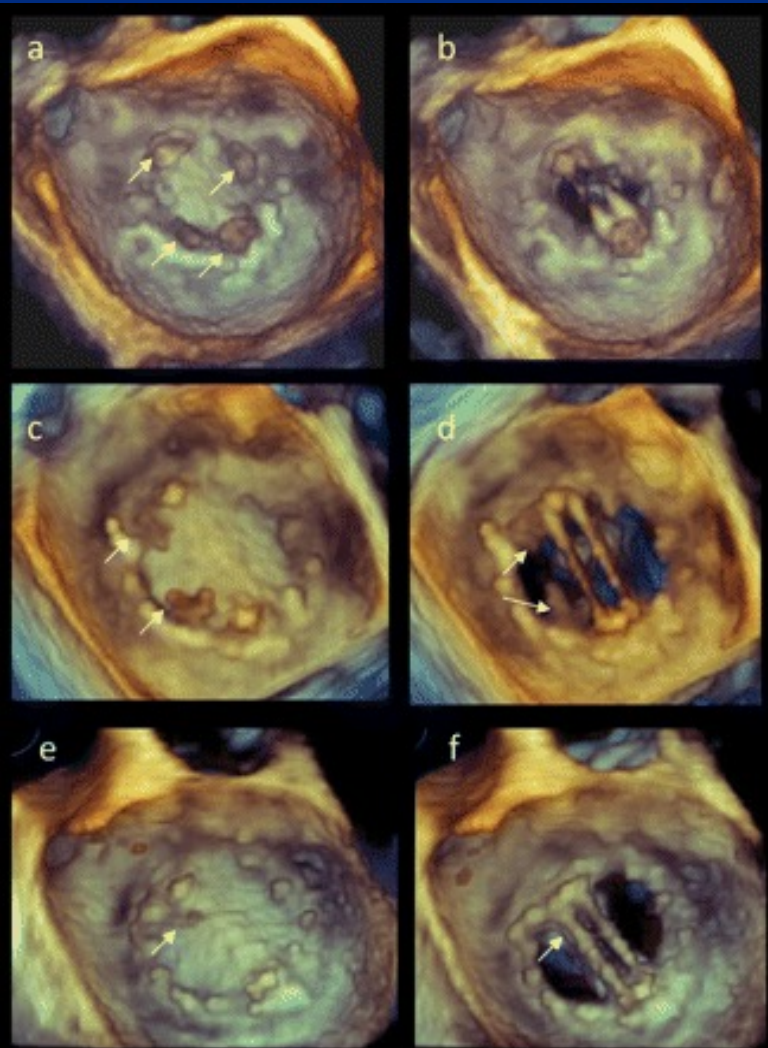


Figure 2. Two-dimensional transesophageal echocardiography with color Doppler demonstrating the mechanical mitral valve in the fixed, semi-open position, with significant mitral regurgitation.

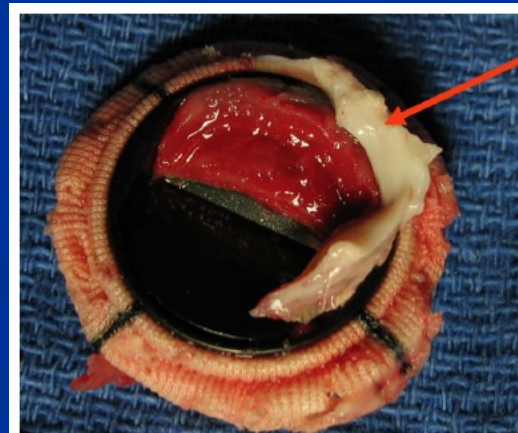


Figure 5. Thrombosed mitral valve prosthesis as seen at the time of surgery. Note the large pannus formation (arrow).

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V

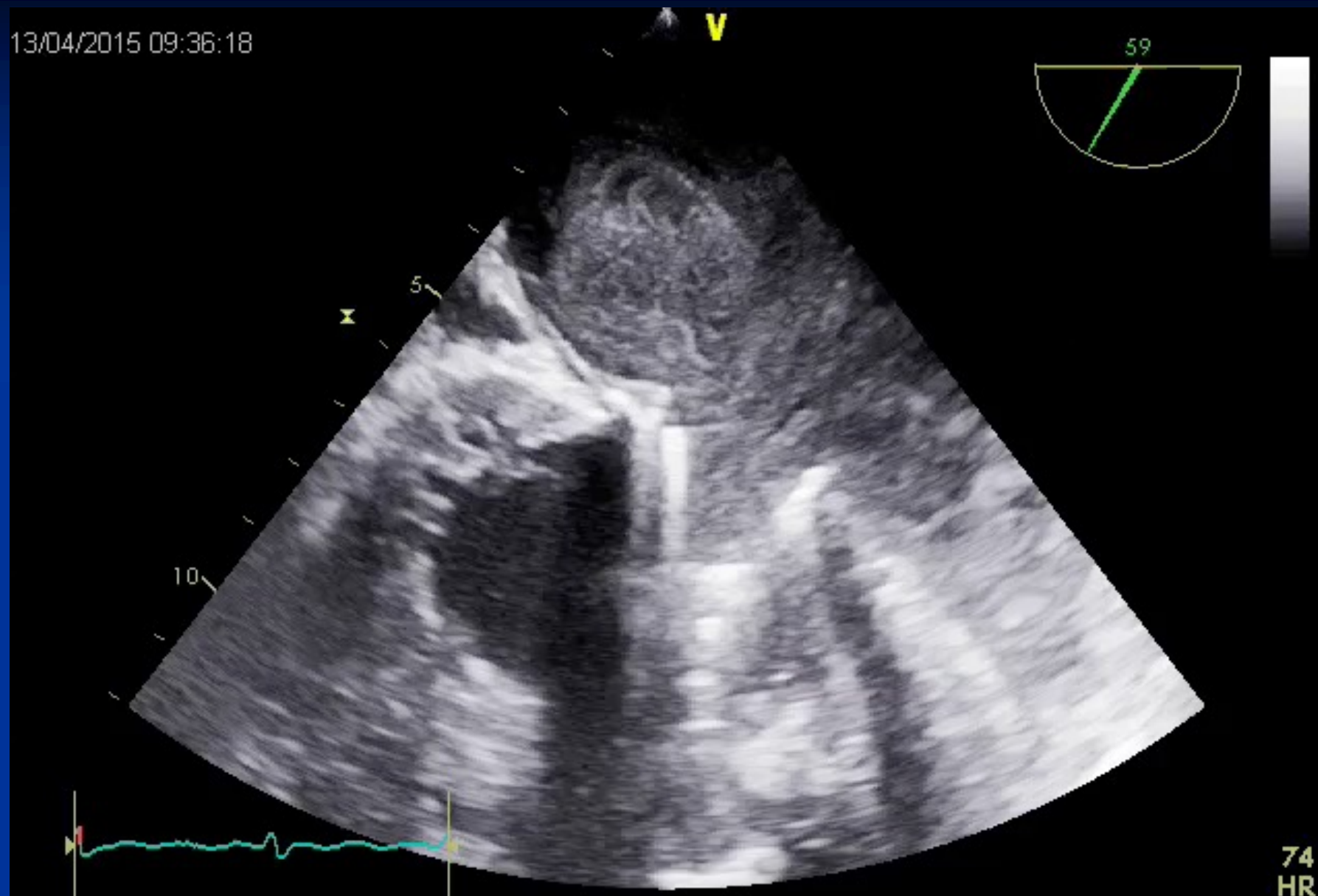
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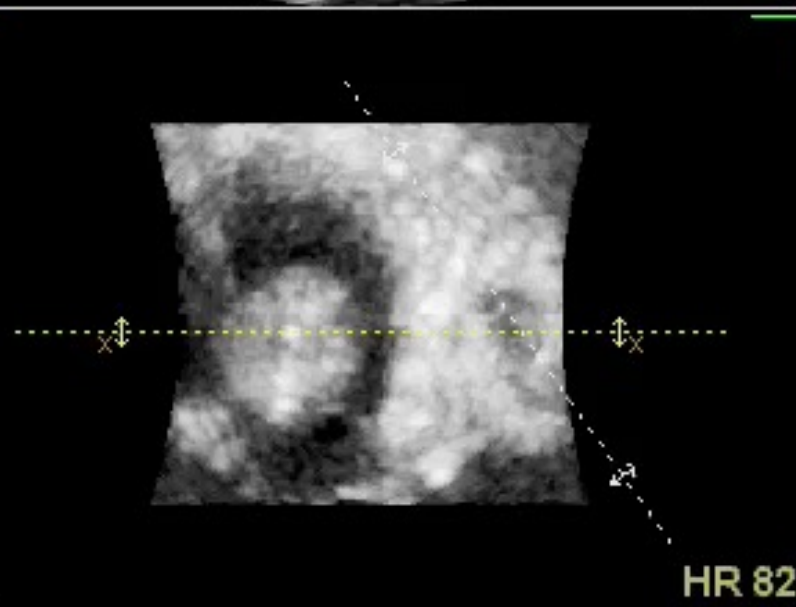
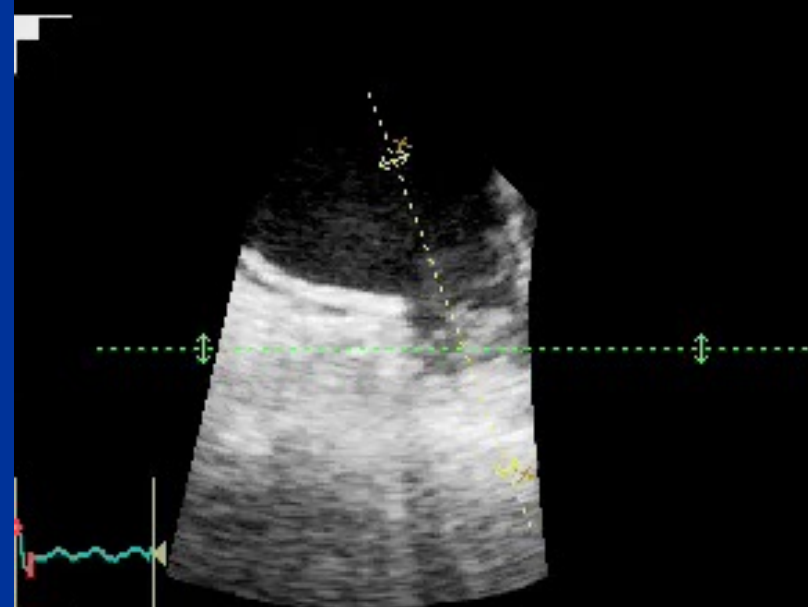
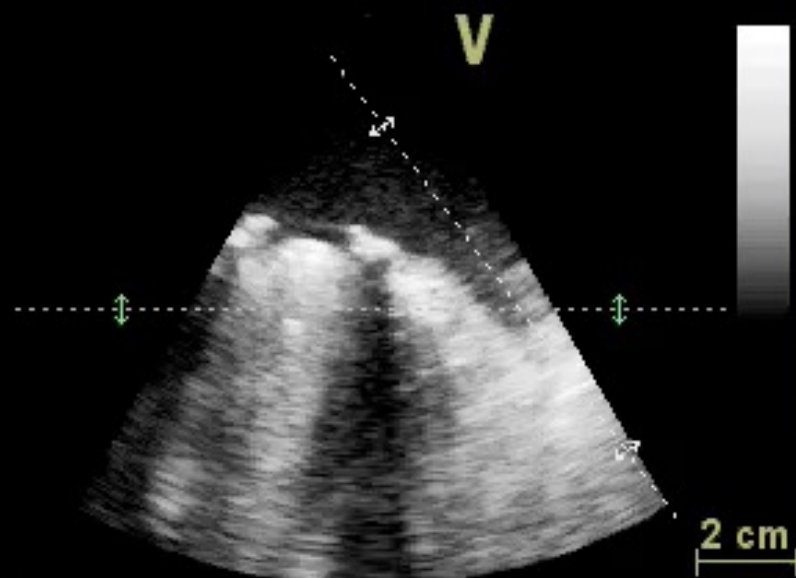
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X

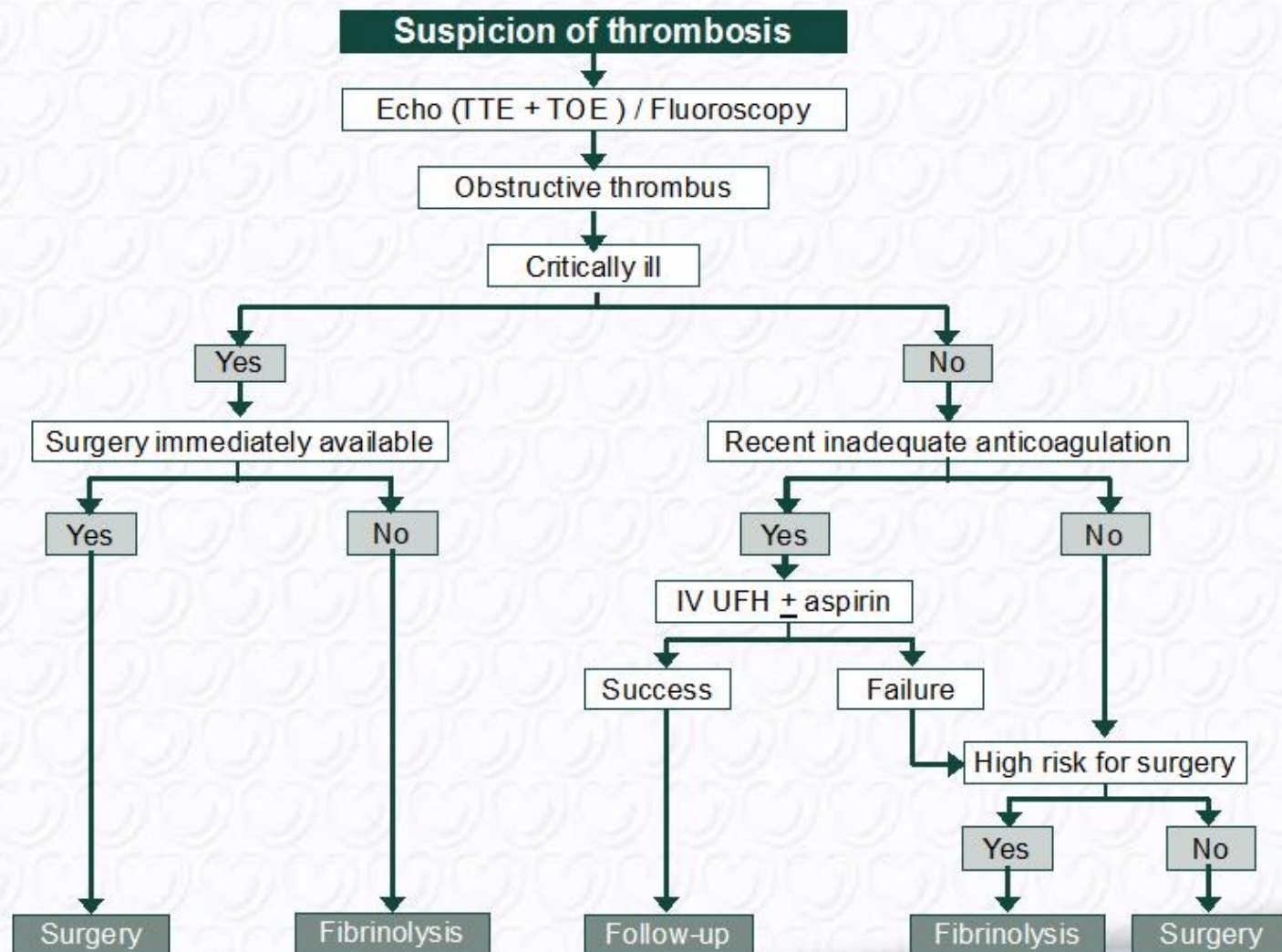
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HR



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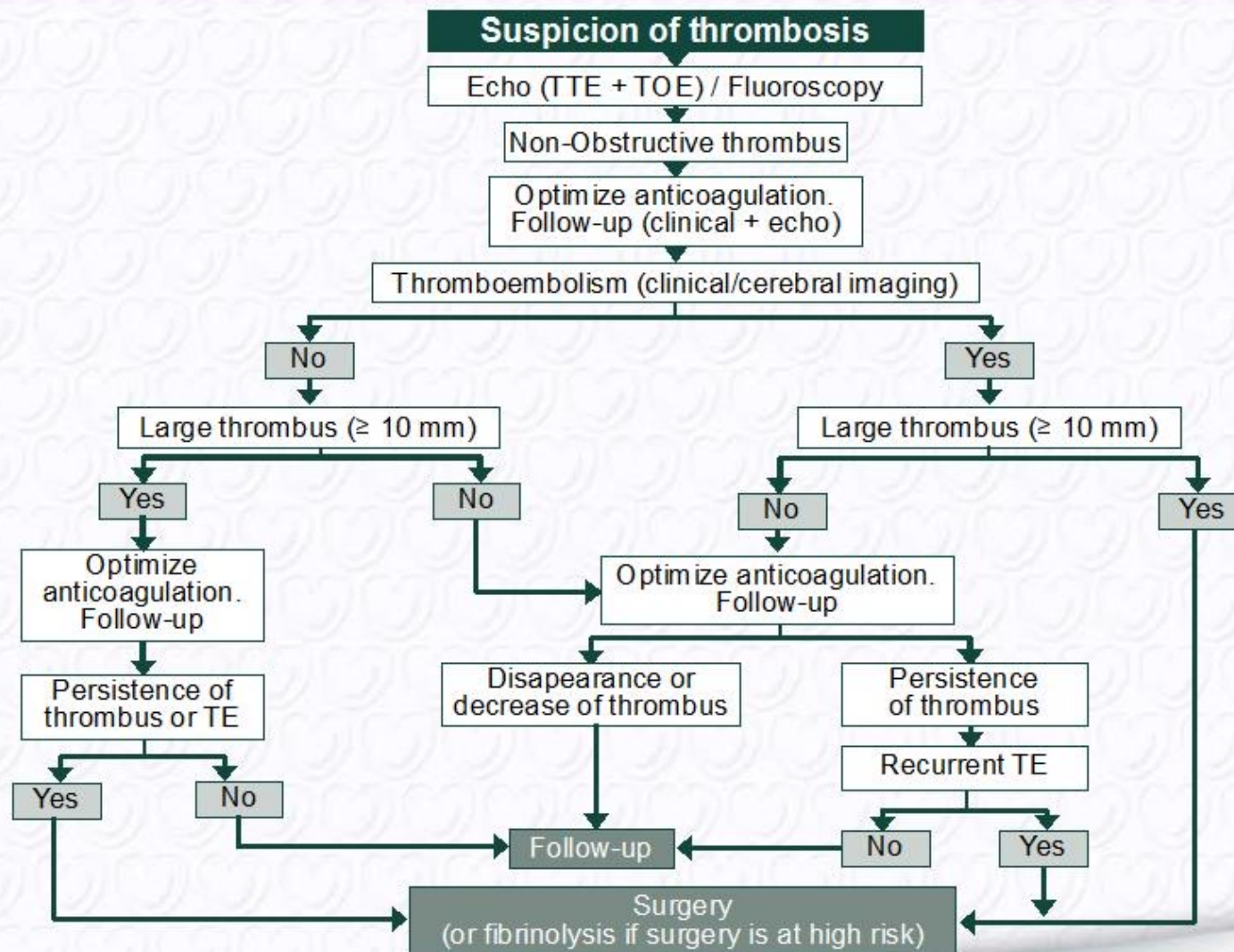


Management of left-sided obstructive prosthetic thrombosis



European Heart Journal 2012 - doi:10.1093/eurheartj/ehs109 &
European Journal of Cardio-Thoracic Surgery 2012 -
doi:10.1093/ejcts/ezs455).

Management of left-sided non-obstructive prosthetic thrombosis



European Heart Journal 2012 - doi:10.1093/eurheartj/ehs109 &
European Journal of Cardio-Thoracic Surgery 2012 -
doi:10.1093/ejcts/ezs455).

