Bevezető gondolatok a szekcióhoz. Antikoaguláció és aggregáció gátlás

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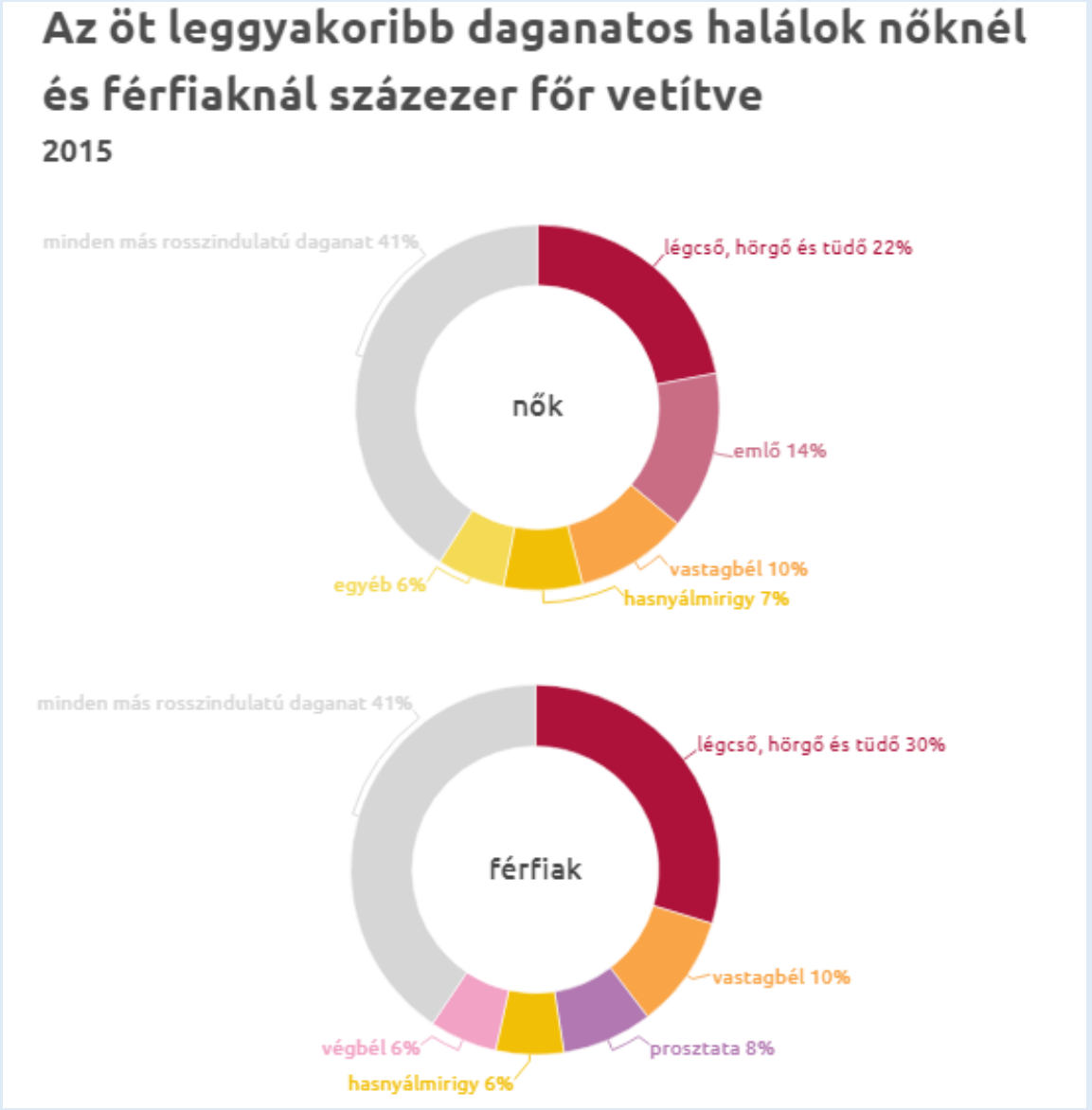
Vezérfonal

- **Bevezető**
- **Gyógyszeres rizikócsökkentés lehetőségei**
- **Antikoaguláció kérdése, újdonságok**
- **Szívelégtelenség, néhány újdonság**

- További előadások témája:
  - Műtéti rizikó meghatározása
  - Funkcionális kapacitás felmérése
  - A műtéti rizikó becslése pontrendszerek segítségével
  - Non-invazív és invazív vizsgálatok helye, szerepe

Magyarország

- Évi 32 000 daganat miatti halálozás
- Colorectalis daganat prevalencia: 27000
- Új daganatos betegek száma évente: kb 100000 fő.
- Halálozás:
  - 50% CV
  - 25% daganat okozta



Jelentőség

- Évi 4% a major műtéti arány
- 70%: minimális CV rizikó
- 30% : CV társbetegség
- Műtéti szövődmény: 7-11%
- Halálozás: 0,8-1,5%
- Kardiális halálozás: össz. halálozás 42%-a
- Egyre több műtét, idősebb betegek

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Gyógyszeres rizikócsökkentés

- 3 féle gyógyszer

- Bétablokkoló
- Aggregatió gátló
- Statin

European Heart Journal (2009) 30, 2769–2812
doi:10.1093/eurheartj/ehp337

ESC GUIDELINES

Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery

The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA)

Authors/Task Force Members: Don Poldermans; (Chairperson) (The Netherlands)*; Jeroen J. Bax (The Netherlands); Eric Boersma (The Netherlands); Stefan De Hert (The Netherlands); Erik Eeckhout (Switzerland); Gerry Fowkes (UK); Bulent Gorenek (Turkey); Michael G. Hennerici (Germany); Bernard Iung (France); Malte Kelm (Germany); Keld Per Kjeldsen (Denmark); Steen Dalby Kristensen (Denmark); Jose Lopez-Sendon (Spain); Paolo Pelosi (Italy); François Philippe (France); Luc Pierard (Belgium); Piotr Ponikowski (Poland); Jean-Paul Schmid (Switzerland); Olav F.M. Sellevold (Norway); Rosa Sicari (Italy); Greet Van den Berghe (Belgium); Frank Vermassen (Belgium)

2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management

The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA)

Authors/Task Force Members: Steen Dalby Kristensen* (Chairperson) (Denmark), Juhani Knuuti* (Chairperson) (Finland), Antti Saraste (Finland), Stefan Anker (Germany), Hans Erik Bøtker (Denmark), Stefan De Hert (Belgium), Ian Ford (UK), Jose Ramón Gonzalez-Juanatey (Spain), Bulent Gorenek (Turkey), Guy Robert Heyndrickx (Belgium), Andreas Hoeft (Germany), Kurt Huber (Austria), Bernard Iung (France), Keld Per Kjeldsen (Denmark), Dan Longrois (France), Thomas F. Lüscher (Switzerland), Luc Pierard (Belgium), Stuart Pocock (UK), Susanna Price (UK), Marco Roffi (Switzerland), Per Anton Sirnes (Norway), Miguel Sousa-Uva (Portugal), Vasilis Voudris (Greece), Christian Funck-Brentano (France).

ESC Committee for Practice Guidelines: Jose Luis Zamorano (Chairperson) (Spain), Stephan Achenbach (Germany), Helmut Baumgartner (Germany), Jeroen J. Bax (Netherlands), Héctor Bueno (Spain), Veronica Dean (France), Christi Deaton (UK), Cetin Erol (Turkey), Robert Fagard (Belgium), Roberto Ferrari (Italy), David Hasdai (Israel), Arno W. Hoes (Netherlands), Paulus Kirchhof (Germany/UK), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Patrizio Lancellotti (Belgium), Ales Linhart (Czech Republic), Petros Nihoyannopoulos (UK), Massimo F. Piepoli (Italy), Piotr Ponikowski (Poland), Per Anton Sirnes (Norway), Juan Luis Tamargo (Spain), Michal Tendera (Poland), Adam Torbicki (Poland), William Wijns (Belgium), Stephan Windecker (Switzerland).

Béta blokkoló DECREASE

ESC guidelines		
Established coronary artery disease or ischaemia on preoperative stress testing	2009	Class I, with dose titration
High-risk surgery		Class I, with dose titration
Intermediate-risk surgery		Class IIa, with dose titration

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ESC, European Society of Cardiology.

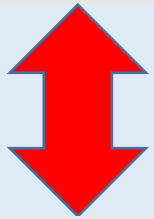


Table 2 Grounds on which the DECREASE family of trials are considered discredited

DECREASE VI	Fictitious methods. 97% of the patients did not undergo a stress echo and the surgery as specified. No consent forms. Falsified description of method of outcome adjudication Fictitious database.
DECREASE V	Falsified methods of patient assessment (myocardial infarction and renal failure) Fictitious adjudication committee No record of the stress echo images or of the '5-member panel' said to have evaluated them No research patient records No evidence of written informed consent
DECREASE IV	Fictitious 'adjudication committee' of cardiologist, anaesthiologist and surgeon (in reality adjudications made by surgeon alone). Fictitious events that did not match hospital records or clinical discharge reports
DECREASE III	Not investigated in detail because: No source data could be found to investigate No written consent forms. No contemporaneous documentation, only current verbal assurances
DECREASE II	Fictitious method of establishing outcome
(DECREASE I	Not investigated as it was more than 10 years old)

Study or Subgroup	Beta-blocker Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Secure trials						
Mangano 1996	4	99	5	101	7.7%	0.82 [0.23, 2.95]
Bayliff 1999	2	49	1	50	2.6%	2.04 [0.19, 21.79]
POBBLE 2005	3	55	1	48	3.0%	2.62 [0.28, 24.34]
MAVS 2006	0	246	4	250	1.8%	0.11 [0.01, 2.09]
DIPOM 2006	20	462	15	459	19.0%	1.32 [0.69, 2.55]
Neary 2006	3	18	5	20	7.7%	0.67 [0.19, 2.40]
BBSA 2007	1	110	0	109	1.5%	2.97 [0.12, 72.19]
POISE 2008	129	4174	97	4177	33.5%	1.33 [1.03, 1.73]
YANG XY 2008	0	51	1	51	1.5%	0.33 [0.01, 8.00]
Subtotal (95% CI)		**5264**		**5265**	**78.3%**	**1.27 [1.01, 1.60]**
Total events	162		129			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.74$, df = 8 (P = 0.68); $I^2 = 0\%$

Test for overall effect: Z = 2.06 (P = 0.04)

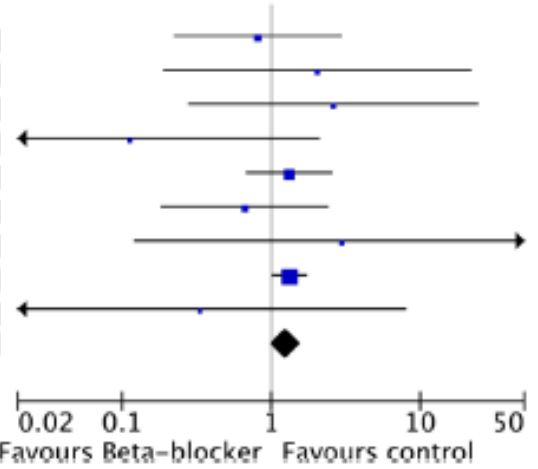
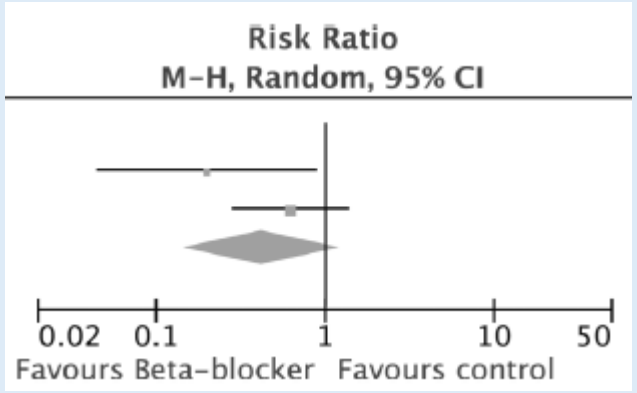


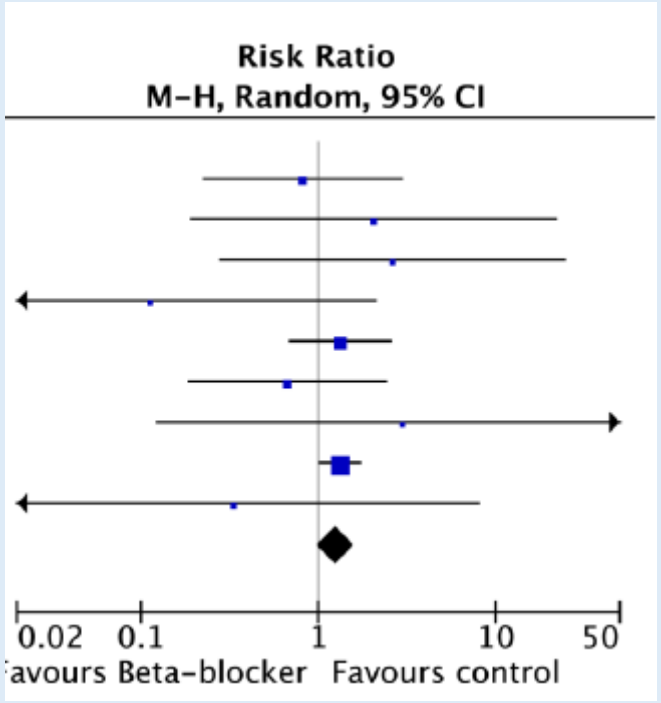
Figure 2 Meta-analysis of nine secure randomised controlled trials showing a significant increase in mortality with perioperative β-blockade.