AC és terhesség

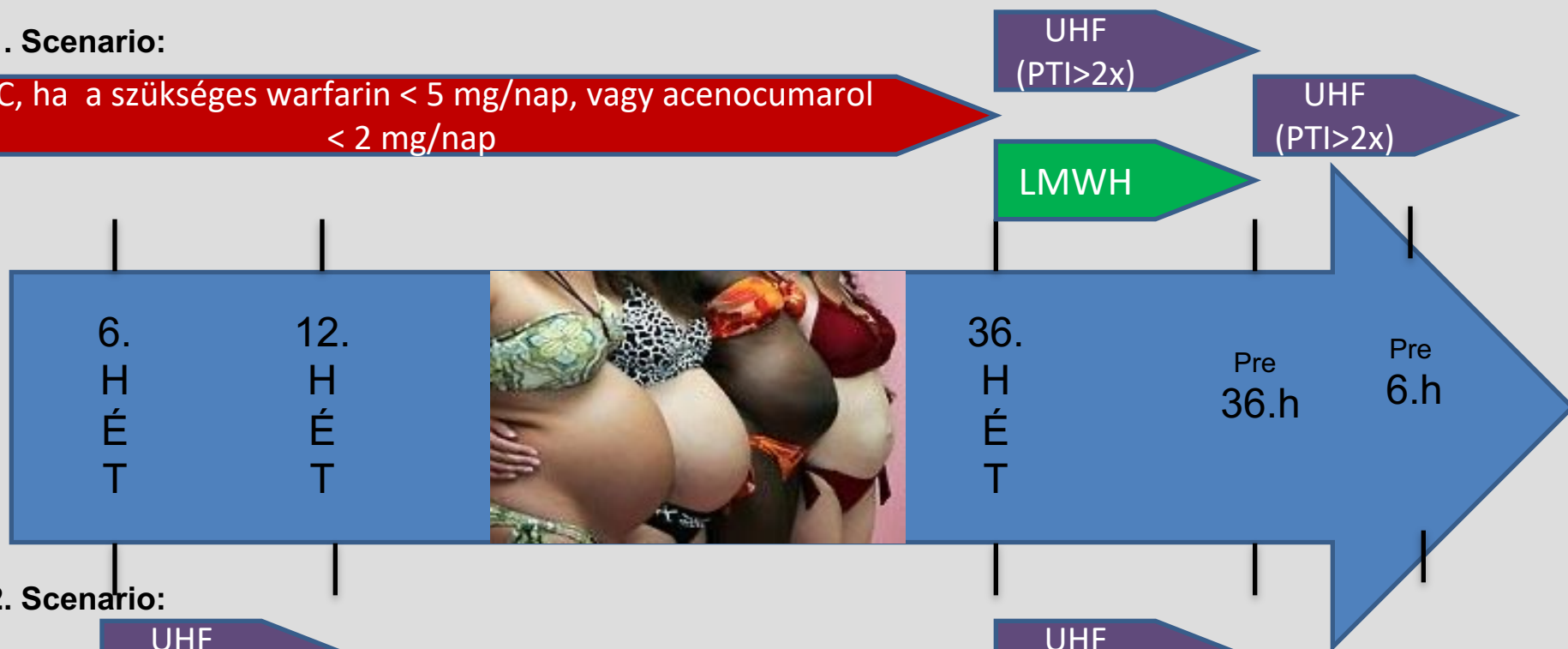


Mechanikus műbillentyű és AC kezelés

Ha LMWH, az anti Xa szint hetente monitorozandó! – I C
Az LMWH kontraindikált anti Xa monitorozás nélkül! – III C
Cél antiXa szint: 0.8-1.2 U/ml 4-6 órával a beadás után/hét

1. Scenario:

OAC, ha a szükséges warfarin < 5 mg/nap, vagy acenocumarol < 2 mg/nap



2. Scenario:



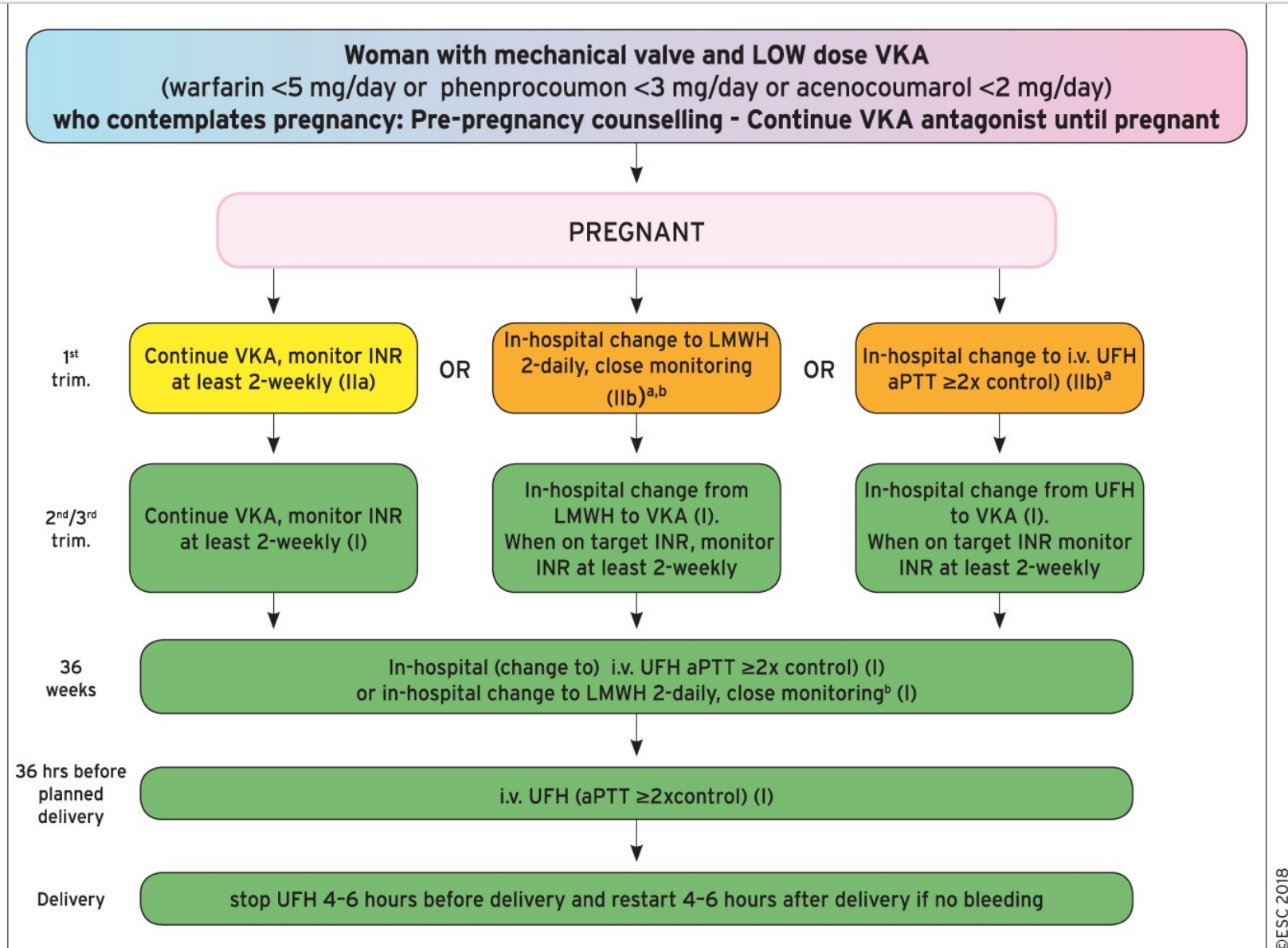


Figure 3 Flowchart on anticoagulation in mechanical valves and low-dose VKA ^aweeks 6–12 ^bmonitoring LMWH: - starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously; -in-hospital daily anti-Xa levels until target, then weekly (I); -target anti-Xa levels: 1.0–1.2 U/ml (mitral and right sided valves) or 0.8–1.2 U/ml (aortic valves) 4–6 hours post-dose (I); -pre-dose anti-Xa levels >0.6 U/ml

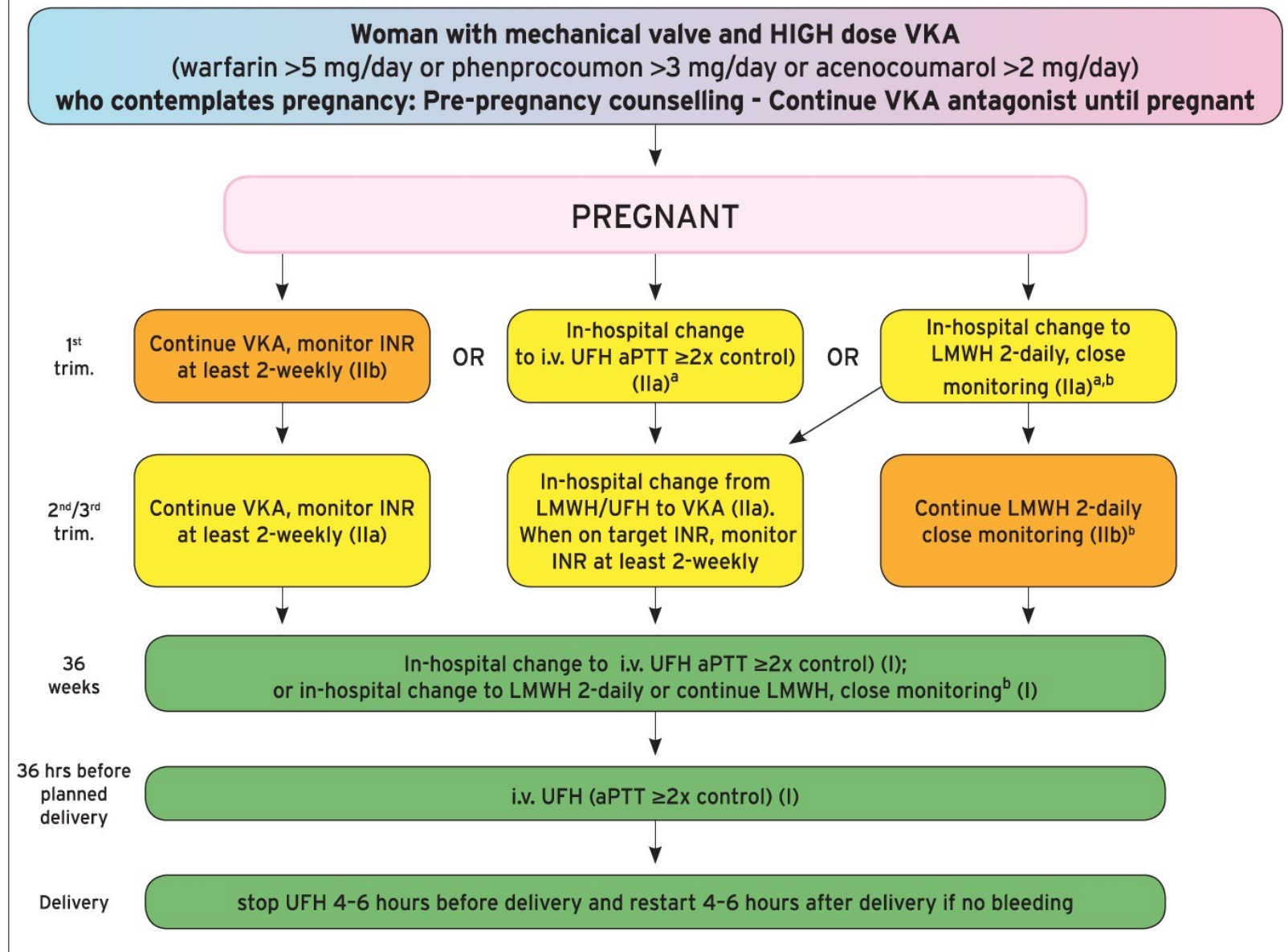


Figure 2 Flowchart on anticoagulation in mechanical valves and high-dose VKA ^aweeks 6–12 ^bmonitoring LMWH: - starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously; -in-hospital daily anti-Xa levels until target, then weekly (I); -target anti-Xa levels: 1.0–1.2 U/ml (mitral and right sided valves) or 0.8–1.2 U/ml (aortic valves) 46 hours post-dose (I); -pre-dose anti-Xa levels >0.6 U/ml (IIb). aPTT =

Thrombemboliás rizikó nem (csak) szívbeteg nőknél

(Royal College of Obstetricians and Gynaecologist: Check)

Megelőző rizikó faktorok	Nőgyógyászati rizikó	Átmeneti rizikó
Megelőző rekuráló VTE	Pre-eclampsia	Szisztémás infekció
Megelőző VTE nem provokált/ösztrogénhez kapcsolt	Hyperemesis, dehydration	Immobilitás
Megelőző VTE provokált	Többszörös terhesség, vagy asszisztált reprodukció	Sebészi beavatkozás a terhesség alatt vagy < 6 hét postpartum
VTE a családban	Sürgősségi sectio cesarea	
Ismert thrombophilia	Elektív sectio cesarea	
Társbetegségek: pl. SLE, Nephrosis sy.	Forgási rendellenességek	
Kor> 35 év	Elhúzódó szülés > 24 h	
BMI> 30 kg/m ²	Peripartum vérzés >1 liter vagy transzfúzió	
Terhességek száma ≥3		
Dohányzás		
Nagy varicosus vénák		

Thrombembolia prevenció

(Royal College of Obstetricians and Gynaecologist: Check)

Rizikó	Rizikó	Prevenció
Magas	-Megelőző rekurrens VTE Vagy -Nem provokált/ösztrogénhez kapcsolt Vagy -1 korábbi VTE + thrombophilia vagy családi anamnézis	LMWH A terhesség kezdetétől a postpartum 6. hétig + Compressziós harisnya a terhesség alatt
Közepes	≥ 3 rizikó faktor > 2 rizikó faktor+hospitalizáció	LMWH Postpartum legalább a 7. napig, a terhesség alatt megfontolandó + Compressziós harisnya megfontolandó
Alacsony	< 3 rizikó faktor	Korai mobilizáció, dehydráció kerülése

Antikoagulálás

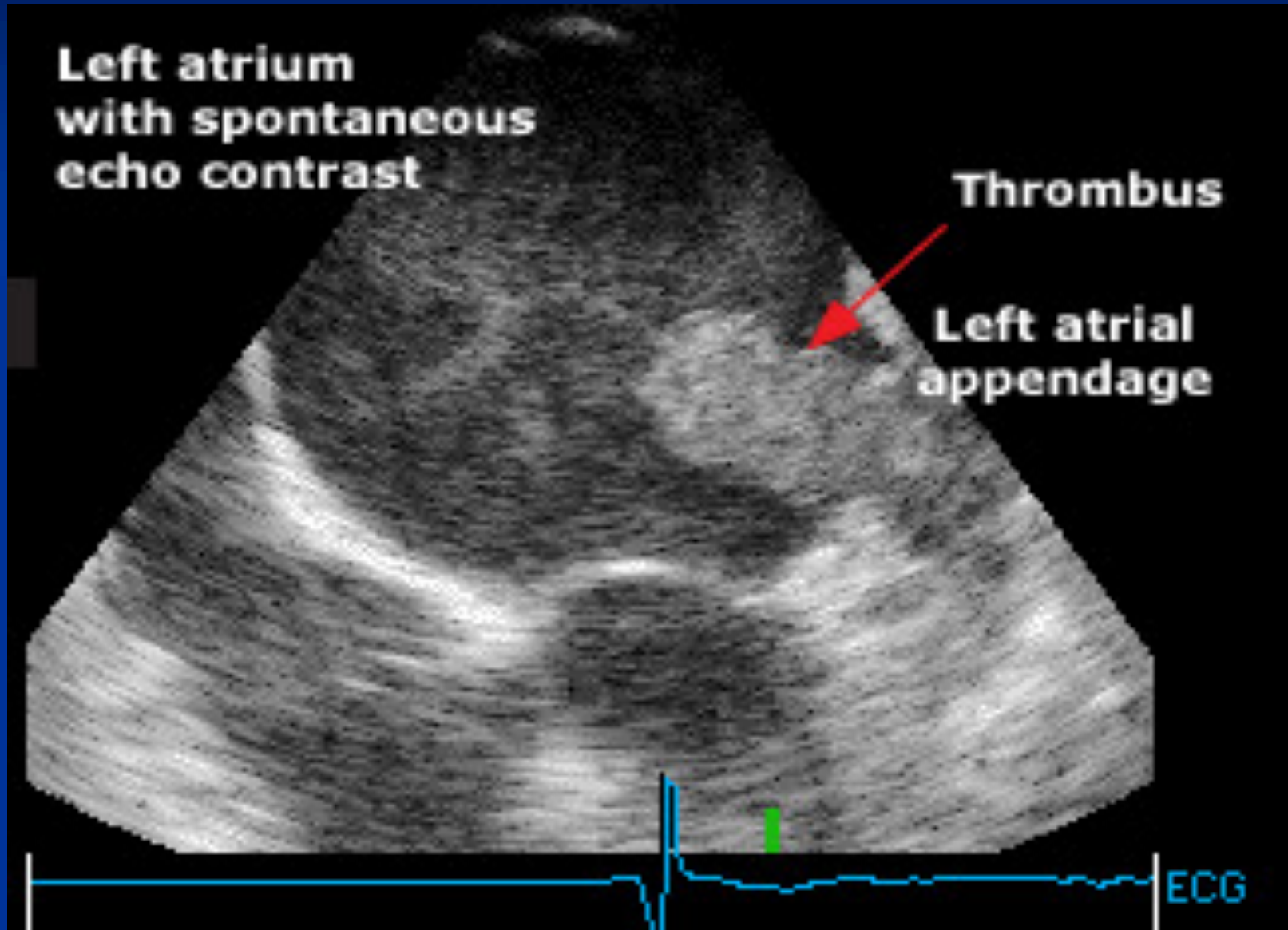
- Mechanikus műbillentyű
- Örökletes antikoaguláns hiányos állapotok
- Mélyvénás trombózis vagy tromboembólia a terhesség alatt
- Antifoszfolipid szindróma
- Permanens pitvarfibrilláció
- Eisenmenger-szindróma

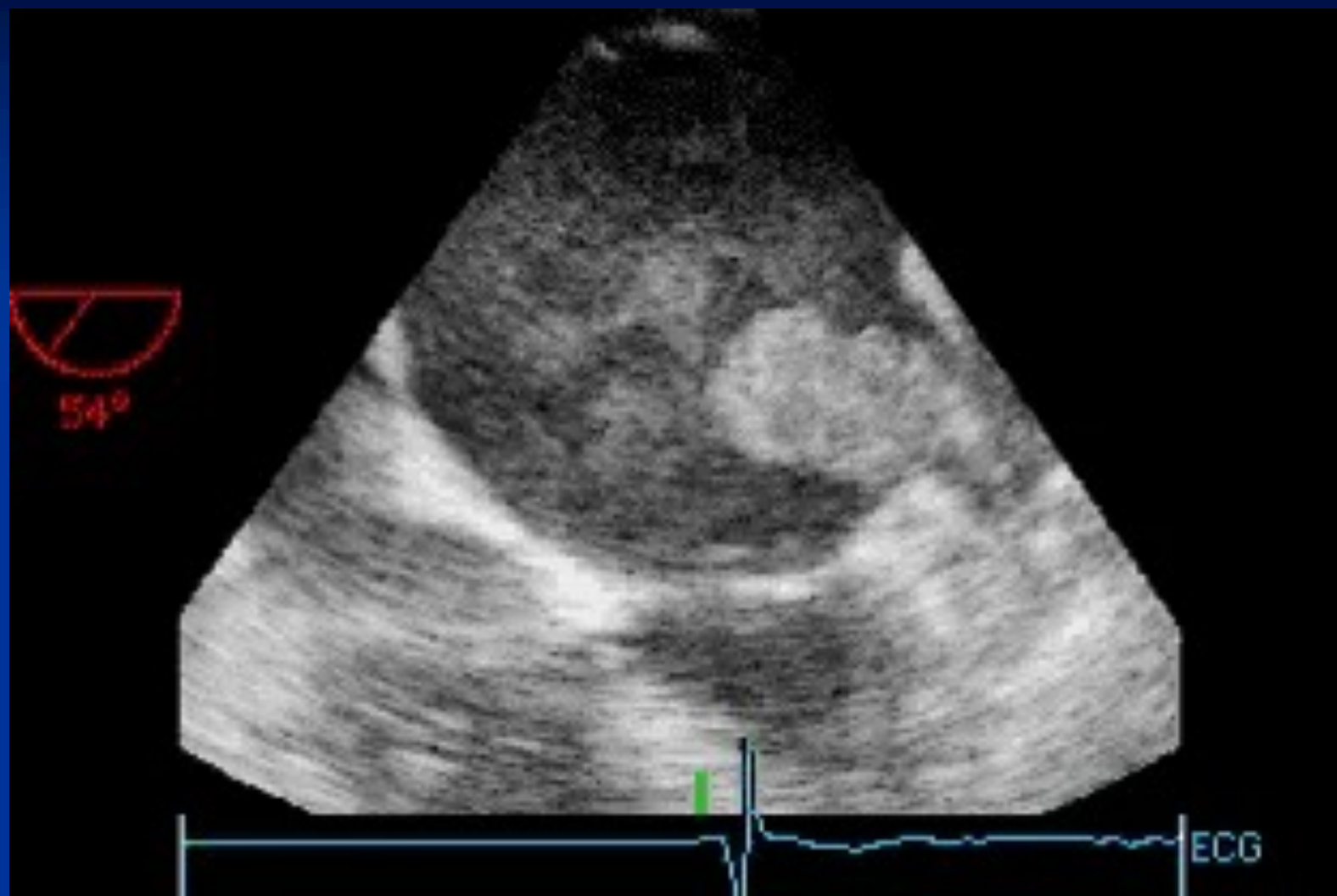
Az antikoaguláns kezelés rizikója (%):

	warfarin	heparin (1. trimeszter)	heparin (végig)	LMWH
Magzati rizikó				
halál	30	24	-	?
embriopátia	4-10	2	-	?
Anyai rizikó				
halál	1,8	4,2	7	?
tromboembólia	3,9	9-24	25	?

Pitvarfibrilláció

Bal pitvari fülcsé thrombus





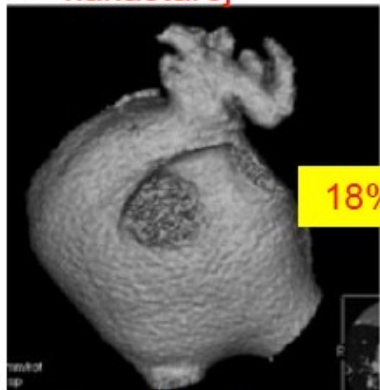
Kardiális embóliaforrások – Bal fülcse

Bal fülcse morfológia

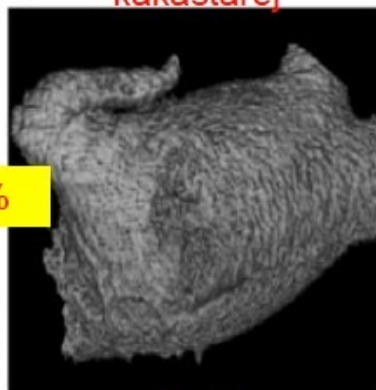
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2010,21:973.

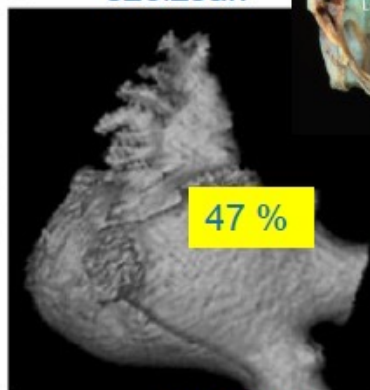
A kakastaréj



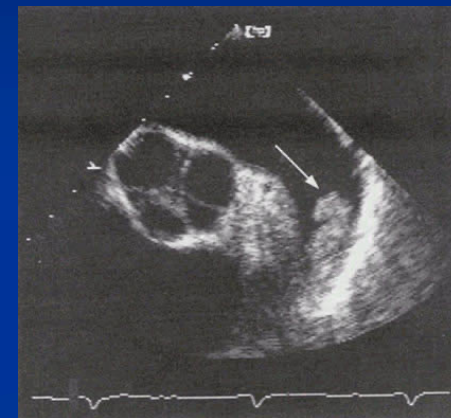
B kakastaréj



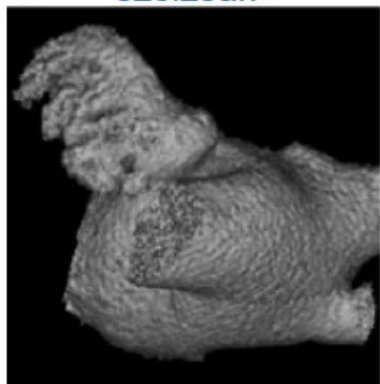
C szélzsák



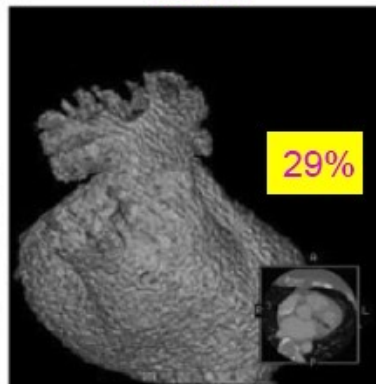
„fésűfogas
zsákutca”



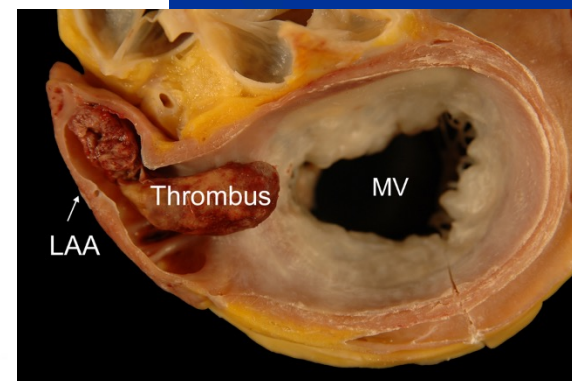
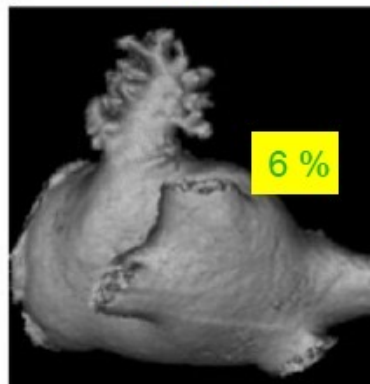
D szélzsák



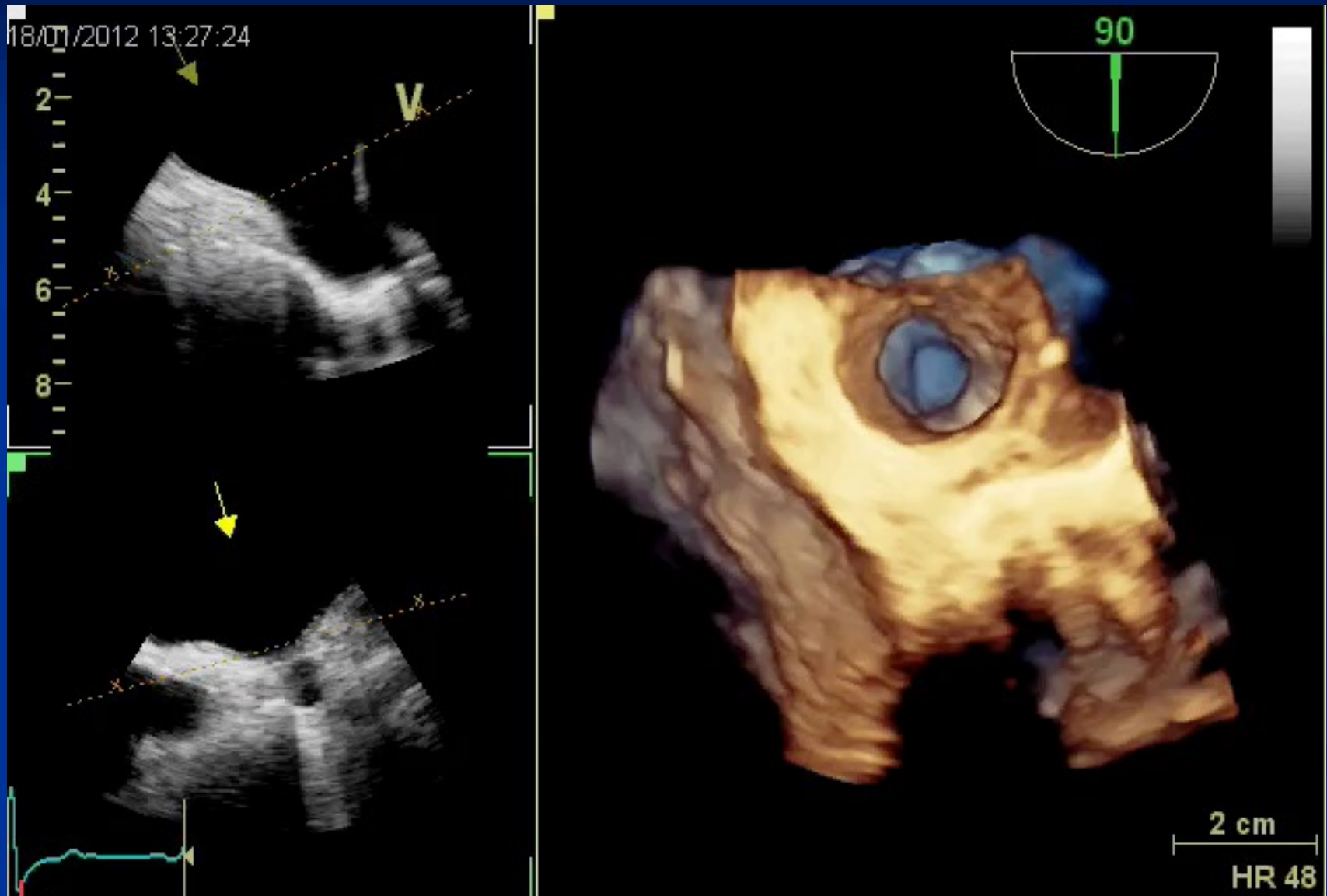
E karfiol



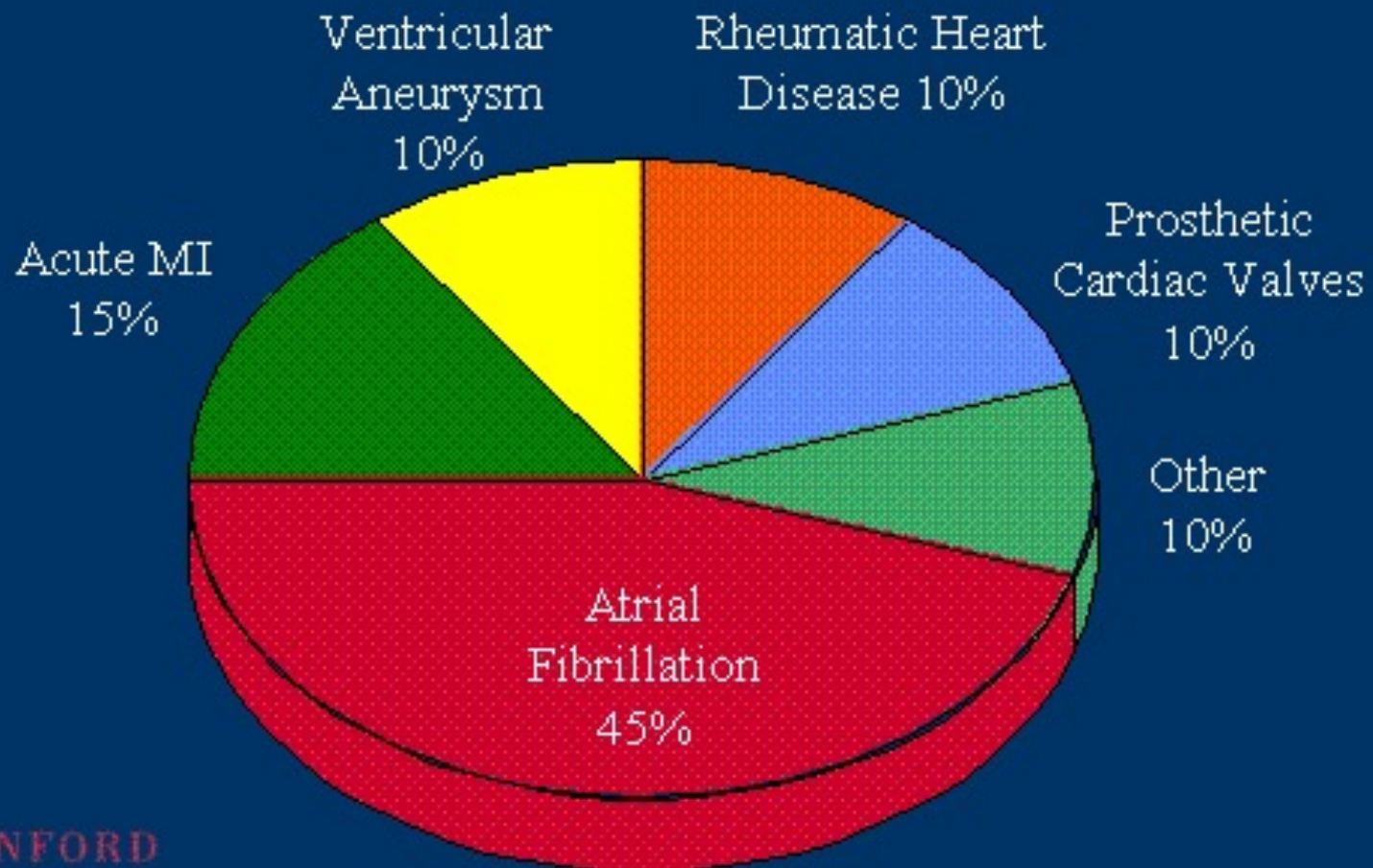
F kaktusz



4D echo



Kardiális embóliaforrások



VÁLTOZÁSOK

A guideline főbb üzenetei:

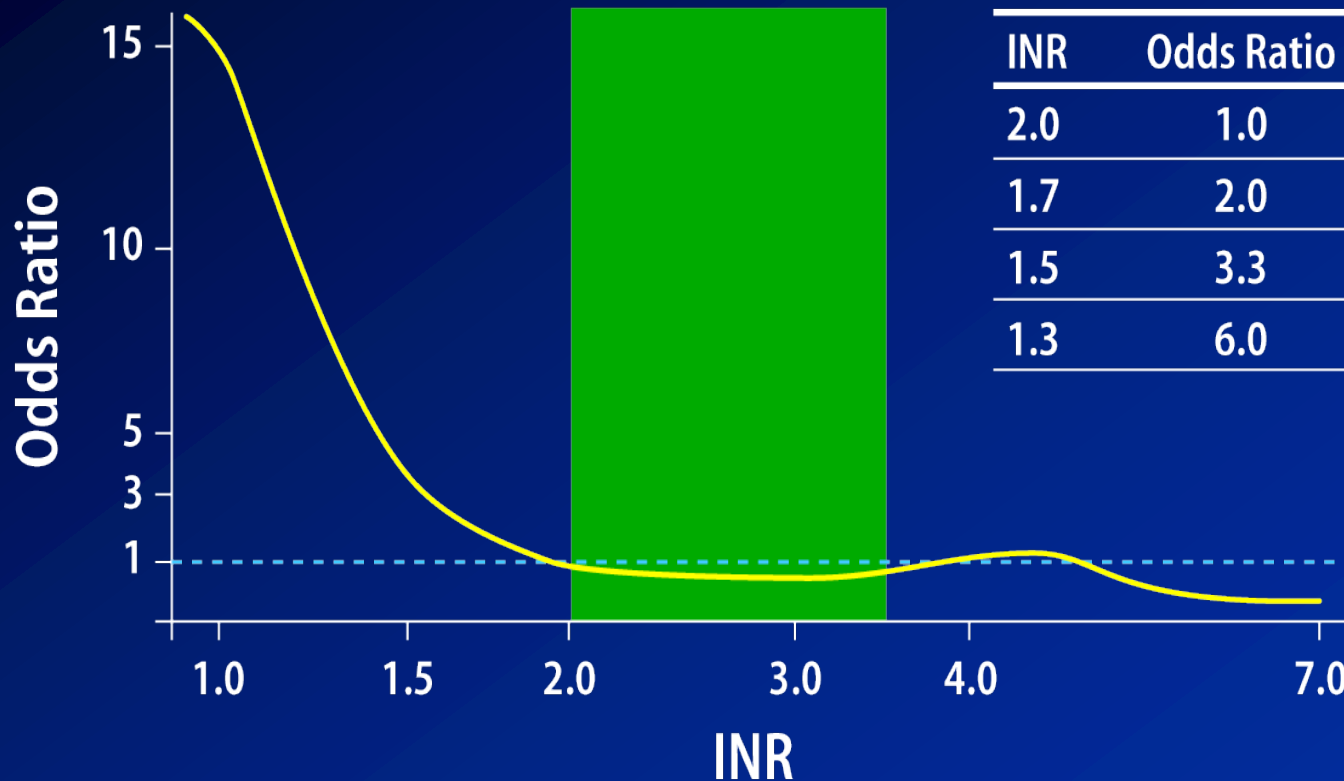
- Még nagyobb hangsúlyt fektet a korai diagnózisra és a tünetmentes, „**silent**” **AF felismerésére**
- A diagnózis alapja a 12-elvezetéses EKG (I B)
- A „silent”, fel nem fedezett AF a leggyakoribb oka a stroke-nak, emiatt a guideline mind az alkalmi, mind a célzott **EKG-szűrést** egyértelműen javasolja a 65 év felettiekben, illetve a stroke-on vagy TIA-n átesett betegekben (I B), 75 év felett ennek hiányában is

Recommendations for screening for atrial fibrillation

Recommendations	Class ^a	Level ^b
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age.	I	B
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours.	I	B
It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy.	I	B
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation.	IIa	B
Systematic ECG screening may be considered to detect AF in patients aged >75 years, or those at high stroke risk.	IIb	B

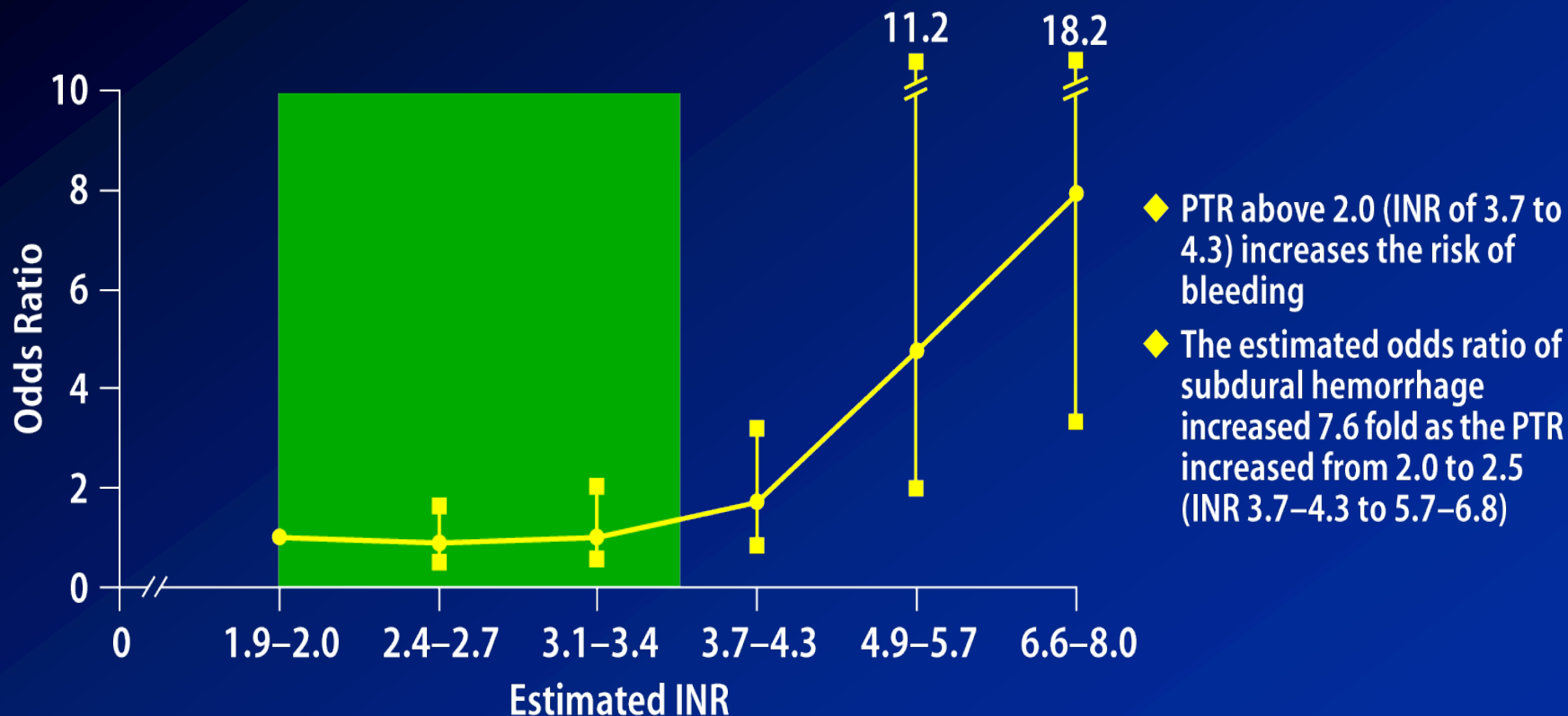
AF = atrial fibrillation; AHRE = atrial high rate episodes; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; TIA = transient ischaemic attack. ^aClass of recommendation. ^bLevel of evidence.