Bétablokkoló Halálozás

- DECREASE



- Metaanalysis: 9 vizsgálat



Nem halálos AMI csökken
Nem halálos sztrók száma nő

Bouri S, *et al*. *Heart* 2013

Bétablokkolók

Recommendations	Class[a]	Level[b]	Ref.[c]
Peri-operative continuation of beta-blockers is recommended in patients currently receiving this medication.	I	B	96–99
Pre-operative initiation of beta-blockers may be considered in patients scheduled for high-risk surgery and who have ≥2 clinical risk factors or ASA status ≥3.[d]	IIb	B	86,95, 97
Pre-operative initiation of beta-blockers may be considered in patients who have known IHD or myocardial ischaemia.[d]	IIb	B	83,88, 106
When oral beta-blockade is initiated in patients who undergo non-cardiac surgery, the use of atenolol or bisoprolol as a first choice may be considered.	IIb	B	97,100 –102
Initiation of peri-operative high-dose beta-blockers without titration is not recommended.	III	B	78
Pre-operative initiation of beta-blockers is not recommended in patients scheduled for low-risk surgery.	III	B	86,97

Statin

Table 7. Number Needed to Treat in Propensity Matched Cohort by Revised Cardiac Risk Index Score

	Revised Cardiac Risk Index Score					
	0	1	2	3	≥4	Overall
Patients, No. (%)	45 371 (34)	43 756 (33)	27 853 (21)	11 706 (9)	3149 (2)	**131 835 (100)**
In-hospital mortality, No. (%)*	647 (1.43)	1136 (2.60)	1253 (4.50)	828 (7.07)	294 (9.34)	**4158** (3.15)
NNT (95% CI)†	186 (168-214)	103 (93-119)	60 (54-69)	39 (35-45)	30 (27-35)	85 (77-98)

Abbreviations: CI, confidence interval; NNT, number needed to treat.
*Among patients who were not treated or who had late treatment in the propensity matched cohort.
†Based on adjusted odds ratios (ORs) from propensity matched cohort. NNT = 1–[PEER × (1–OR)]/[(1–PEER) × PEER × (1–OR)], in which PEER is the patient expected event rate (eg, the event rate in the control or untreated group).

Lindenauer et al, JAMA, 2004

Statin

Recommendations	Class[a]	Level[b]	Ref.[c]
Peri-operative continuation of statins is recommended, favouring statins with a long half-life or extended-release formulation.	I	C	
Pre-operative initiation of statin therapy should be considered in patients undergoing vascular surgery, ideally at least 2 weeks before surgery.	IIa	B	112,113, 115

Aspirin

- Metaanalysis: 50000 beteg, 41 vizsgálat
- ASA marad vs elvonás
- ASA-val 50%-kal több vérzés
- A vérzések nem nagyobbak
- Akiknél ismert ISZB vagy ISZB rizikó: az elvonással MACE háromszorosára nőtt

Burger, J Int Med, 2005

Aspirin
POISE-2 vizsgálat

- 10000 beteg
- Részben folytatott/elhagyott, részben indított/nem indított ASA
- Nagy vérzés: 4,6 vs 3,8 %
- Halál és nem fatalis AMI: idem.

Aspirin ajánlás

- Elhagyandó, ha a vérzésveszély nagyobb mint az ASA előnye
- De elhagyandó, ha kis vérzés is nagy bajt csinálhat: központi idegrendszeri opus, bizonyos szemműtétek
- Elhagyás: 7 nappal előtte

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MJ 65 éves nőbeteg

- Anamnesisben aorta és mitrális mechanikus műbillentyű beültetés
- 2011. 6. 23.: Jobb emlőben sectorectomia és sentinel ny. csomó eltávolítás 5 mm-es tu miatt
  - Szövettan: Invazív ductalis cc, ER 90% poz és PR 50%poz, HER2+poz, sentinel ny. cs. pozitív
  - 1 mm-re a metszési felszíntől a tumor
- 2011. 6. 30.: Emlőben nagy hematoma, infektálódva, műtét

- 2011. 08. 3.: Reexcizió és ABD
- 2011. 08. 10.: Hematomia miatt reoperáció

FGO, 48 éves nőbeteg

- Anamnesiben mechanikus mitrális éa aorta műbillentyű
- 2007: Tapintható bal emlő tumor miatt opus terve, preoperativ echo: nagyon magas aorta műbillentyű gradiens, emiatt TEE
- 2007. 2. 14: TEE: Non obstruktív műbillentyű thrombózis a mitrális műbillentyűn. Max méret egy cm. Ther: Heparin pumpa
- 2007. 2. 20: Thrombus eltűnt.
- 2007. 3. 12.: Ablatio és ABD.
  - Szövettan: Kétféle tu: Invazív lobuláris cc és invazív ductalis cc .
  - ER, PR 70-80%,
  - HER2++, FISH-

Multiple Valvular Complications of Hypereosinophilic Syndrome

Zoltán Pozsonyi[1,2], Szabolcs Benedek[1], Pál Sármán[1], Lívia Jánoskuti[1], Tivadar Hüttl[2], Astrid Apor[2]

[1]*3rd Department of Internal Medicine and* [2]*Heart Center, Semmelweis University, Budapest, Hungary*

Endomyocardial fibrosis (EMF) is the most common cardiac abnormality in hyeperosinophilic syndrome (HES), sometimes complicated with mitral valve disease. Mitral valve disease without ventricular manifestation is very rare, however. Case reports link HES to prosthetic valve thrombosis (PVT), but the optimal type of prosthetic valve in HES is not known. Herein is reported the case of a young female HES patient with secondary mitral valve degeneration and severe regurgitation. A mechanical prosthetic valve was implanted six months after she was diagnosed with HES, but despite anticoagulation and antiplatelet therapy she developed PVT three months later. Partially successful thrombolysis was followed by biological prosthetic valve implantation, with no further complications during the subsequent four years. The eosinophil count and treatment for HES was basically unchanged during the follow up period, following the initiation of treatment. Based on these findings it is suggested that, in HES, the implantation of a biological prosthetic valve might be preferable over a mechanical valve.