Hatékony Warfarin kezelés a pitvarfibrilláció stroke prevenciójában



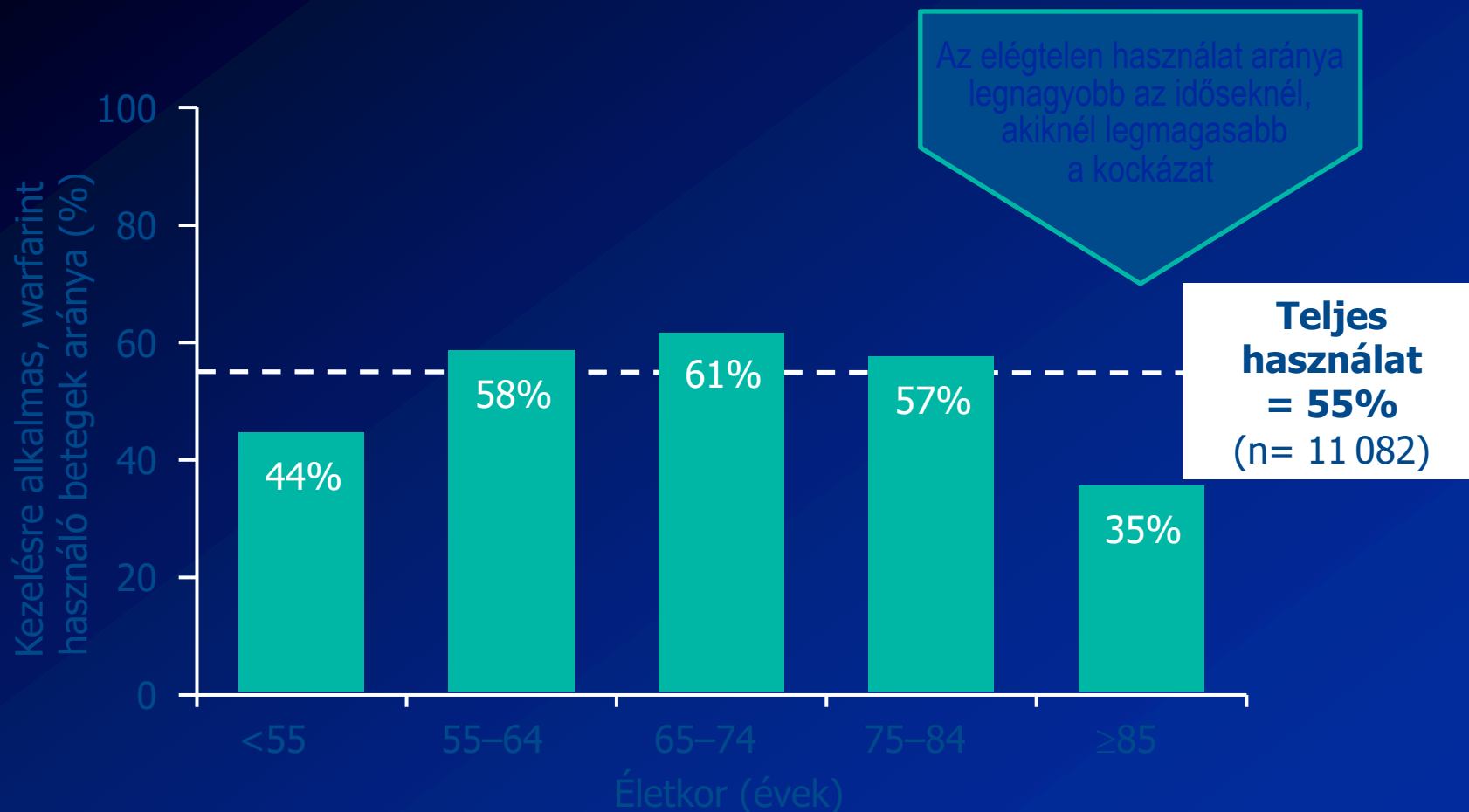
INR below 2.0 results in a higher risk of stroke

AC kezelés és az intracraniális vérzés rizikója



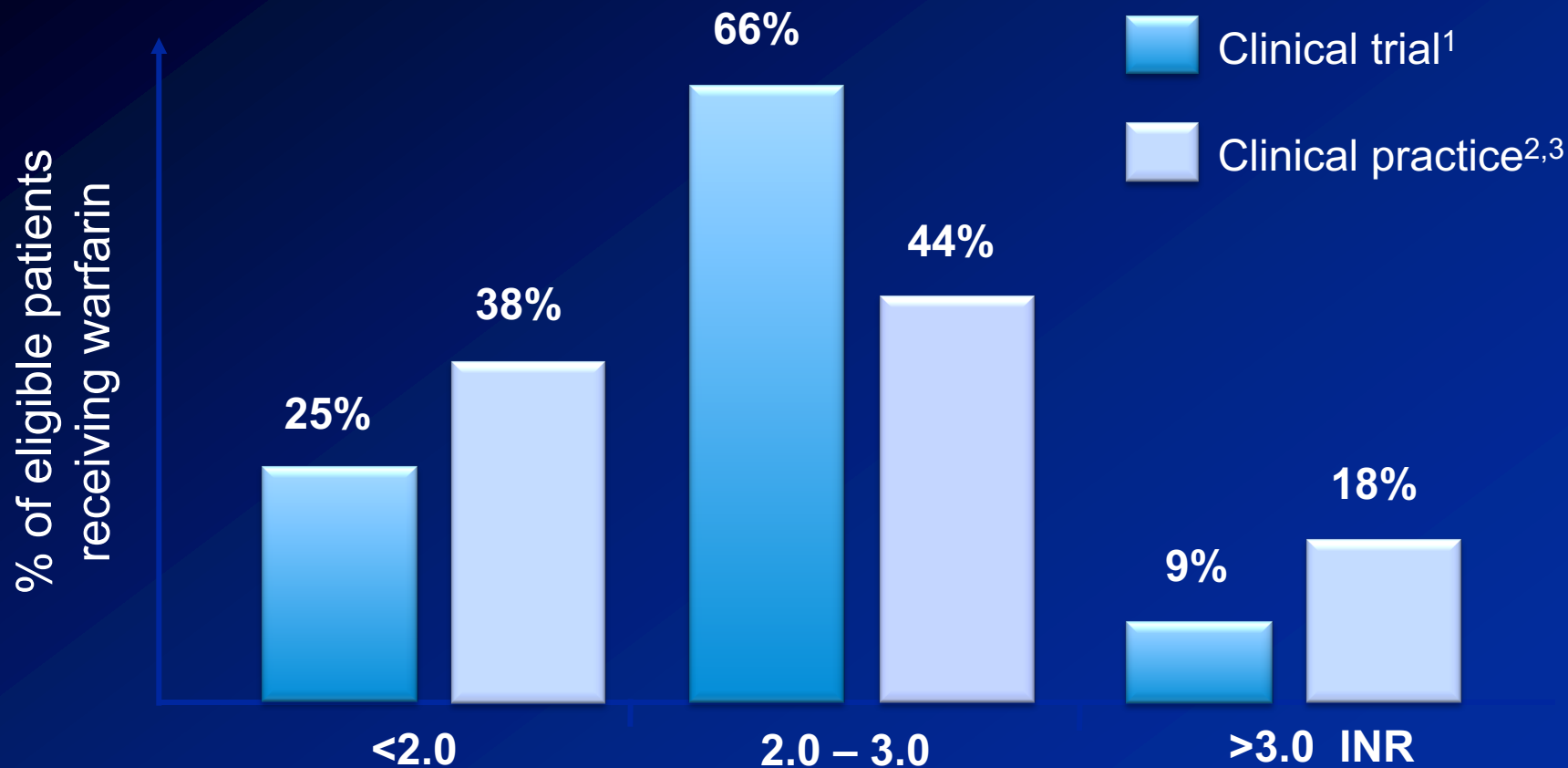
Adapted from: Hylek EM, Singer DE, Ann Int Med
1994;120:897-902

A warfarin-t csak a kezelésre alkalmas PF betegek felénél alkalmazzák



INR control: klinikai vizsgálat vs. való világ

INR* control in clinical trial versus clinical practice (TTR**)



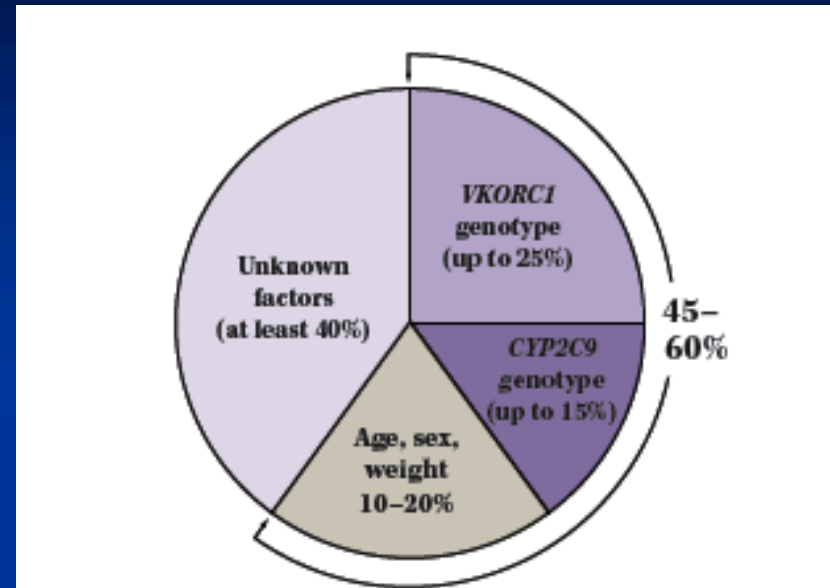
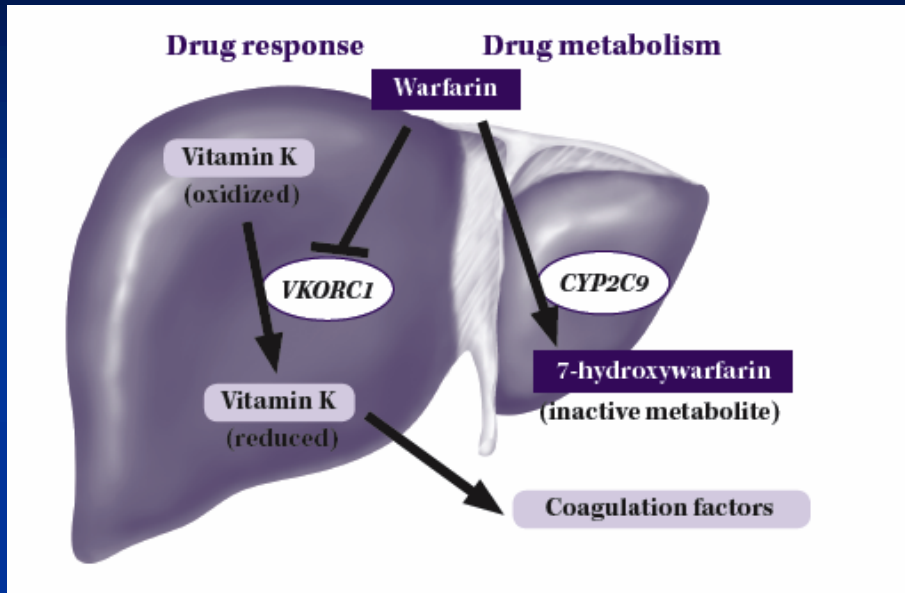
*INR = International normalized ratio

** TTR = Time in Therapeutic Range (INR 2.0-3.0)

1. Kalra L, et al. *BMJ* 2000;320:1236-1239 * Pooled data: up to 83% to 71% in individualized trials; 2. Samsa GP, et al. *Arch Int Med* 2000

3. Matchar DB, et al. *Am J Med* 2002; 113:42-51.

Warfarin genetika



CYP2C9 (warfarin metabolizmust befolyásolja) és VKORC1 (warfarin sensitivitásra van hatással)

A vizsgálat analízise szerint minden “quality-adjusted life year gained” több mint 170,000 \$-ba kerül.

"Personalized, predictive medicine offers great promise, but we need to carefully examine benefits and understand the cost-effectiveness of such strategies before we spend a lot of money on very expensive tests"

A kumarin kezelés korlátai

**Kiszámíthatatlan
válasz**

**Gyakori dózis
módosítás**

**Szűk terápiás ablak
(INR range 2-3)**

**Számos gyógyszer-
táplálék interakció**

**Rendszeres labor
ellenőrzés**

**A kumarin kezelés
nehézségei a
klinikai rutin során**

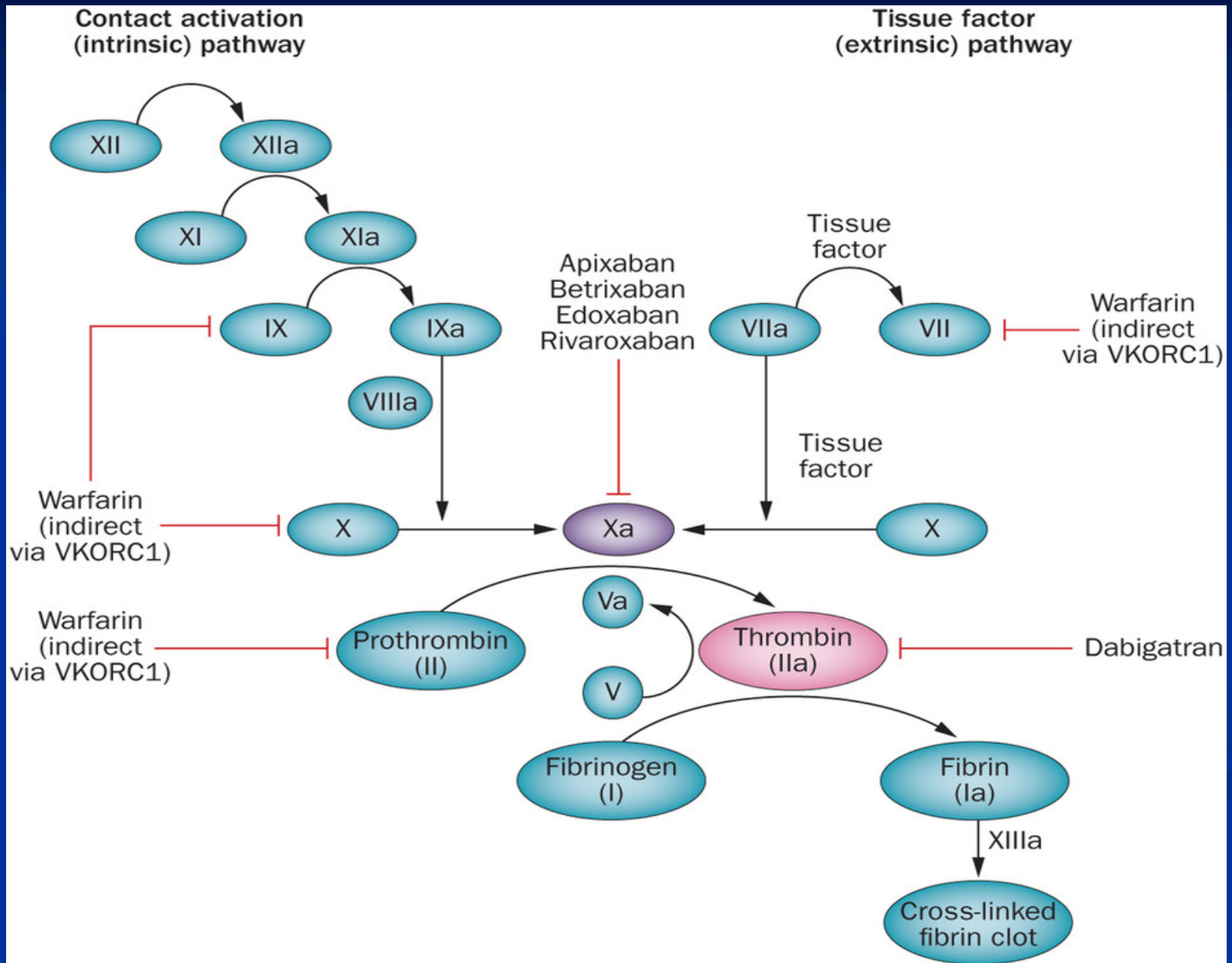
**Számos gyógyszer-
gyógyszer
interakció**

**Lassú hatás/hatás
vesztés**

**Warfarin
rezisztencia**

**Vonakodás a VKA felírástól
Főként idős betegek esetén, mert a vérzéses
szövődmények rizikóját magasnak tartják a lehetséges
haszonhoz képest**

Új antikoagulánsok – NOAC, TSOAC, DOAC



ESC 2012 guideline: a stroke és vérzési kockázat felmérésére

CHADS₂

Stroke Risk Factor	Score
C ongestive Heart Failure	1
H ypertension	1
A ge (> 75 years)	1
D iabetes	1
Prior S troke / TIA	2
Max Score	6

CHA₂DS₂-VASc

Stroke Risk Factor	Score
C ongestive Heart Failure / LV Dysfunction	1
H ypertension	1
A ge (≥ 75 years)	2
D iabetes	1
Prior S troke / TIA / thrombo-embolism	2
V ascular Disease ¹	1
A ge 65-74	1
S ex C ategory (female)	1
Max Score	9

HAS-BLED

Bleeding Risk Factor	Score
H ypertension	1
A bnormal renal or liver function (1 pt. each)	1 or 2
S troke	1
B leeding	1
L abile INRs	1
E lderly (age > 65 years)	1
D rugs or alcohol (1pt. each)	1 or 2
Max Score	9



Note: 1) Prior myocardial infarction, peripheral artery disease, aortic plaque
 Source: ESC Guidelines for the Management of Atrial Fibrillation, European Heart Journal 2010

CHA2DS2-VASc score és a trombotikus rizikó

- Congestive heart failure/
LV dysfunction 1
- Hypertension 1
- Age ≥ 75 2
- Diabetes mellitus 1
- Stroke/TIA/TE 2
- Vascular disease
(CAD, AoD, PAD) 1
- Age 65-74 1
- Sex category (female) 1

Score 0 – 9

Validated in 1084 NVAF patients not on OAC with known TE status at 1 year in Euro Heart Survey

OR for stroke if:

Female: 2.53 (1.08 – 5.92), $p=0.029$;

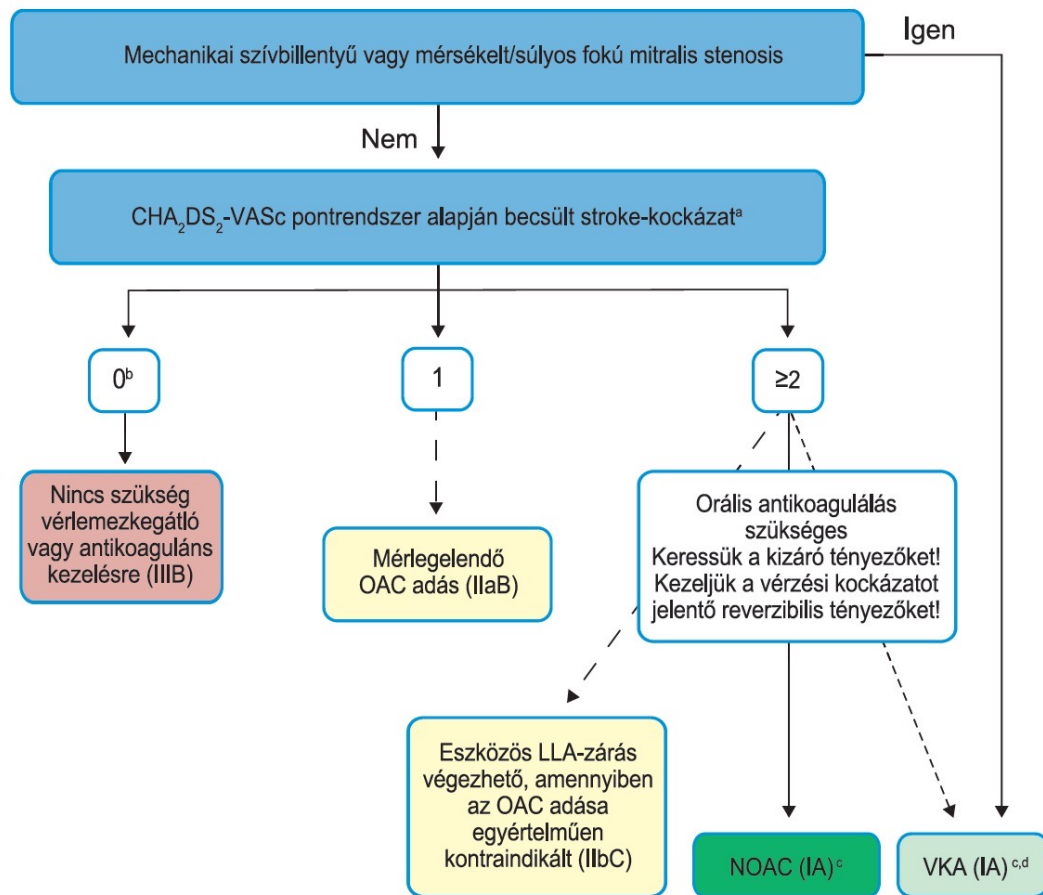
Vascular disease: 2.27 (0.94 – 5.46), $p=0.063$

Score	Annual stroke rate, %	
n	1084	73 538
0	0	0.78
1	1.3	2.01
2	2.2	3.71
3	3.2	5.92
4	4.0	9.27
5	6.7	15.26
6	9.8	19.78
7	9.6	21.50
8	6.7	22.38
9	15.2	23.64

Lip GYH, et al.
Chest 2009

Olesen JB et al.
BMJ 2011;342:124

A pitvarfibrilláció stroke prevenciója



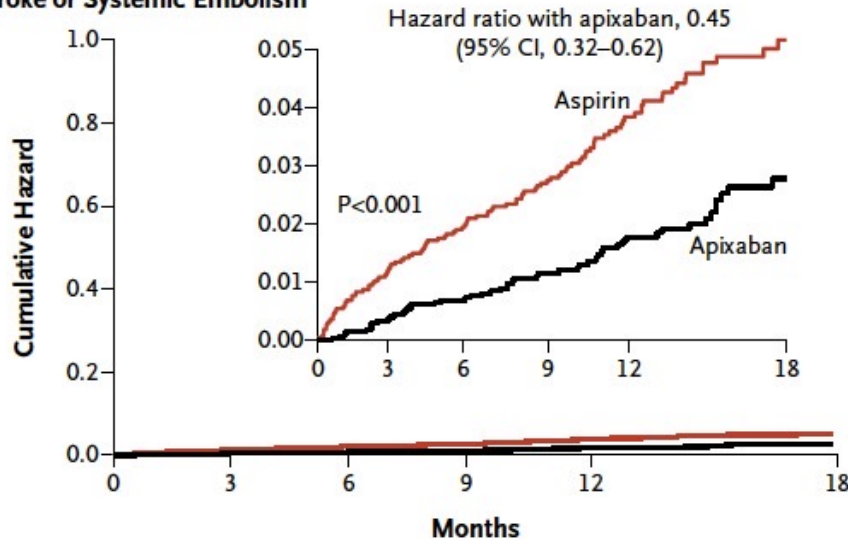
PF: pitvarfibrilláció; LAA: bal pitvari fülcs; NOAC: nem K-vitamin-antagonista orális antikoaguláns; OAC: orális antikoaguláns; VKA: K-vitamin-antagonista
^apangásos szívelégtelenség, magas vérnyomás, életkor ≥ 75 (kétszeres szorzóval), diabétesz, stroke (kétszeres szorzóval), érbetegség, 65–74 év közötti életkor, nem (női nem). ^bAz egyéb stroke-kockázati tényezőkkel nem rendelkező nőket beleértve. ^cIIaB csak további 1 stroke-kockázati tényezővel rendelkező nőknél. ^dIB mitralis stenosisos vagy mechanikai szívbillentyűvel rendelkező betegeknél.

Table 1 Selected indications and contraindications for NOAC therapy in AF patients

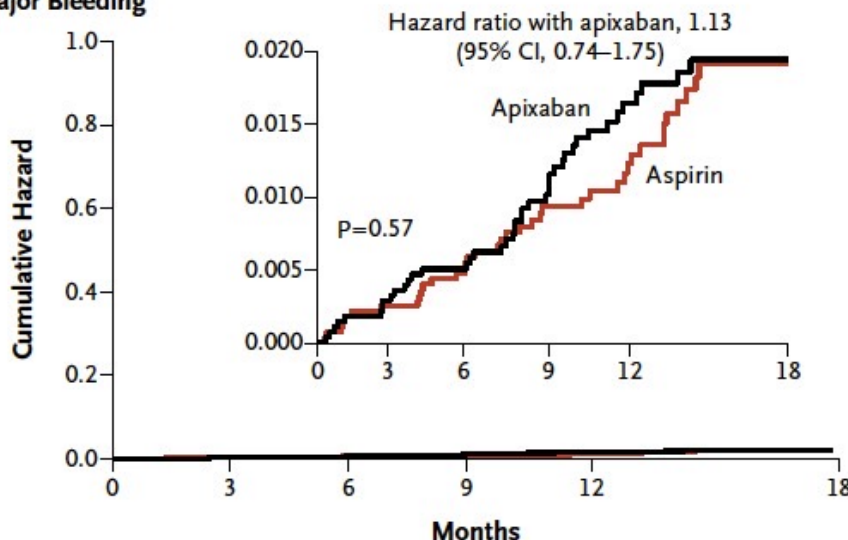
Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome ^{15,16}
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.) Bioprosthetic valve/valve repair (after >3 months postoperative)	Included in NOAC trials Acceptable	Data regarding efficacy and safety overall consistent with patients without valvular heart disease ^{12,17–22} Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA ²⁴ Patients without AF usually on ASA after 3–6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT ^{25,26}
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rationale for less efficacy and safety vs. VKA Observational data positive for NOACs ^{33–36}

AVERROES

A Stroke or Systemic Embolism



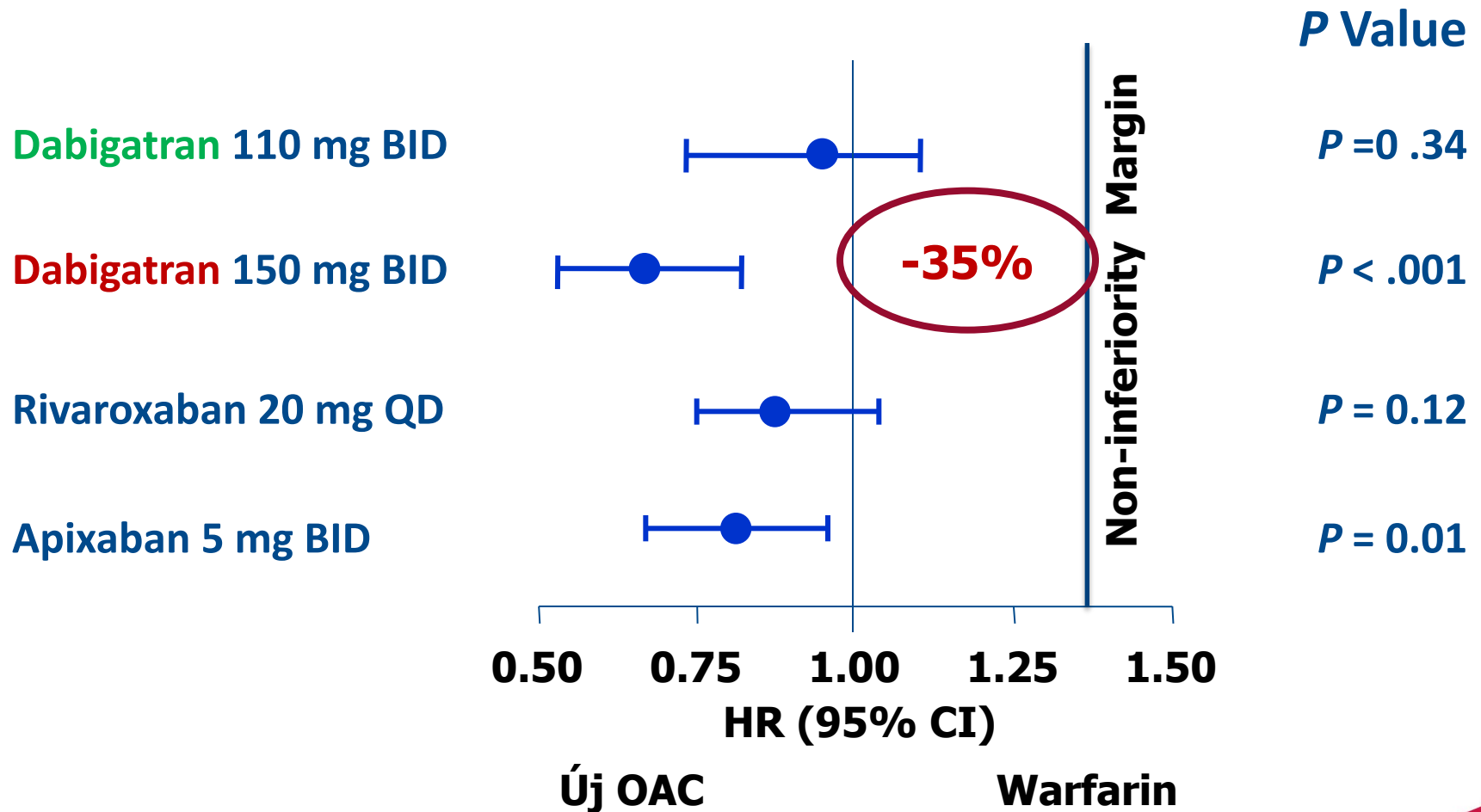
B Major Bleeding



1. Assessment that the INR could not be maintained in the therapeutic range;
2. Adverse event during VKA therapy;
3. A serious bleeding event on VKA therapy;
4. Assessment that INR could not or was unlikely to be measured at requested interval;
5. Expected difficulty in contacting patient for urgent change in dose of VKAs;
6. Uncertainty about patient's ability to adhere to instructions regarding VKA therapy;
7. Concurrent medications that could alter activity of VKAs;
8. Concurrent medications whose metabolism could be affected by VKAs;
9. Assessment that patient would be unable or unlikely to adhere to restrictions on factors such as alcohol and diet;
10. Hepatic disease;
12. A CHADS2 score of 1 or less;
13. VKA therapy not recommended by the physician;
15. Patient's refusal to take VKAs; and

Új OAC-k:

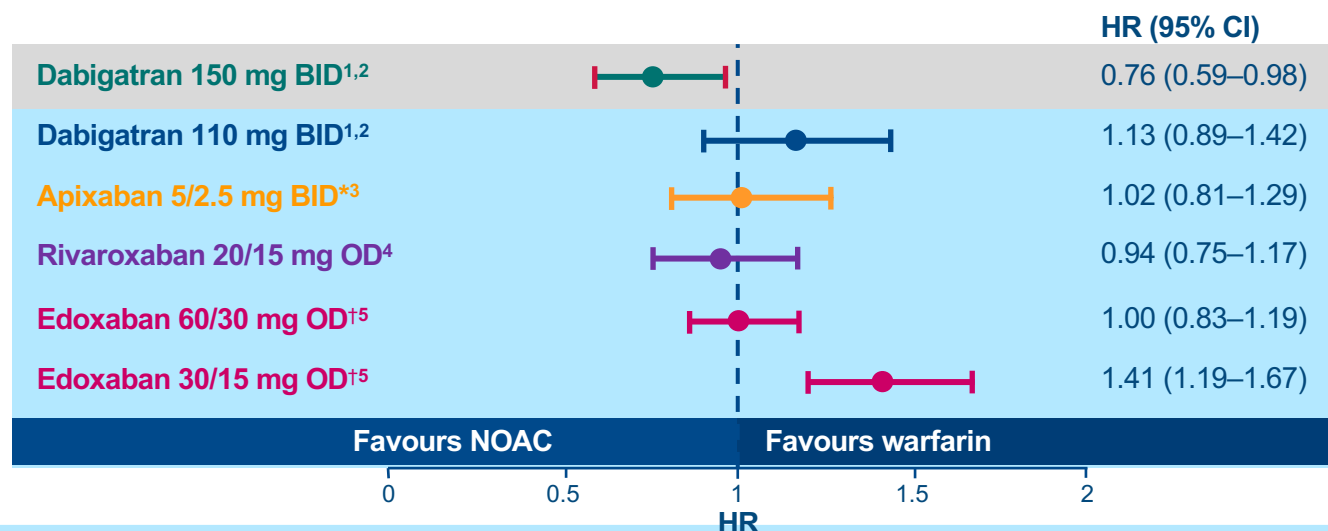
PRIMER EP- Stroke és szisztémás embolizáció megelőzése a klinikai vizsgálatok alapján



Not head to head comparison – For illustrative purposes only

Connolly SJ, et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6; Patel MR, et al. N Engl J Med 2011;365:883–91; Granger C, et al. N Eng J Med 2011;365:981–92.

Dabigatran 150 mg BID reduced the risk of ischaemic stroke (the most common stroke associated with AF) vs warfarin

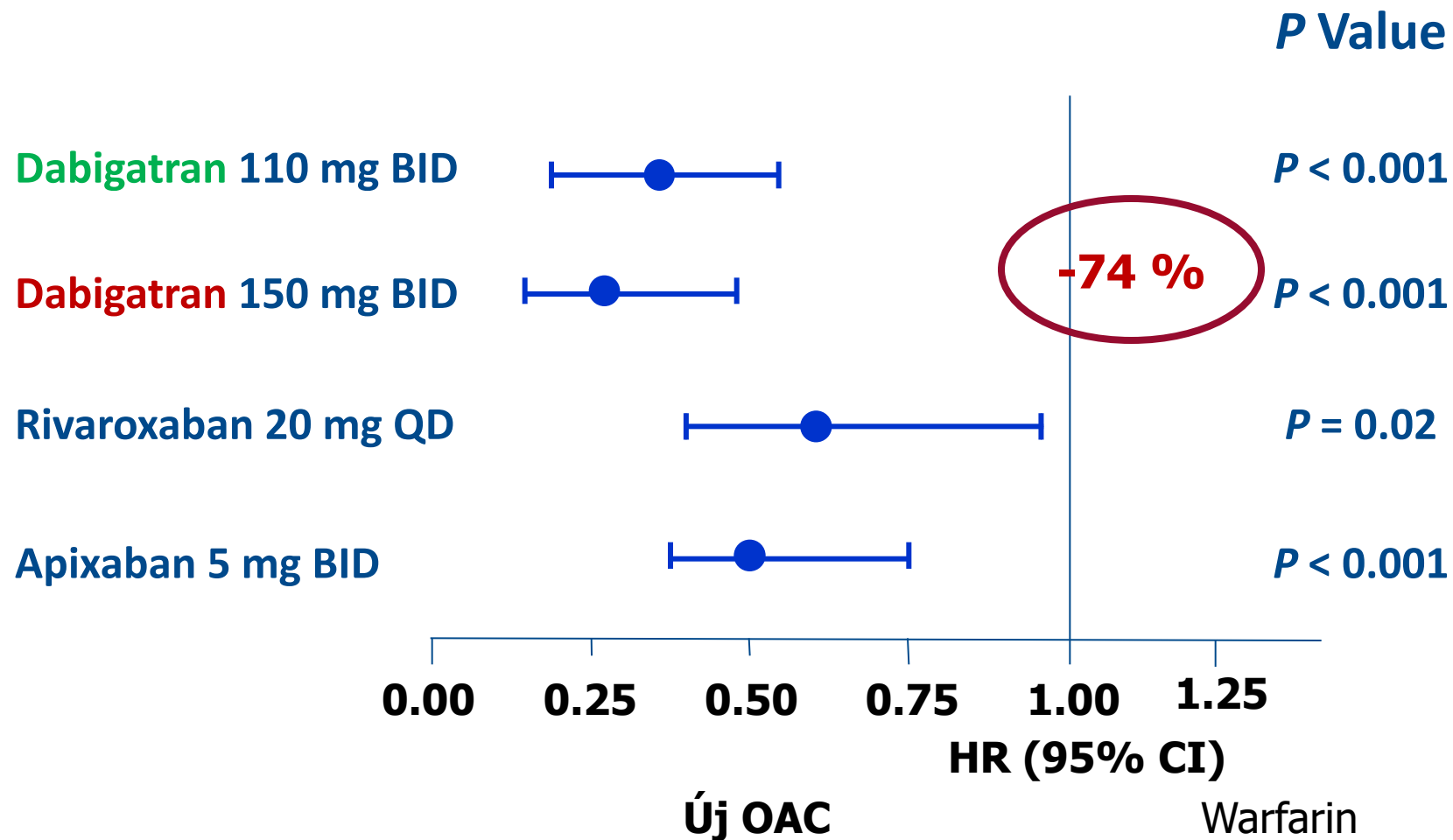


Similar risk of ischaemic stroke for other NOACs vs warfarin in clinical trials

Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–5

^{*}Revised data; re-categorized following original publication. [†] Edoxaban dose halved (from 60 mg to 30 mg OD in the high-dose group; from 30 mg to 15 mg OD in the low-dose group) if CrCl 30–50 mL/min, weight ≤60 kg, or concomitant verapamil, quinidine, or dronedarone. 1. Connolly SJ et al. N Engl J Med 2009; 2. Pradaxa®: EU SPC, 2015; 3. Lopes et al. Lancet 2012; 4. Patel MR et al. N Engl J Med 2011; 5. Giugliano RP et al. N Engl J Med 2013

SECUNDER EP - A vérzések stroke előfordulása

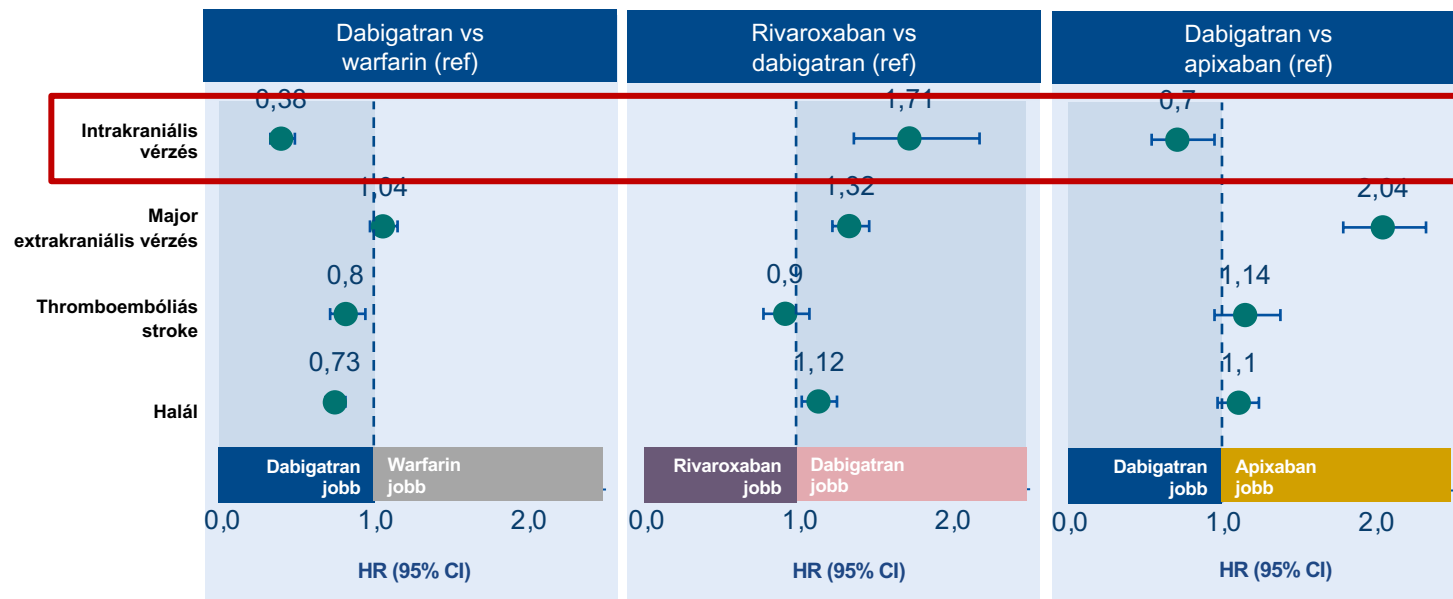


Not head to head comparison – For illustrative purposes only

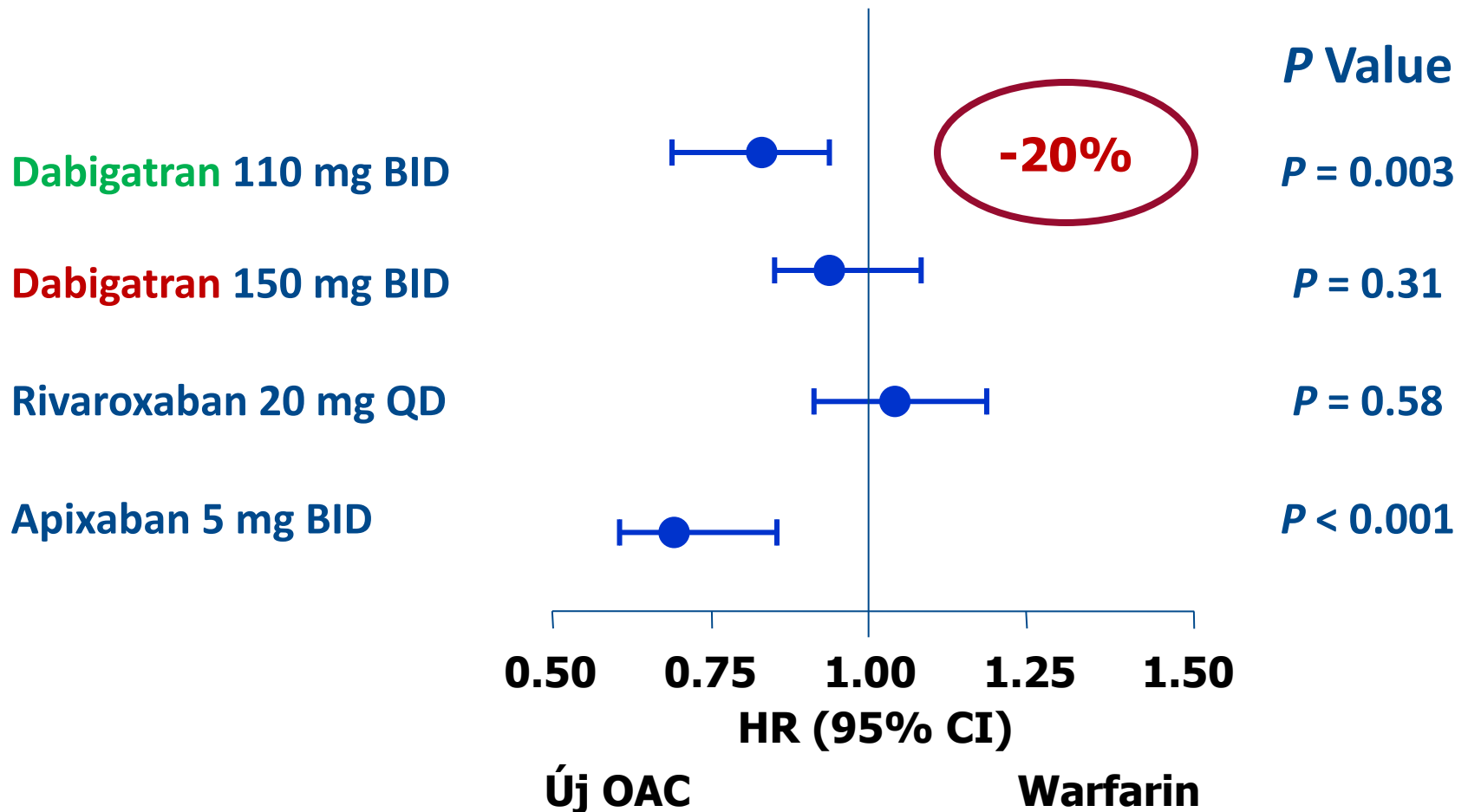
Connolly SJ, et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6; Patel MR, et al. N Engl J Med 2011;365:883–91; Granger C, et al. N Engl J Med 2011;365:981–92.

GRAHAM 2019:

A dabigatran mellett szignifikánsan alacsonyabb az intrakraniális vérzés kockázata, mint bármelyik NOAC esetében a warfarinhoz viszonyítva



SECUNDER EP - Major vérzés a SPAF vizsgálatokban



Not head to head comparison – For illustrative purposes only

Connolly SJ, et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6; Patel MR, et al. N Engl J Med 2011;365:883–91; Granger C, et al. N Engl J Med 2011;365:981–92.