The Journal of Heart Valve Disease 2016;25:

Kumarin

- A nem magas thrombosis kockázat esetén kumarin elhagyható, opus után egy-két nappal újra indul. Opus napján INR<1,5.
- Akinél „bridging” kell:
    - Mechanikus műbillentyű
    - Friss xenograft, friss MVRepair, friss thromboembolia
    - CHA2DS2-VASC>=4
- LMWH utolsó adag: legalább 12 órával műtét előtt,
- Műtét után (12-48 órával) újból LMWH vagy UFH, kumarin újrakezdés (első 2 napon +50%-os adagban)

ESC European Society of Cardiology

European Heart Journal (2018) 39, 1330–1393
doi:10.1093/eurheartj/ehy136

SPECIAL ARTICLE

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Jan Steffel[1]*, Peter Verhamme[2], Tatjana S. Potpara[3], Pierre Albaladejo[4], Matthias Antz[5], Lien Desteghe[6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[2], Ronan Collins[12], A. John Camm[13], and Hein Heidbüchel[6,14]

Advisors: Martin van Eickels, M.D. (Bayer Healthcare), Jutta Heinrich-Nols, M.D. (Boehringer Ingelheim), Markus Müller, M.D., Ph.D. (Pfizer), Wolfgang Zierhut M.D. (Daiichi-Sankyo) and Poushali Mukherjea, Ph.D. (Bristol-Myers Squibb)

Document reviewers (ESC scientific document group): Gregory YH Lip (EHRA Review Coordintaor; UK, Denmark), Jeffrey Weitz (Canada), Laurent Fauchier (France), Deirdre Lane (UK), Giuseppe Boriani (Italy), Andreas Goette (Germany), Roberto Keegan (Argentina), Robert MacFadyen (Australia), Chern-En Chiang (Taiwan), Boyoung Joung (Korea), and Wataru Shimizu (Japan)

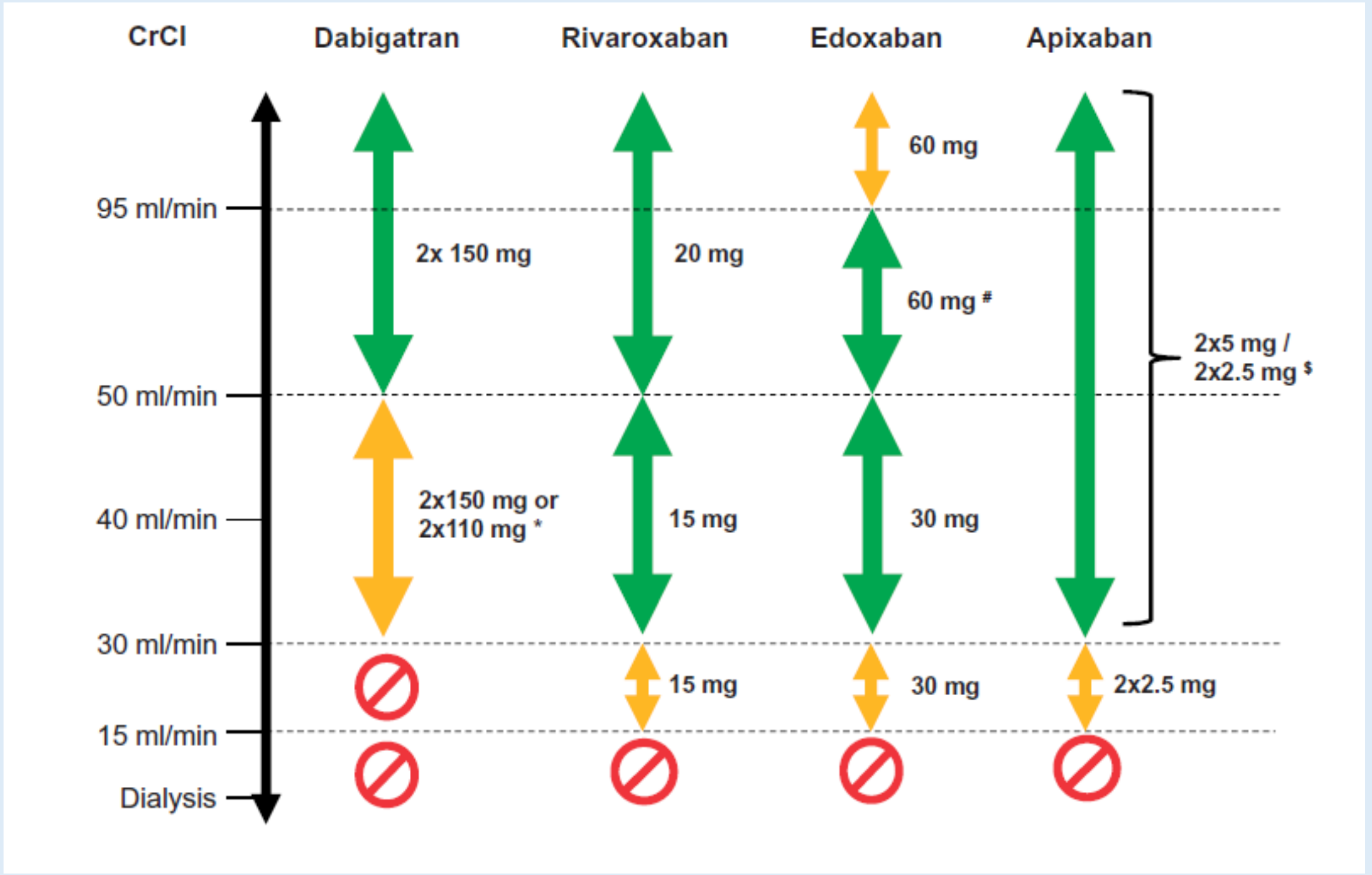

CrCl
Dabigatran
Rivaroxaban
Edoxaban
Apixaban
95 ml/min
50 ml/min
40 ml/min
30 ml/min
15 ml/min
Dialysis
2x 150 mg
2x150 mg or
2x110 mg *
20 mg
15 mg
15 mg
60 mg
60 mg #
30 mg
30 mg
2x5 mg /
2x2.5 mg $
2x2.5 mg