Ajánlások a pitvarfibrilláló betegek stroke-prevenációjához			
Ajánlások	Osztály ^a	Szint ^b	
Tromboembólia megelőzése céljából orális antikoaguláns terápiában javasolt részesíteni a 2 vagy magasabb CHA ₂ DS ₂ -VASc pontszámot elérő pitvarfibrilláló férfiakat.	I	A	
Tromboembólia megelőzése céljából orális antikoaguláns terápiában javasolt részesíteni a 3 vagy magasabb CHA ₂ DS ₂ -VASc pontszámot elérő pitvarfibrilláló nőket.	I	A	
Tromboembólia megelőzése céljából megfontolandó az orális antikoaguláns terápia indítása az 1 vagy magasabb CHA ₂ DS ₂ -VASc pontszámot elérő pitvarfibrilláló férfiaknál, figyelembe véve a beteg egyéni sajátosságait és preferenciáit.	IIa	B	
Tromboembólia megelőzése céljából megfontolandó az orális antikoaguláns terápia indítása az 2 vagy magasabb CHA ₂ DS ₂ -VASc pontszámot elérő pitvarfibrilláló nőknél, figyelembe véve a beteg egyéni sajátosságait és preferenciáit.	IIa	B	
K-vitamin-antagonista kezelés (INR 2–3 között vagy magasabb) javasolt stroke-prevenció céljából a mérsékelt-súlyos fokú mitralis stenosisban szenvedő vagy a mechanikai műbillentyűvel rendelkező betegeknél.	I	B	
Ha orális antikoagulálásban kell részesíteni egy olyan PF-beteget aki szedhet NOAC-ot (apixaban, dabigatran, edoxaban, rivaroxaban), akkor a NOAC-ot kell választani a K-vitamin-antagonistával szemben.	I	A	
A K-vitamin-antagonistával kezelt betegeknél az a cél, hogy a terápiás tartományban (TTR) töltött idő minél magasabb legyen és szorosan monitorozzuk a beteget.	I	A	
A K-vitamin-antagonistával kezelt PF-betegeknél megfontolandó a NOAC-ra történő váltás, amennyiben a TTR a megfelelő beteg-együttműködés ellenére sem jól kontrollált, vagy amennyiben a beteg ehhez ragaszkodik és nem áll fenn a NOAC-oknak kontraindikációja (pl. műbillentyű).	IIb	A	
PF-betegeknél az orális antikoagulánsok és a vérlemezkegátlók együttes alkalmazása növeli a vérzés kockázatot, ezért ha nem áll fenn egyéb indikáció a vérlemezkegátlók alkalmazására, kombinációjuk kerülendő.	III (káros)	B	
Egyéb stroke-kockázati tényezők hiányában nem ajánlott antikoaguláns vagy vérlemezkegátló terápiát folytatni stroke-prevenció céljából sem pitvarfibrilláló nőknél, sem pitvarfibrilláló férfiaknál.	III (káros)	B	
A vérlemezkegátlók adása önmagában nem javasolt stroke-prevenció céljára PF-betegeknél a stroke-kockázat mértékétől függetlenül.	III (káros)	B	
Nem javasolt a NOAC-ok (apixaban, dabigatran, edoxaban, rivaroxaban) alkalmazása sem a mechanikai műbillentyűvel rendelkező betegeknél („B” szintű evidencia), sem pedig mérsékelt-súlyos fokú mitralis stenosisban („C” szintű evidencia).	III (káros)	B	C

VÁLTOZÁSOK – 4.

A guideline főbb üzenetei:

- A vérzés kivédése
kiemelten **fontos** az OAC-
terápiában részesülő
betegekben.
- Ennek érdekében a
guideline felsorolja a
legfontosabb,
befolyásolható vérzéses
kockázati tényezőt,
amelyeket a klinikusnak
igyekeznie kell
kiküszöbölni.
- Ugyanakkor speciális
vérzéses score
alkalmazására nincs a
továbbiakban szükség.

Table 9 Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on bleeding risk scores

Modifiable bleeding risk factors

Hypertension (especially when systolic blood pressure is >160 mmHg)^{a,b,c}

Labile INR or time in therapeutic range <60%^a in patients on vitamin K antagonists

Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs^{a,d}

Excess alcohol (≥8 drinks/week)^{a,b}

Potentially modifiable bleeding risk factors

Anaemia^{b,c,d}

Impaired renal function^{a,b,c,d}

Impaired liver function^{a,b}

Reduced platelet count or function^b

Non-modifiable bleeding risk factors

Age^e (> 65 years)^a (≥75 years)^{b,c,d}

History of major bleeding^{a,b,c,d}

Previous stroke^{a,b}

Dialysis-dependent kidney disease or renal transplant^{a,c}

Cirrhotic liver disease^a

Malignancy^b

Genetic factors^b

Biomarker-based bleeding risk factors

High-sensitivity troponin^e

Growth differentiation factor-15^e

Serum creatinine/estimated CrCL^e

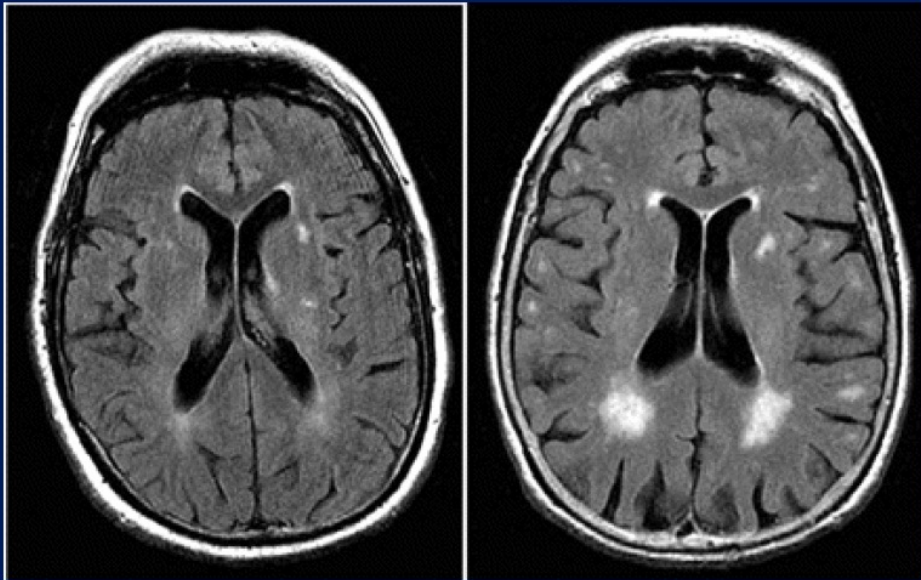
Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.

IIa

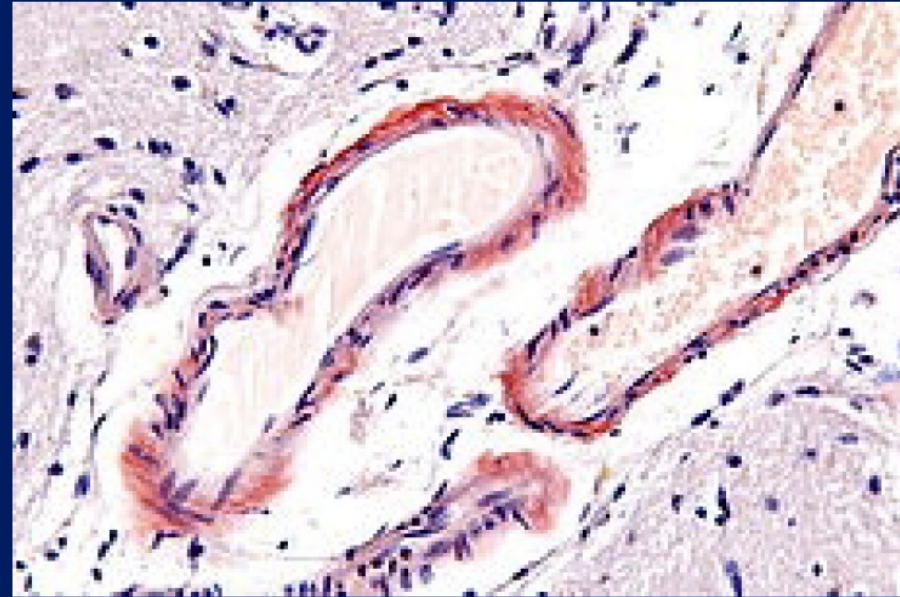
B

AC kezelés és agyvérzés kockázata

80 years of age

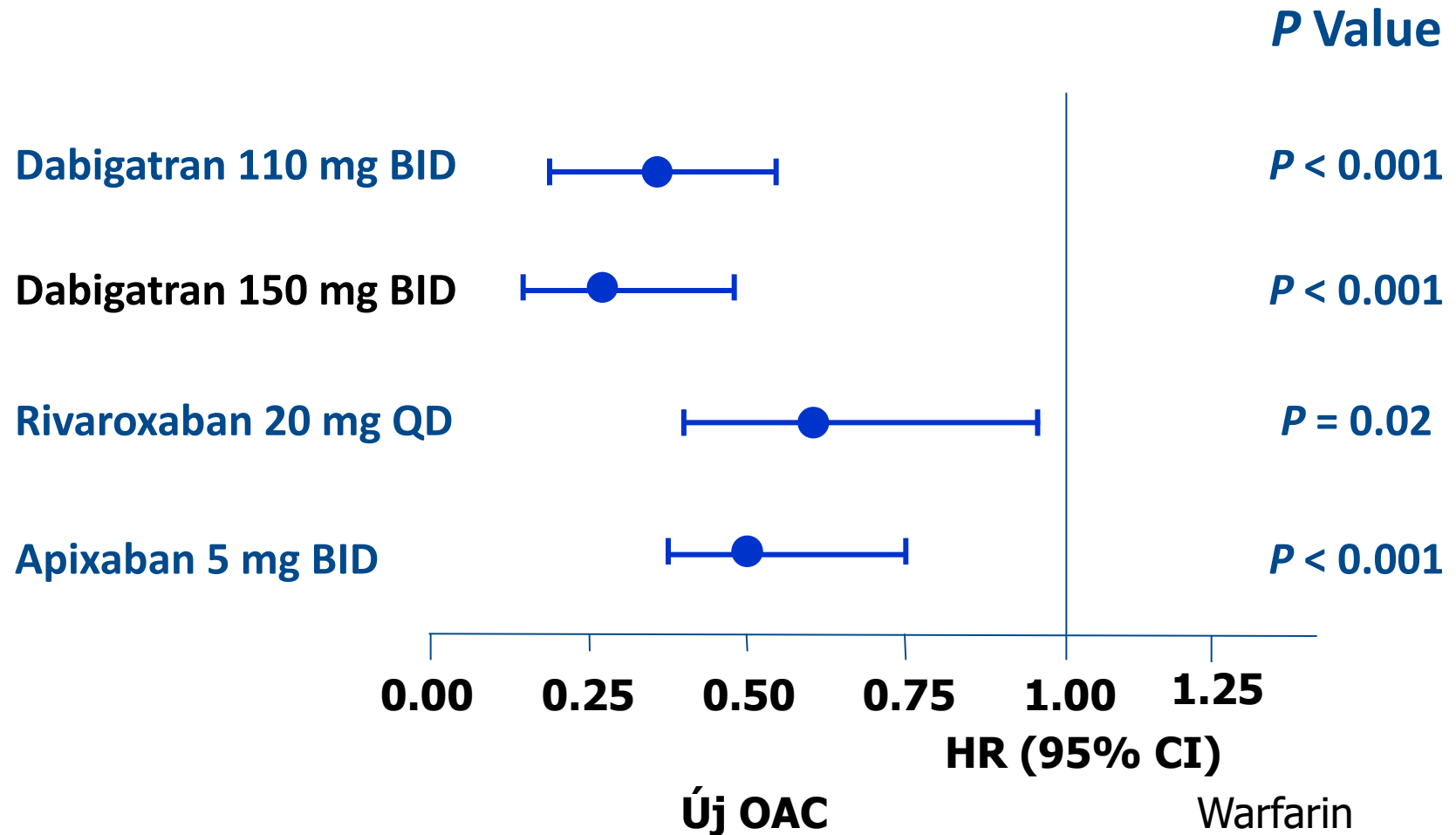


Leukoaraiosis
Hypertensive-deep white matter



Amyloid
Lobar hemorrhage

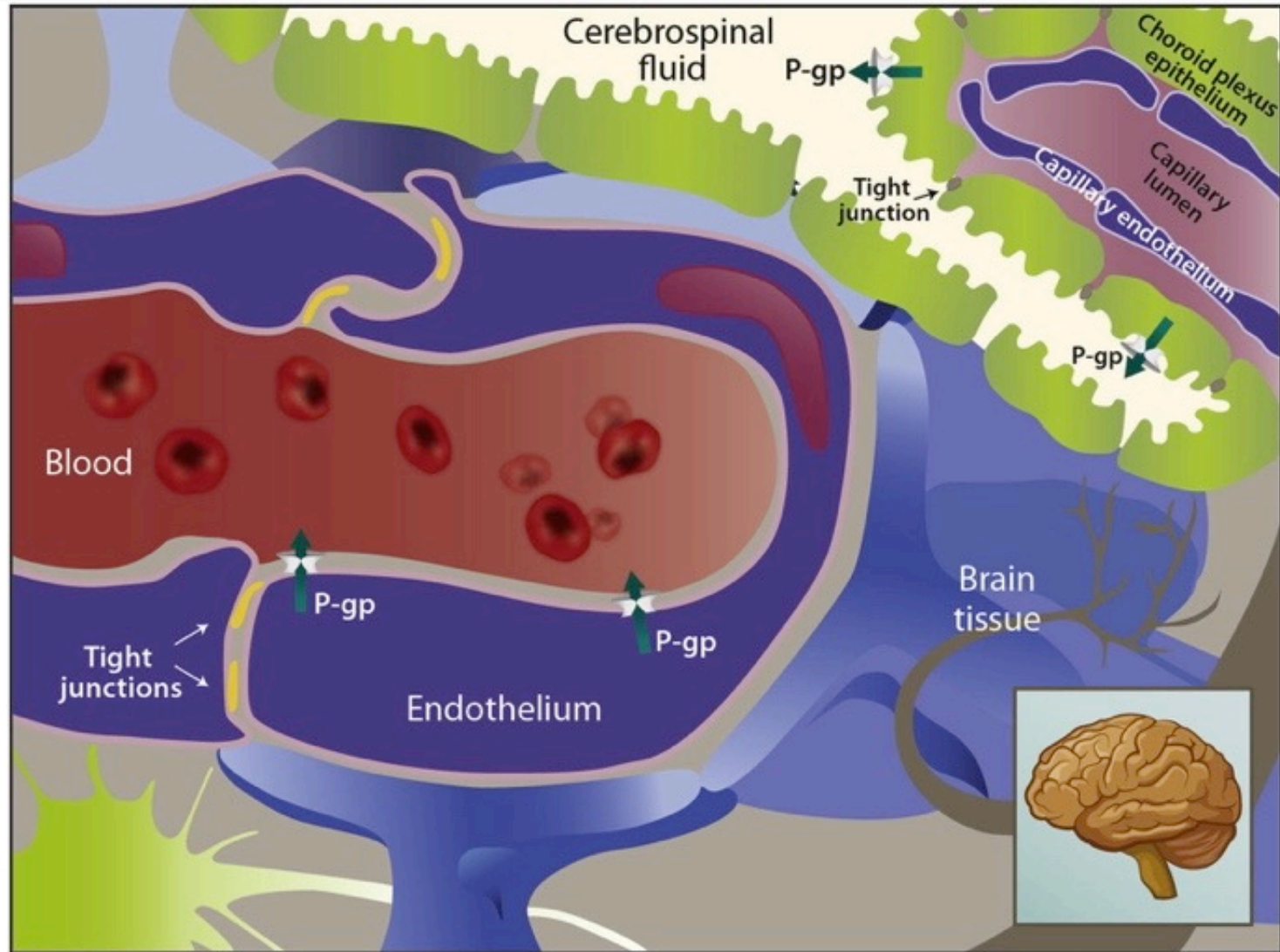
SECUNDER EP - A vérzéses stroke előfordulása



Not head to head comparison – For illustrative purposes only

Connolly SJ, et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6; Patel MR, et al. N Engl J Med 2011;365:883–91; Granger C, et al. N Eng J Med 2011;365:981–92.

Role of P-gp in efflux transport at Blood Brain Barrier



Home | Health Faculties | Study | Studentships | Do blood brain-barrier (BBB) efflux proteins confer a protective property against intracranial haemorrhage (ICH) in those patients prescribed the novel oral anticoagulants (NOACs), dabigatran and rivaroxaban?

STUDENTSHIPS

ABOUT

HISTORY

RESEARCH

STUDY

Studentships

Advertise a Studentship
(internal only)

Teaching facilities

WHAT'S ON

GIVING

Do blood brain-barrier (BBB) efflux proteins confer a protective property against intracranial haemorrhage (ICH) in those patients prescribed the novel oral anticoagulants (NOACs), dabigatran and rivaroxaban?

First supervisor: [Jignesh P.Patel](#)

Second supervisor: [Sarah A.Thomas](#)

Division: [Institute of Pharmaceutical Science](#)

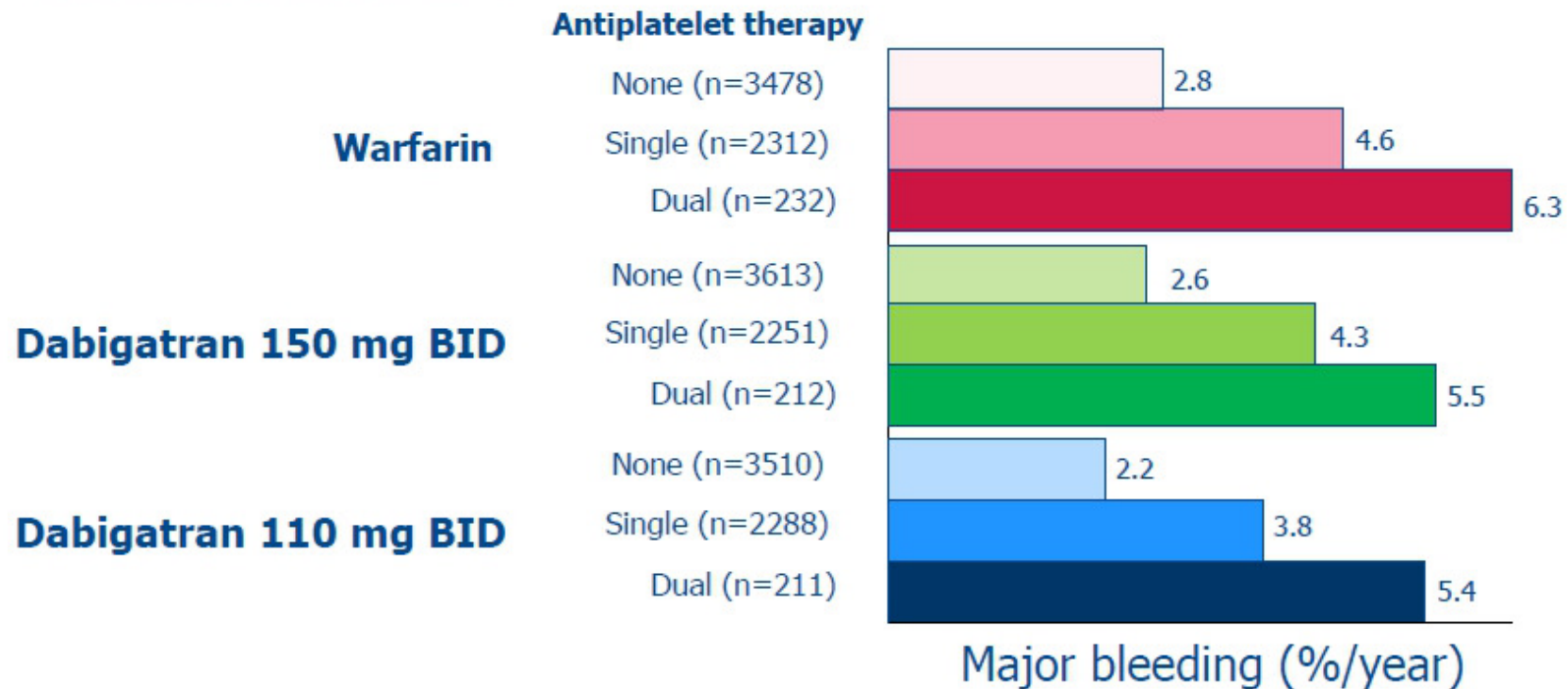
Type of programme: 4 Years

Project code: IPSPatelJ



A kombinációs terápia PF-ban és ACS-ben szenvedő betegeknek a vérzés fokozott kockázatával jár együtt

Outcomes from RE-LY®:



Triple therapy is associated with the greatest increase in bleeding risk both with dabigatran and with warfarin, but the risk is not higher with dabigatran

Figure 20 (1) Post-procedural management of patients with AF and ACS/PCI (full-outlined arrows represent a default strategy; graded/dashed arrows show treatment modifications depending on individual patient's ischaemic and bleeding risks)

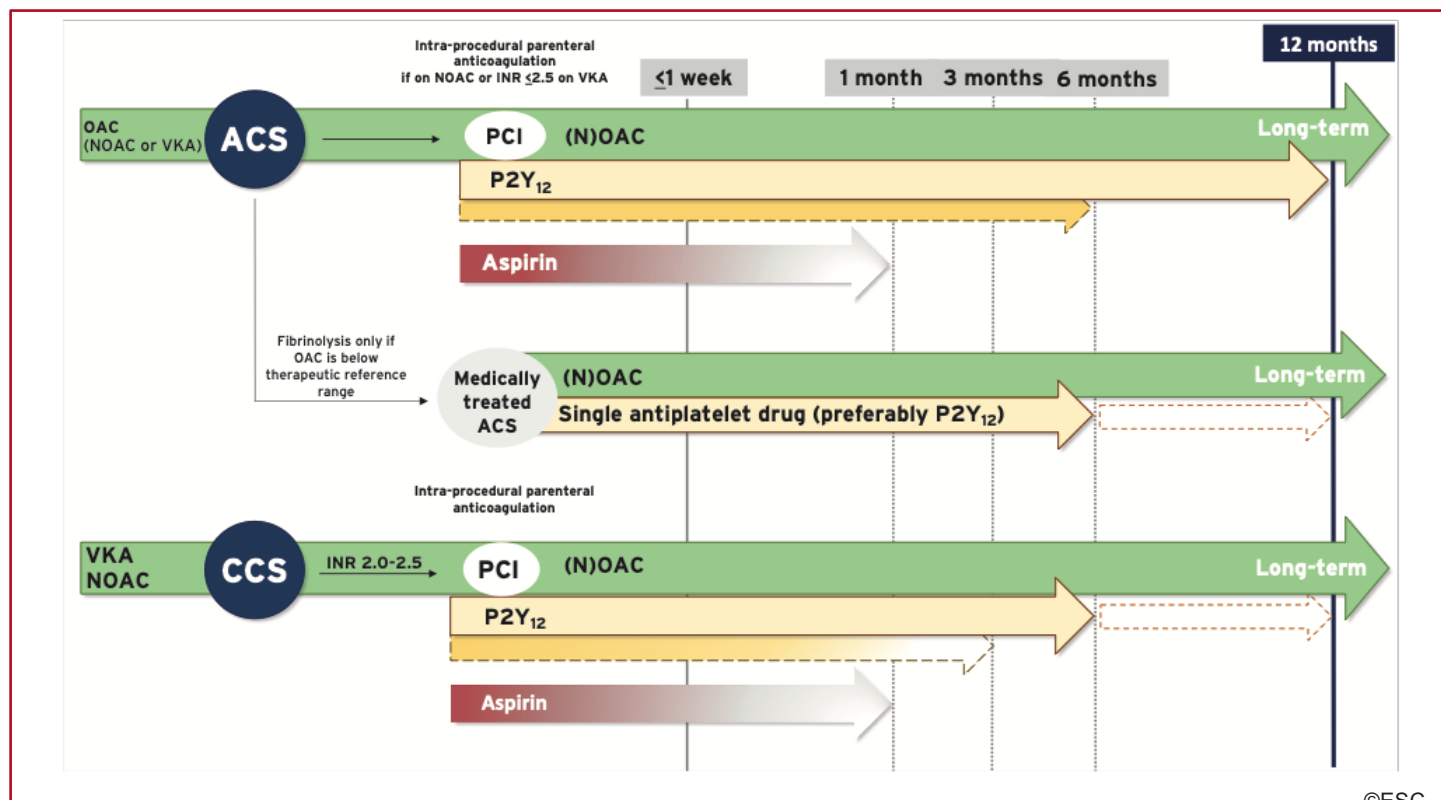


Figure 20 (2) Post-procedural management of patients with AF and ACS/PCI (full-outlined arrows represent a default strategy; graded/dashed arrows show treatment modifications depending on individual patient's ischaemic and bleeding risks)

THROMBOTIC RISK FACTORS

- Diabetes mellitus requiring therapy
- Prior ACS/recurrent myocardial infarction
- Multivessel CAD
- Concomitant PAD
- Premature CAD (occurring at age of <45 y) or accelerated CAD (new lesion within 2 years)
- CKD (eGFR <60 mL/min)
- Clinical presentation (ACS)
- Multivessel stenting
- Complex revascularisation (left main stenting, bifurcation lesion stenting, chronic total occlusion intervention, last patent vessel stenting)
- Prior stent thrombosis on antiplatelet treatment
- Procedural factors (stent expansion, residual dissection, stent length, etc.)

BLEEDING RISK FACTORS

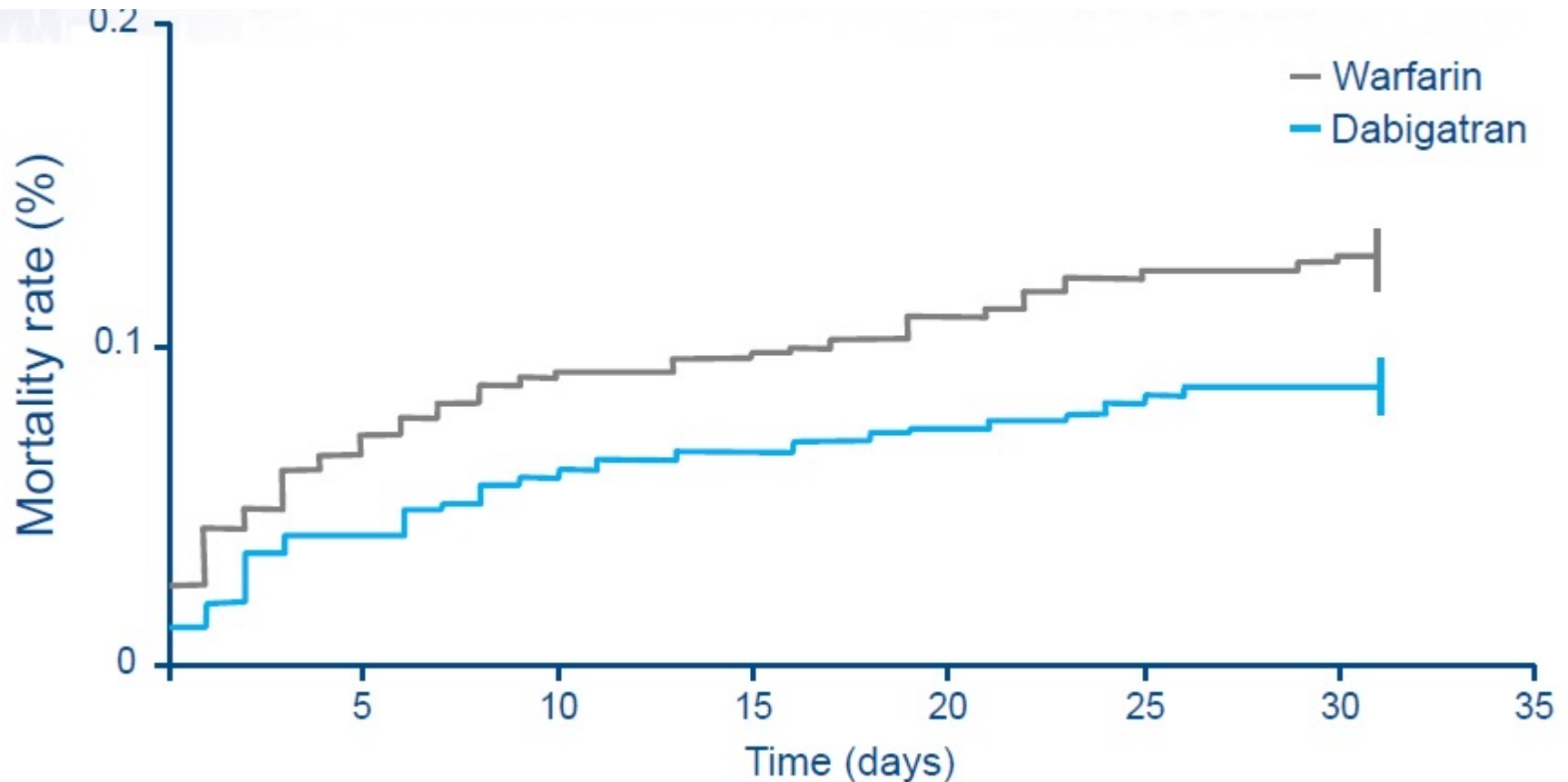
- Hypertension
- Abnormal renal or liver function
- Stroke or ICH history
- Bleeding history or bleeding diathesis (e.g., anaemia with haemoglobin <110 g/L)
- Labile INR (if on VKA)
- Elderly (>65 years)
- Drugs (concomitant OAC and antiplatelet therapy, NSAIDs), excessive alcohol consumption

STRATEGIES TO REDUCE BLEEDING ASSOCIATED WITH PCI

- Radial artery access
- PPIs in patients taking DAPT who are at increased risk of bleeding (e.g., the elderly, dyspepsia, gastro-oesophageal reflux disease, Helicobacter pylori infection, chronic alcohol use)
- Non-administration of unfractionated heparin in patients on VKA with INR >2.5
- Pre-treatment with aspirin only, add a P2Y₁₂ inhibitor when coronary anatomy is known or if STEMI
- GP IIb/IIIa inhibitors only for bailout or periprocedural complications
- Shorter duration of combined antithrombotic therapy

©ESC

A mortalitás alacsonyabb dabigatran kezelés során major vérzés esetén



Kaplan–Meier analysis indicated a reduced risk for death with dabigatran vs warfarin during 30 days from the bleeding ($P=0.052$)
Data are derived from five Phase III trials: (RE-LY®, RE-COVER™, RE-COVER™ II, RE-MEDY™, RE-SONATE™) and the total number of patients randomized ($N=27\,419$)

The first patient trial of a NOAC-specific antidote



RE-VERSE AD™

Study of reversal effects of idarucizumab
in patients on active dabigatran

Clinical practice study to evaluate reversal of the anticoagulant effects of dabigatran with idarucizumab in



Bleeding patients – overt bleeding judged by the physician to require a reversal agent

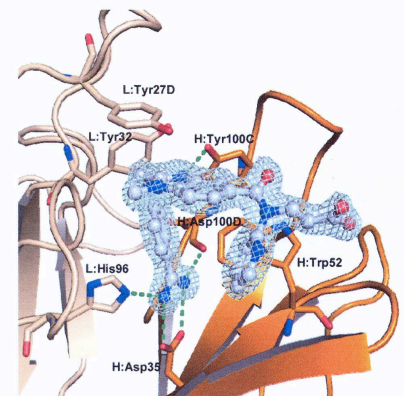


Surgical patients – require an emergency surgery or procedure for a condition other than bleeding

Started in April 2014

Currently recruiting in >35 countries worldwide

The antidote is still under investigation and has not yet been approved for clinical use



Dabigatran binding to the neutralizing monoclonal antibody, aDabi-Fab. See Figure 2 in the article by Schiele et al that begins on page 3554.

Az idarucizumab megfelel az „ideális” ellenszer ismérveinek



Az idarucizumab a dabigatrán kezelés szövődményeinek hathatós ellenszereként hozzásegíti az orvosokat ahhoz, hogy a sürgősségi betegellátás más, életfontosságú vonatkozásaira összpontosíthassanak.

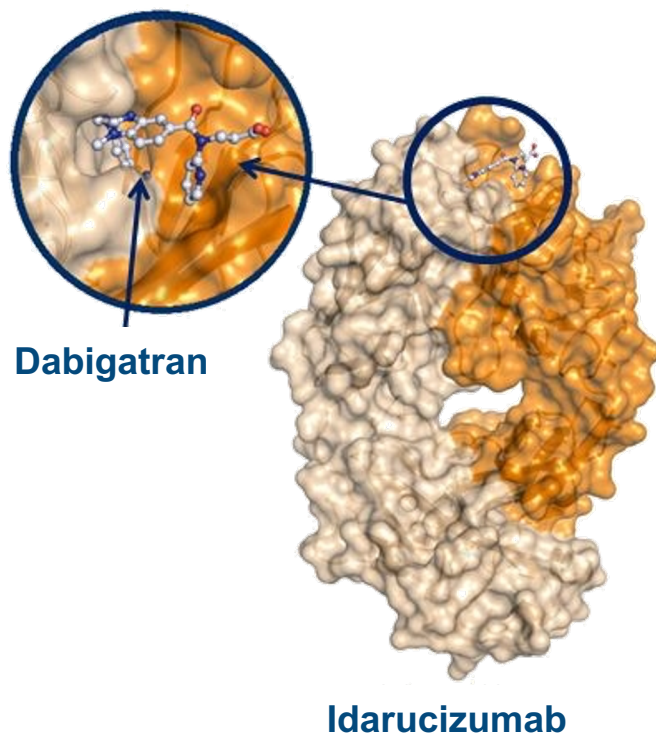
Idarucizumab - Praxbind®

NOAC reversal agent	Target	Mechanism of action	Investigation status
Idarucizumab ¹	Dabigatran	Humanized Fab: binds dabigatran with high affinity ²	Phase III: patients requiring urgent surgery/procedure <u>or</u> with uncontrolled bleeding ^{3,4}
Andexanet alfa (PRT064445) ¹	FXa inhibitors	Inactivated FXa: competes with FXa for direct FXa inhibitors ⁵	Phase III: bleeding patients ⁶
Aripazine (PER977) ¹	Universal	Synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin) ⁷	Phase II ⁸

Idarucizumab specifically targets dabigatran; does not interact with other components of the coagulation cascade

1. Lauw et al. Can J Cardiol 2014;
2. Schiele et al. Blood 2013;
3. Clinicaltrials.gov: NCT02104947;
4. Pollack et al. ISC 2015;
5. Lu et al. Nat Med 2013;
6. ClinicalTrials.gov Identifier: NCT02329327;
7. Ansell N Engl J Med 2014;
8. ClinicalTrials.gov Identifier: NCT02207257

Az idarucizumabot szelektív, a dabigatrán véralvadásgátló aktivitását felfüggesztő ellenszerként fejlesztették

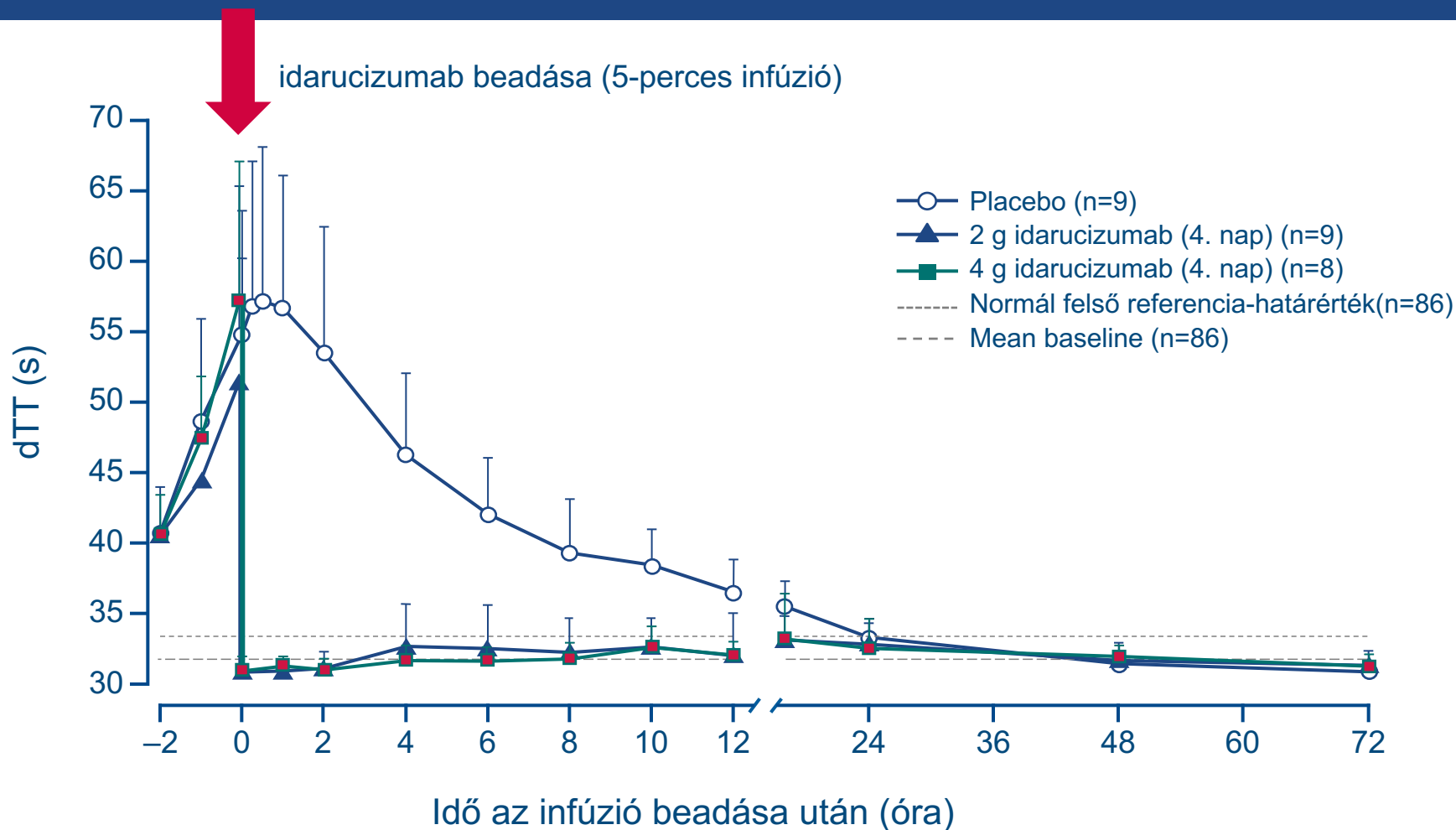


- Humanizált antitest-fragmentum (Fab)
- Szelektíven kötődik a dabigatránhoz
- A thrombinénál kb. 350-szer nagyobb affinitással kötődik a dabigatránhoz, mint az utóbbi a thrombinhoz – vagyis kötődése lényegében irreverzibilis
- Intravénás alkalmazásra kész oldatként kerül forgalomba, hatása azonnal érvényesül
- Nincs intrinsic prokoaguláns, vagy véralvadásgátló aktivitása
- Nincsenek endogén célpontjai a szervezetben
- Az idarucizumab-dabigatrán komplex gyorsan (néhány óra alatt) eliminálódik

Az idarucizumabot nem engedélyezték minden országban. Kérjük, a részletekért tanulmányozza az *Alkalmazási előírás* helyi verzióját!

Schiele és mtsai. *Blood* 2013; közleménye alapján; Stangier és mtsai. *ISTH* 2015; Pradaxa® EU SPC, 2016.

Idarucizumab: a dabigatran alvadásgátló hatásának azonnali, teljes, és fenntartott visszafordítása*



- *egészséges önkéntesekben
- Normál felső referencia-határérték: +2SD dózis előtti mérések; Glund et al. AHA 2013

- **Idarucizumab –PRAXBIND® EMA törzskönyv: 2015. november 20.**

Lehetséges gyógyszer-gyógyszer interakciók – NOAC plazmaszintekre gyakorolt hatás (I)

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvasztatin	P-gp/ CYP3A4	+18%	még nincsenek adatok	nincs hatás	nincs hatás
Digoxin	P-gp	nincs hatás	még nincsenek adatok	nincs hatás	nincs hatás
Verapamil	P-gp/ wk CYP3A4	+12–180% (csökkentse a dózist)	még nincsenek adatok	+ 53% (SR) (csökkentse a dózist 50 %-kal)	enyhe hatás
Diltiazem	P-gp/ wk CYP3A4	nincs hatás	+40%	nincsenek adatok	enyhe hatás
Kinidin	P-gp	+50%	még nincsenek adatok	+80% (csökkentse a dózist 50 %-kal)	+50%
Amiodaron	P-gp	+12–60%	még nincsenek adatok	nincs hatás	enyhe hatás
Dronedaron	P-gp/CYP3A4	+70–100%	még nincsenek adatok	+85% (csökkentse a dózist 50 %-kal)	még nincsenek adatok
Ketoconazol; itraconazol; voriconazol; posaconazol	P-gp és BCRP/ CYP3A4	+140–150%	+100%	még nincsenek adatok	akár +160%

Piros = kontraindikált; Narancssárga = módosítsa a dózist; Sárga = mérlegelje a dóziscsökkentést, ha két sárga interakció áll fenn egyidejűleg

Heidbuchel H et al. Europe 2013;15:625–51

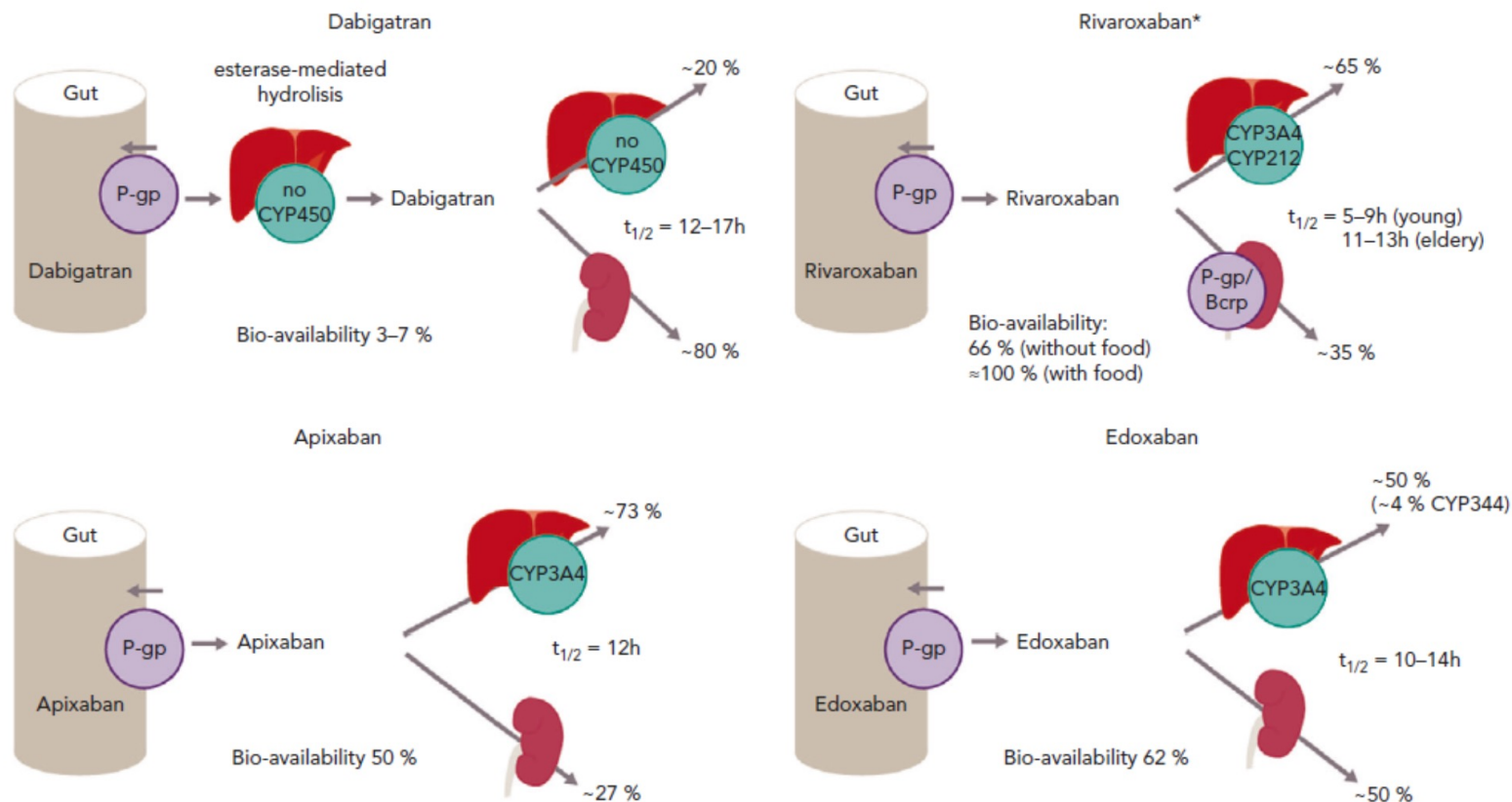
Lehetséges gyógyszer-gyógyszer interakciók – NOAC plazmaszintekre gyakorolt hatás (II)