Table 11 Timing of last non-vitamin K antagonist oral anticoagulant intake before start of an elective intervention

	Dabigatran		Apixaban – Edoxaban – Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. 12 h or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 mL/min	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–49 mL/min	≥48 h	≥96 h	≥24 h	≥48 h
CrCl 15–29 mL/min	Not indicated	Not indicated	≥36 h	≥48 h
CrCl <15 mL/min	No official indication for use			
No bridging with LMWH/UFH				
Resume full dose of NOAC ≥24 h post-low bleeding risk interventions and 48 (–72) h post-high-bleeding risk interventions (see also *Figure 8*)				
Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention, and the date and time of the last intake of their NOAC (and any other medication)				

Interventions with high bleeding risk (i.e. frequent and/or with high impact)
Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)

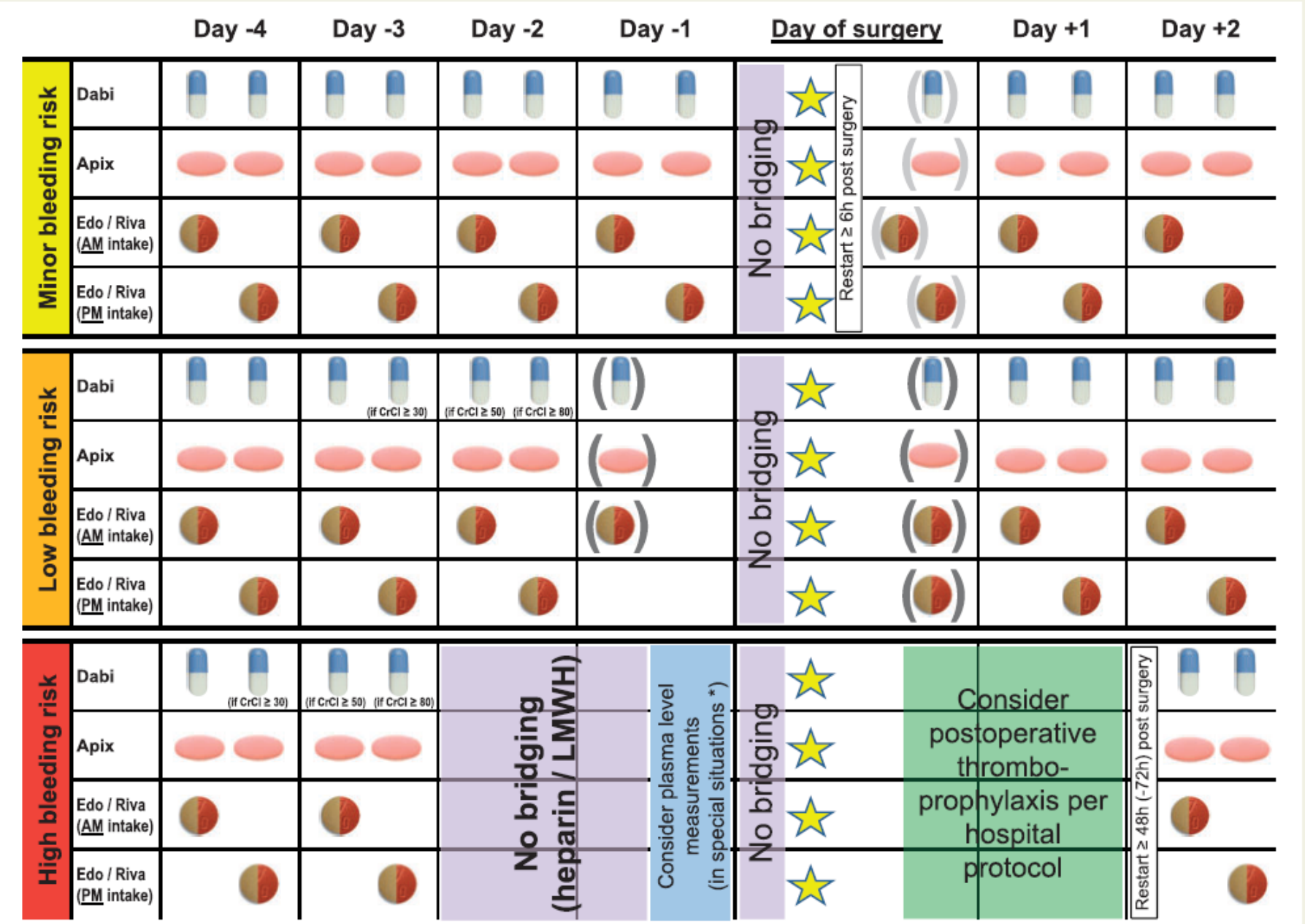
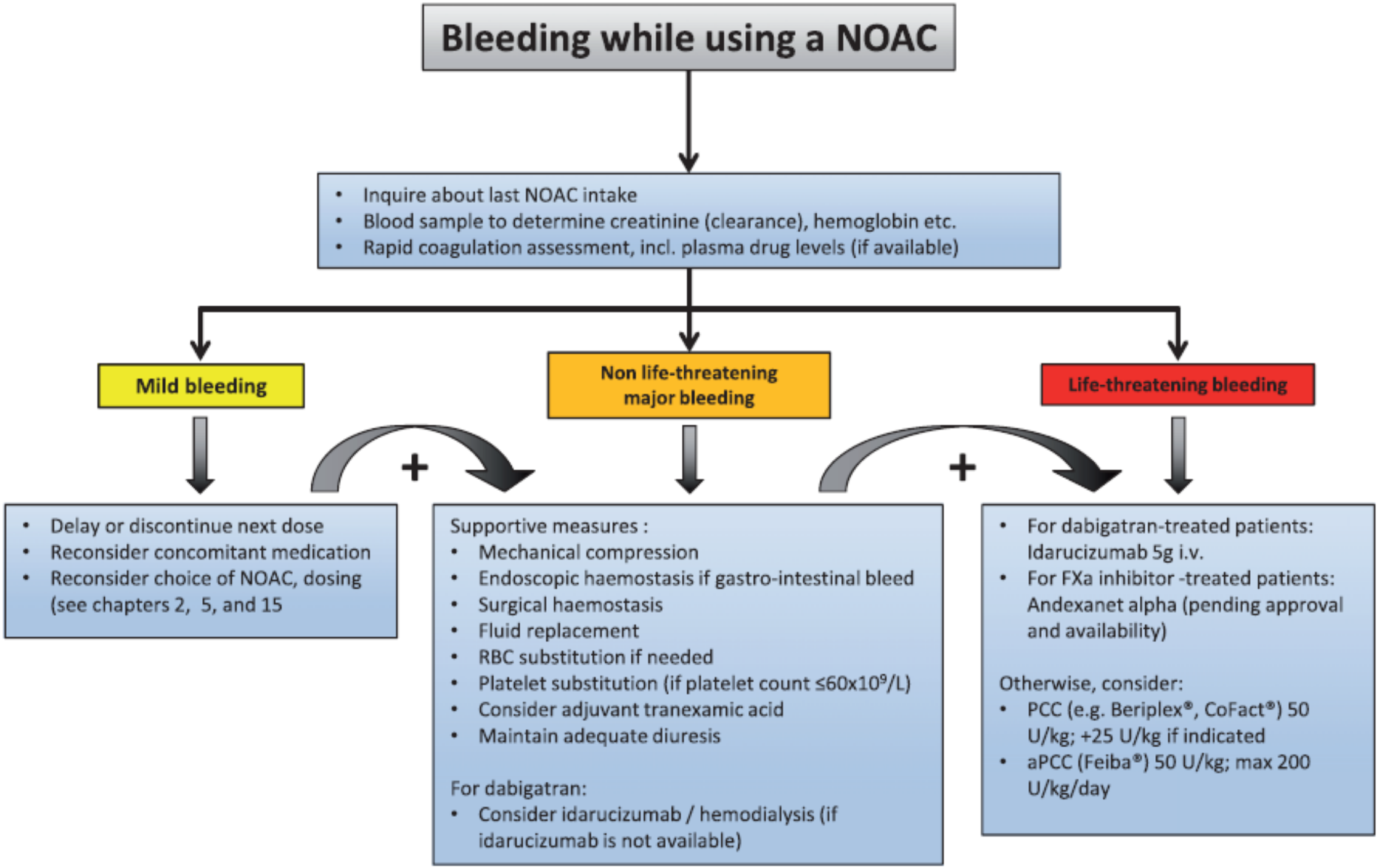
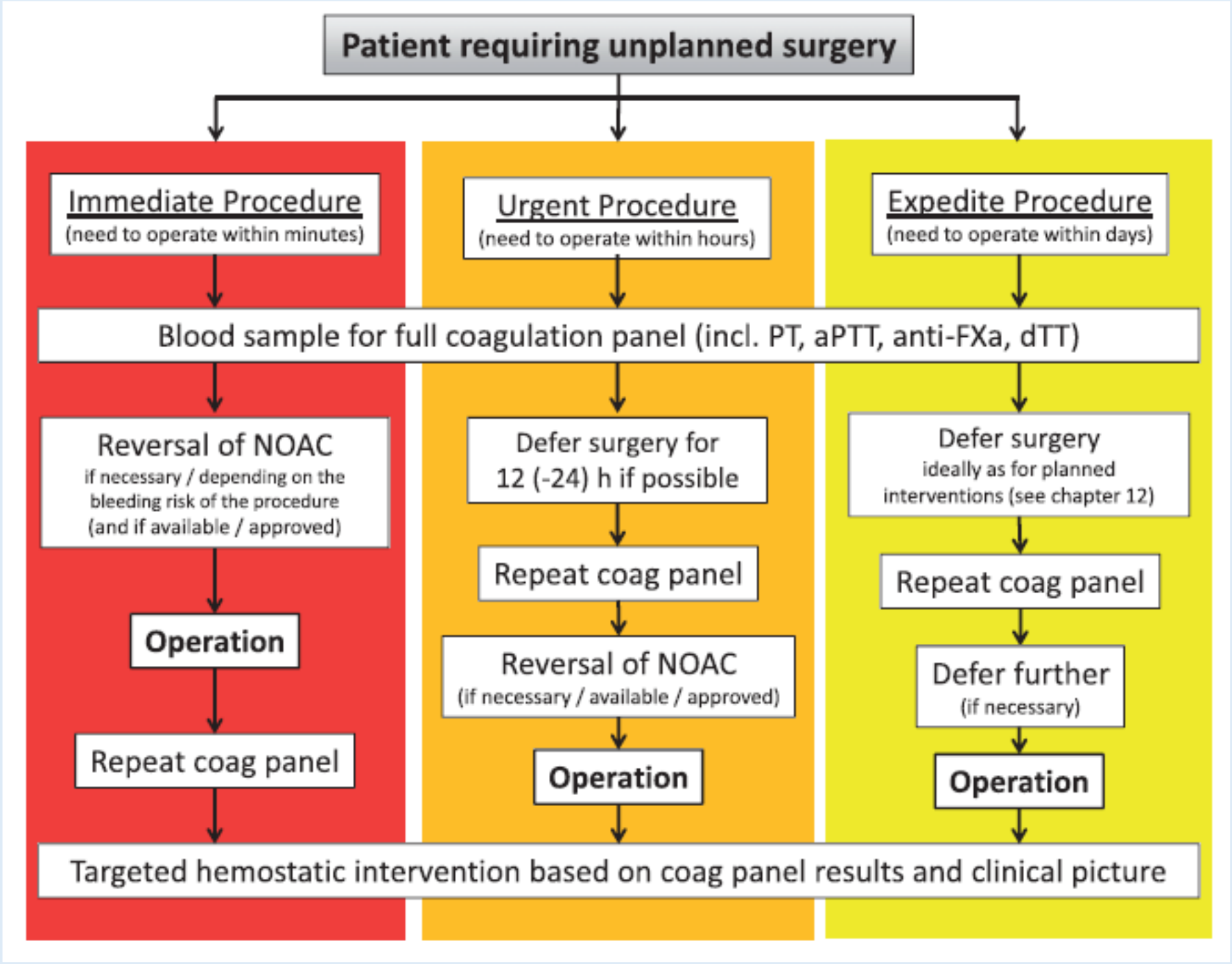


Figure 8 Stopping and re-initiation of non-vitamin K antagonist oral anticoagulant therapy in elective surgery. Yellow star, time point of the inter-

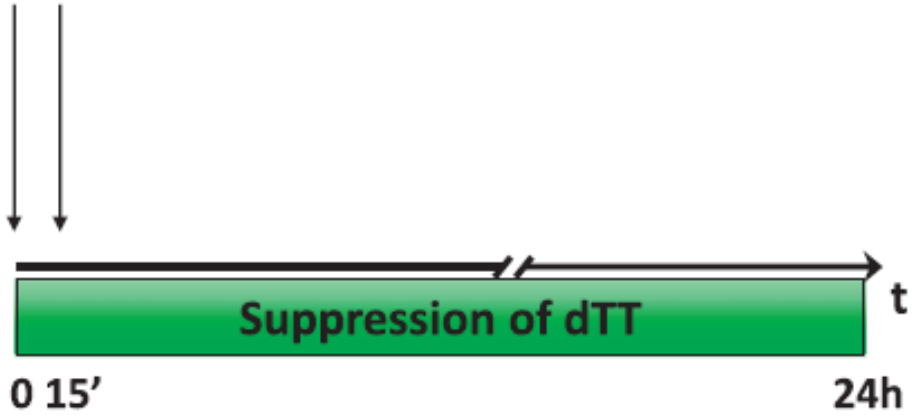

Bleeding while using a NOAC
Inquire about last NOAC intake
Blood sample to determine creatinine (clearance), hemoglobin etc.
Rapid coagulation assessment, incl. plasma drug levels (if available)
Mild bleeding
Non life-threatening major bleeding
Life-threatening bleeding
+
+
Delay or discontinue next dose
Reconsider concomitant medication
Reconsider choice of NOAC, dosing (see chapters 2, 5, and 15
Supportive measures :
Mechanical compression
Endoscopic haemostasis if gastro-intestinal bleed
Surgical haemostasis
Fluid replacement
RBC substitution if needed
Platelet substitution (if platelet count ≤60x10⁹/L)
Consider adjuvant tranexamic acid
Maintain adequate diuresis
For dabigatran:
Consider idarucizumab / hemodialysis (if idarucizumab is not available)
For dabigatran-treated patients: Idarucizumab 5g i.v.
For FXa inhibitor -treated patients: Andexanet alpha (pending approval and availability)
Otherwise, consider:
PCC (e.g. Beriplex®, CoFact®) 50 U/kg; +25 U/kg if indicated
aPCC (Feiba®) 50 U/kg; max 200 U/kg/day


Patient requiring unplanned surgery
Immediate Procedure
(need to operate within minutes)
Urgent Procedure
(need to operate within hours)
Expedite Procedure
(need to operate within days)
Blood sample for full coagulation panel (incl. PT, aPTT, anti-FXa, dTT)
Reversal of NOAC
if necessary / depending on the bleeding risk of the procedure (and if available / approved)
Defer surgery for 12 (-24) h if possible
Defer surgery
ideally as for planned interventions (see chapter 12)
Operation
Repeat coag panel
Repeat coag panel
Reversal of NOAC
(if necessary / available / approved)
Defer further
(if necessary)
Repeat coag panel
Operation
Operation
Targeted hemostatic intervention based on coag panel results and clinical picture

Application of Idarucizumab

Reversal of dabigatran: 5g i.v. in two doses at 2.5g i.v. no more than 15 minutes apart

Praxbind



*Application of Andexanet Alpha (if approved and available)**

- Reversal of rivaroxaban (last intake >7h before) or apixaban: 400mg bolus, 480mg infusion at 4mg/min
- Reversal of rivaroxaban (last intake <7h before or unknown), enoxaparin or edoxaban: 800mg bolus, 960mg infusion at 8mg/min

Ondexxya

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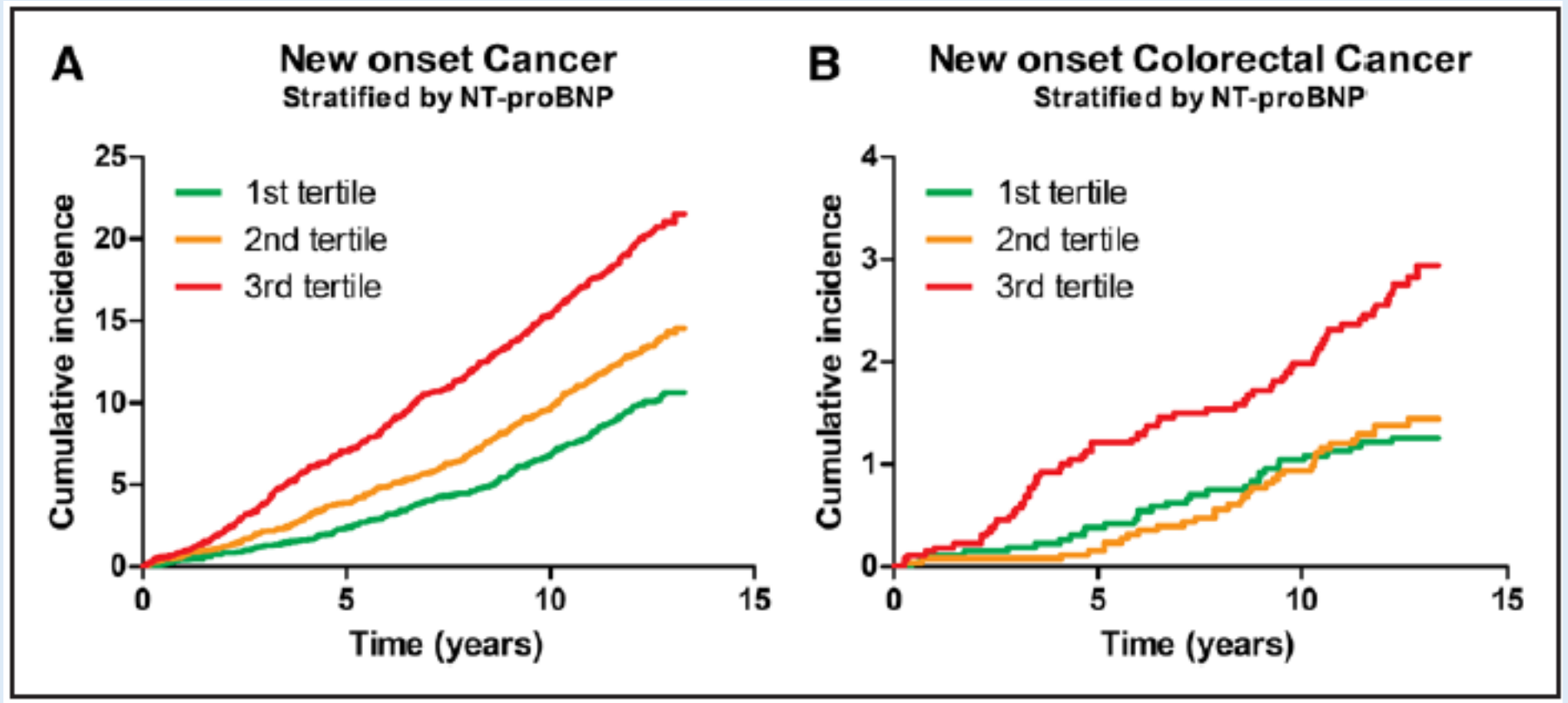
- **Szívelégtelenség, néhány újdonság**