	Interakció	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazol	CYP3A4	nincsenek adatok	nincsenek adatok	nincsenek adatok	+42%
Cyclosporin; tacrolimus	P-gp	nincsenek adatok	nincsenek adatok	nincsenek adatok	+50%
Clarithromycin; erythromycin	P-gp/ CYP3A4	+15–20%	nincsenek adatok	nincsenek adatok	+30–54%
HIV proteáz inhibitorok	P-gp és BCRP/ CYP3A4	nincsenek adatok	jelentős emelkedés	nincsenek adatok	akár +153%
Rifampicin; orbáncfű; carbamezepin; phenytoin; phenobarbital	P-gp és BCRP/ CYP3A4/CYP2J2	-66%	-54%	-35%	akár -50%
Antacidumok	GIT abszorpció	-12–30%	nincsenek adatok	nincs hatás	nincs hatás

Piros = kontraindikált; Narancssárga = módosítsa a dózist; Sárga = mérlegelje a dóziscsökkentést, ha két sárga interakció áll fenn egyidejűleg

Heidbuchel H et al. Europace 2013;15:625–51

A DOAC-ok felszívódása és metabolizmusa

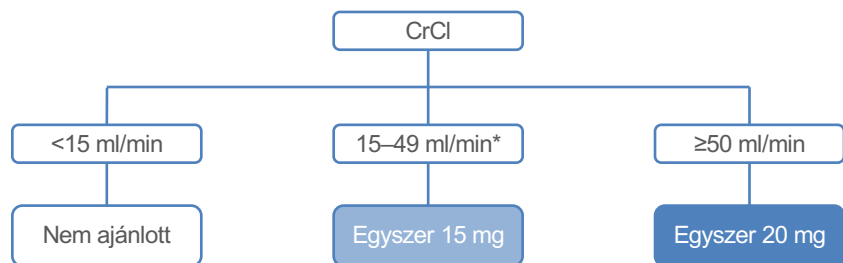


* these rivaroxaban figures are valid only for doses exceeding 20 mg.

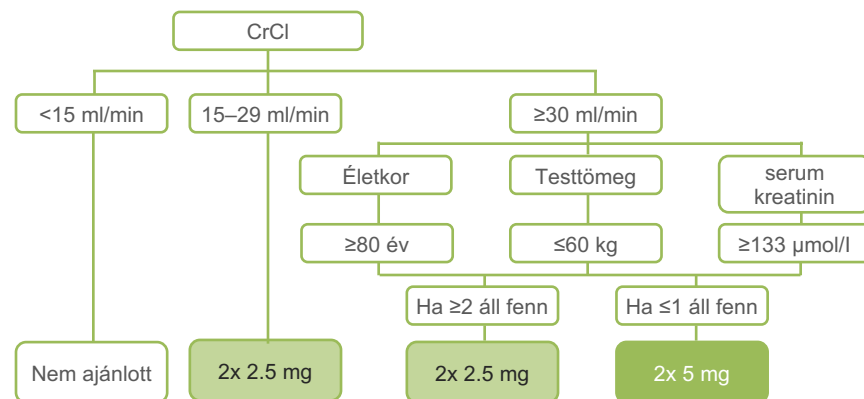
Adapted from: Heidbuchel, et al., 2015.²⁴

A DOAC-ok dózismódosítása PF betegek stroke prevenciójában

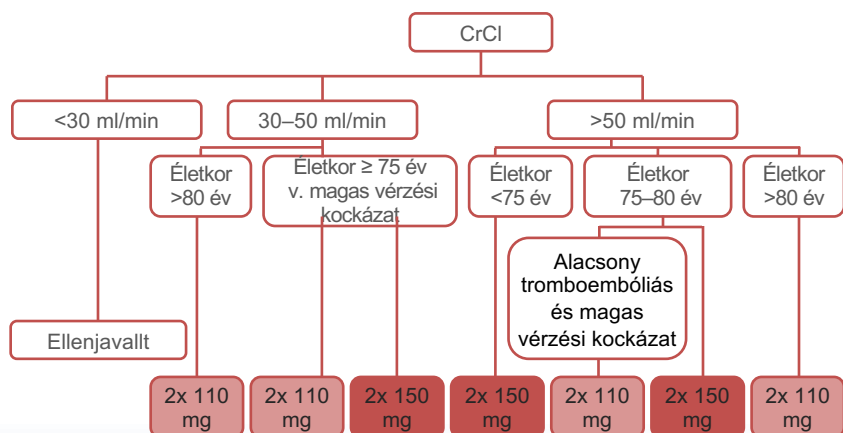
Rivaroxaban¹



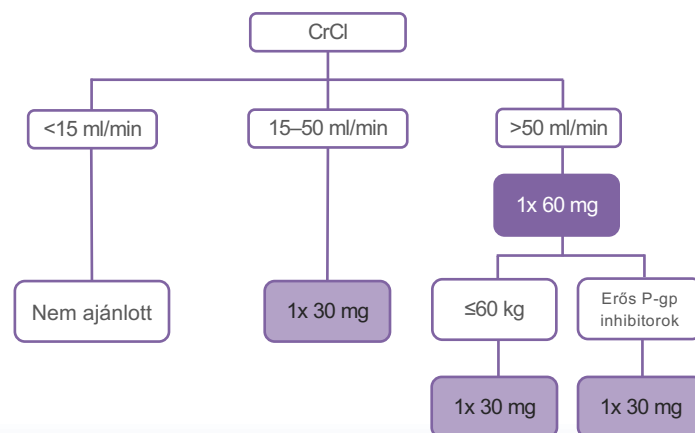
Apixaban²



Dabigatran³



Edoxaban⁴



1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC

*Xarelto®-t óvatosan kell alkalmazni olyan betegeknél, akiknek a CrCl 15–29 mL/min közötti

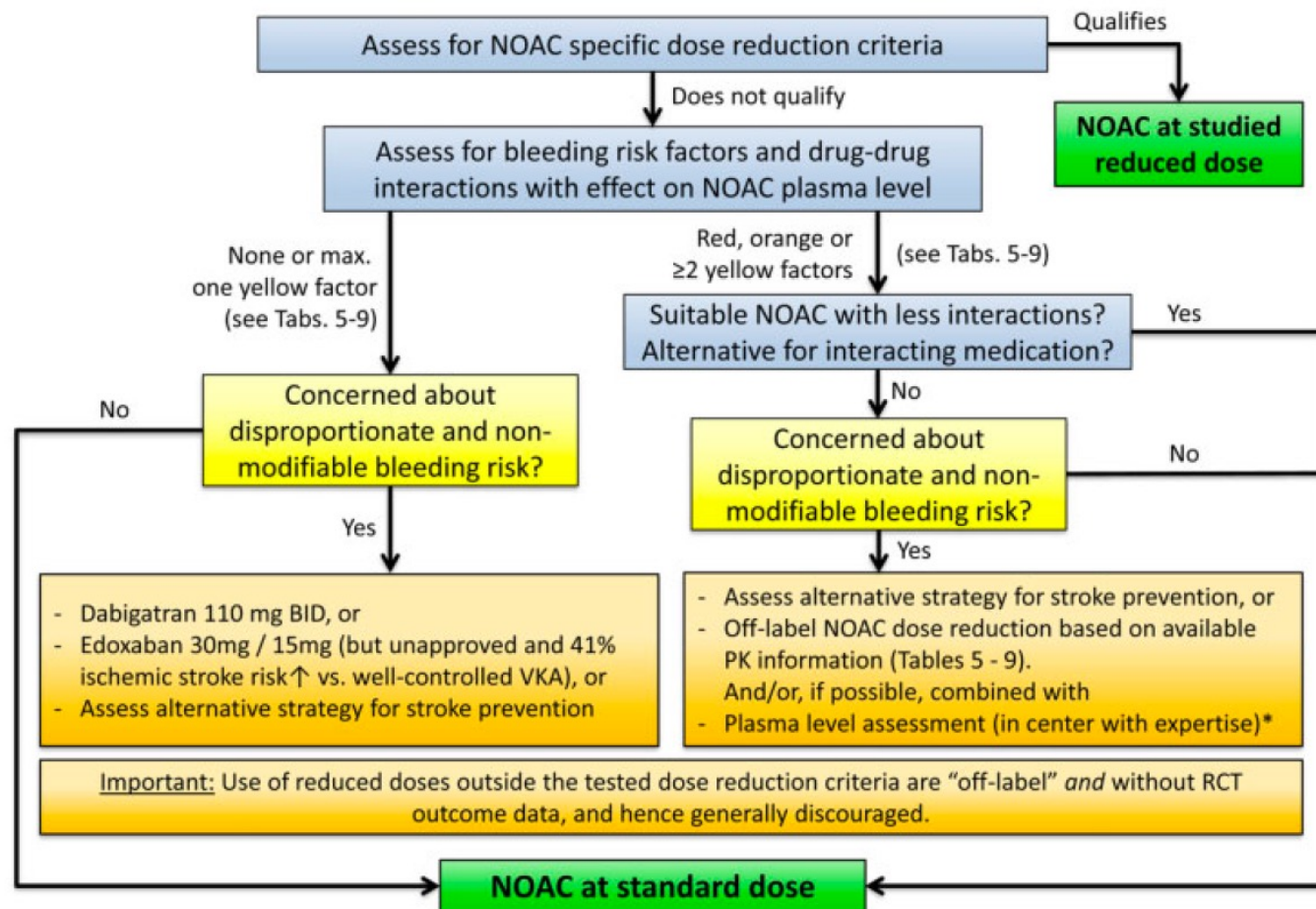


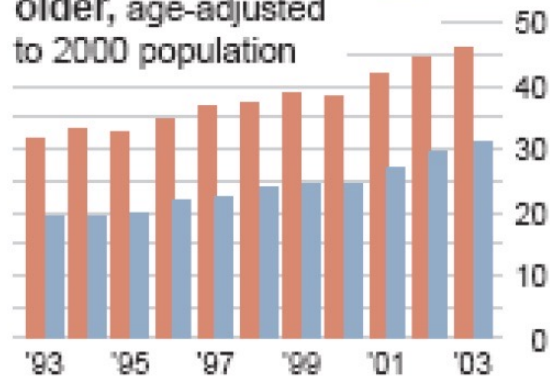
Figure 6 NOAC selection based on drug–drug interactions and/or risk of bleeding. Dose reduction of all NOACs is primarily recommended along the published dose reduction criteria (see ‘NOAC eligibility and dosing’ section, Table 2). Whenever possible, the tested and approved dosing regimen of NOACs should be used. See text for details. *Use of plasma level measurements to guide dosing is generally discouraged and should only be used in rare cases of potentially substantial interactions or special situations, and only in centers with great experience in the performance and interpretation of such assays as well as the care of NOAC-treated patients (see ‘NOAC plasma level measurements: technical approach, indications, pitfalls’ section). BID, twice daily; NOAC, non-vitamin K antagonist oral anticoagulant; PK, pharmacokinetic; RCT, randomized clinical trial; VKA, vitamin K antagonist.

ENGAGE AF–TIMI 48 – edoxaban (*J Am Coll Cardiol.* 2016;68(11):1169-1178.)

Fatal falls rising among the elderly

The death rate for elderly people falling has risen 55.3 percent from 1993-2003.

Rate of fatal falls for people 65 or older, age-adjusted to 2000 population



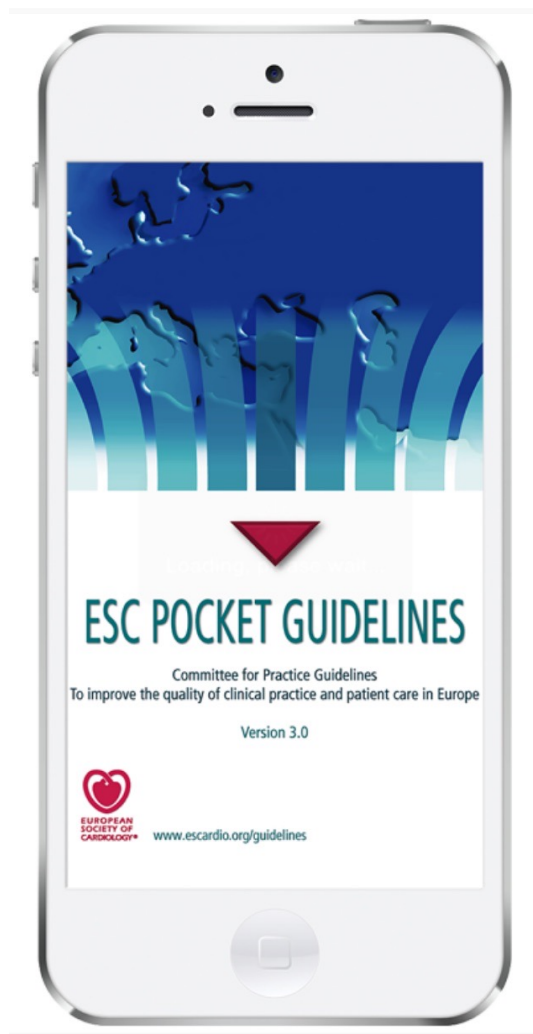
SOURCE: Centers for Disease Control and Prevention

AP



900 beteg (4.3%) emelkedett elesési rizikóval, életkor 77 vs. 72 év, több komorbiditás, csonttörés, vérzés, halálozás, azonos számú tromboemboliás

ESC Pocket guideline – smartphone applikáció



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CHA2DS2-VASc score (AFib/HF)

Diabetes mellitus	0	1
Stroke/TIA/TE	0	2
Vascular disease ^a	0	1
Age 65-74	0	1
Sex category (i.e., female gender)	0	1

Score 3

Stroke and thromboembolism event rate at 1 year follow-up (%)^b

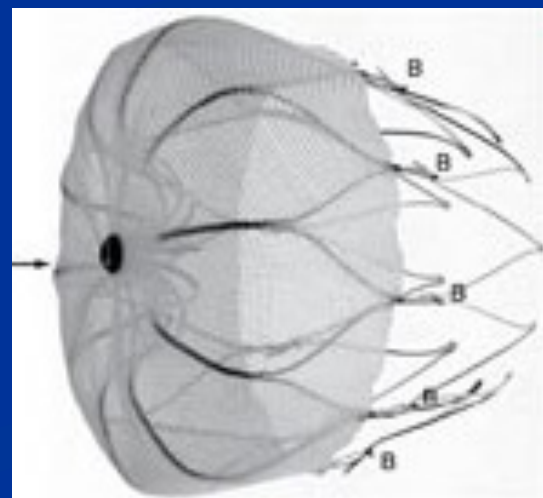
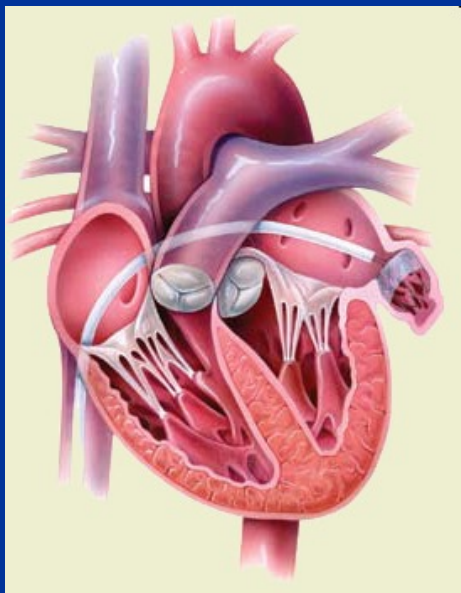
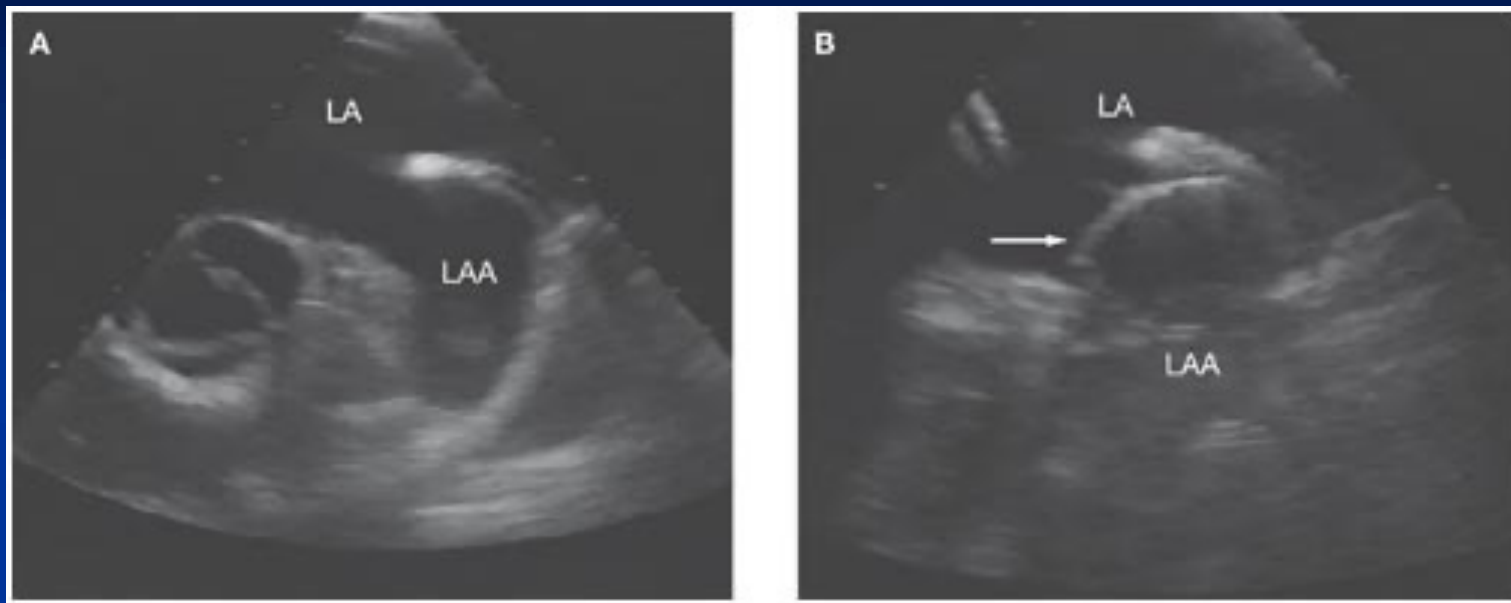
5.92

Treatment recommendation

Oral anticoagulant therapy with NOAC (recommended) or VKA (alternative).

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A bal pitvari fülcsé TEE képe





AMERICAN
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CARDIOLOGY

LAAOS III

Left Atrial Appendage Occlusion Study III

Multicenter, randomized trial

OBJECTIVE: To evaluate surgical left atrial appendage occlusion compared with no occlusion among patients with atrial fibrillation (AFib) undergoing open heart surgery for another indication.

4,770
PATIENTS

INCLUSION CRITERIA: Patients undergoing cardiac surgery with cardiopulmonary bypass, AFib and CHA₂DS₂-VASc ≥ 2



**SURGICAL OCCLUSION
(N=2379)**

vs.



**NO OCCLUSION
(N=2391)**

PRIMARY OUTCOME

**ISCHEMIC STROKE OR SYSTEMIC EMBOLISM AT 3.8 YEARS:
4.8% vs. 7.0% (P = 0.001)**

**ISCHEMIC STROKE OR SYSTEMIC EMBOLISM <30 DAYS:
2.2% vs. 2.7% (P = NOT SIGNIFICANT)**

**ISCHEMIC STROKE OR SYSTEMIC EMBOLISM >30 DAYS:
2.7% vs. 4.6% (P = 0.001)**

Köszönöm a figyelmet!