Szívelégtelenség

- Prevalencia: 1-2%, 70 év felett 10%
- 65 év feletteik műtéteinél 18% SZE, bennük a halálozás kockázata 63%-kkal magasabb (Medicare)
- HFpEF és HFrEF között nincs különség

Szívelégtelenség és daganat



Meijers et al, 2018, Circulation

9307 dán SZE beteg követése (Banke et al 2016, Eur J Heart Fail)

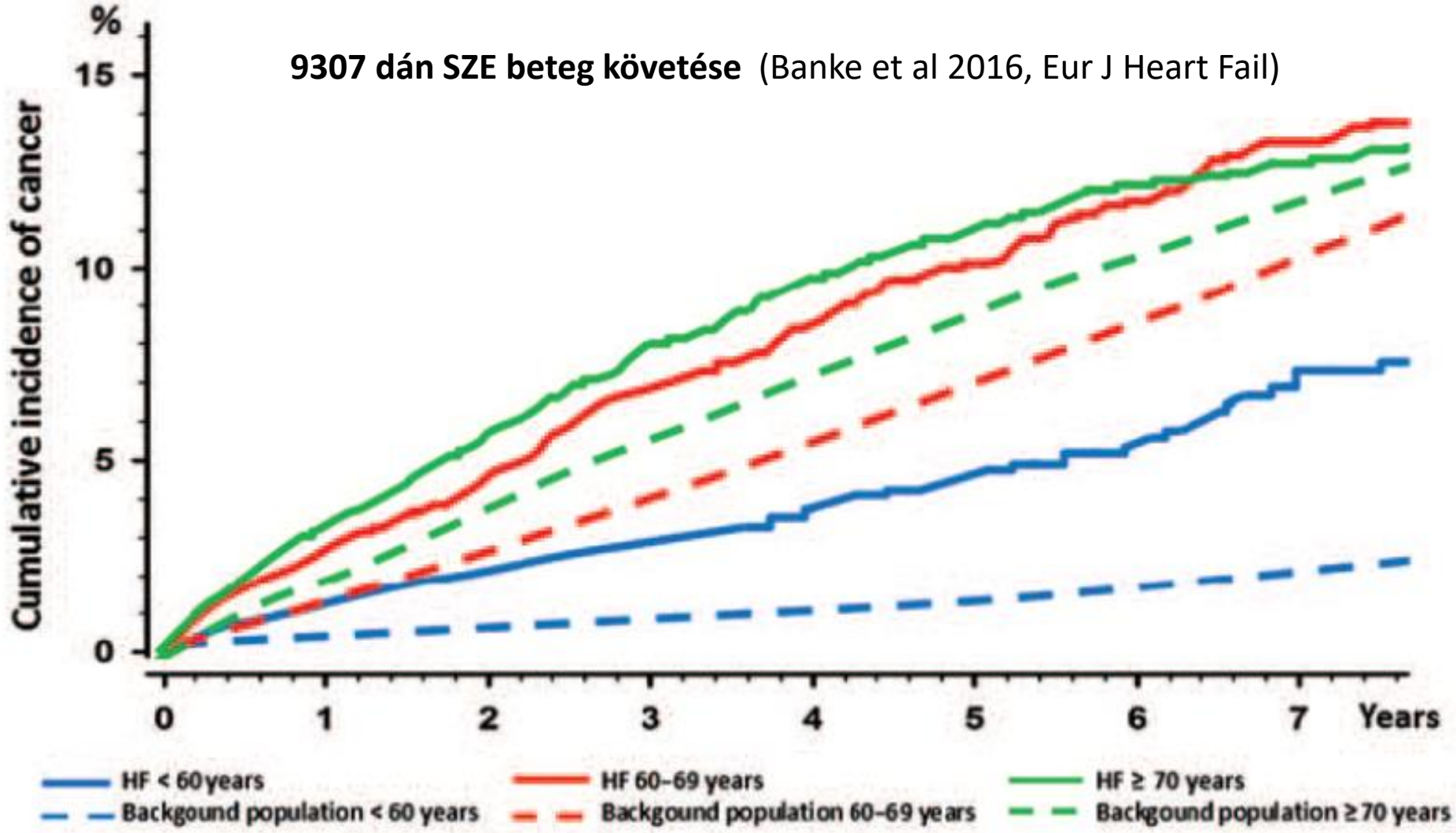
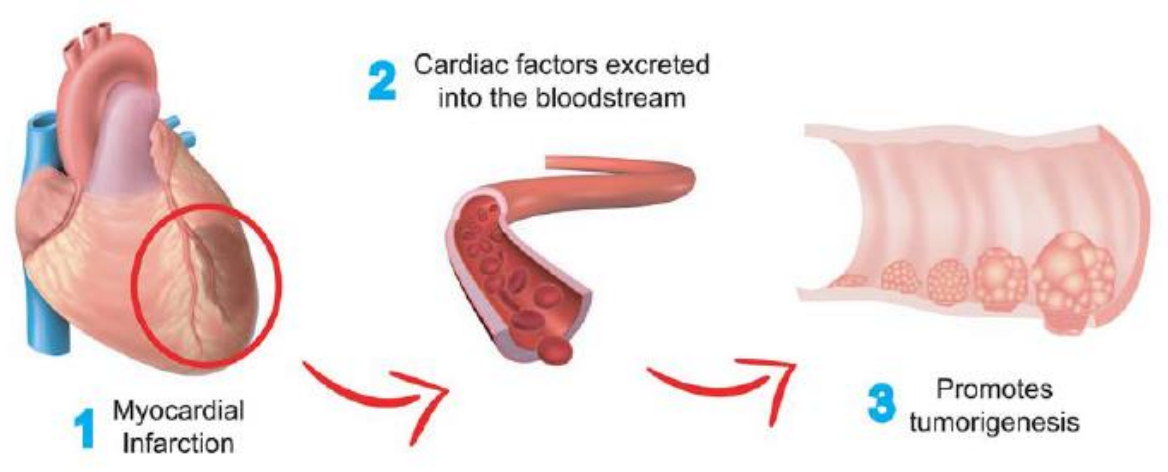


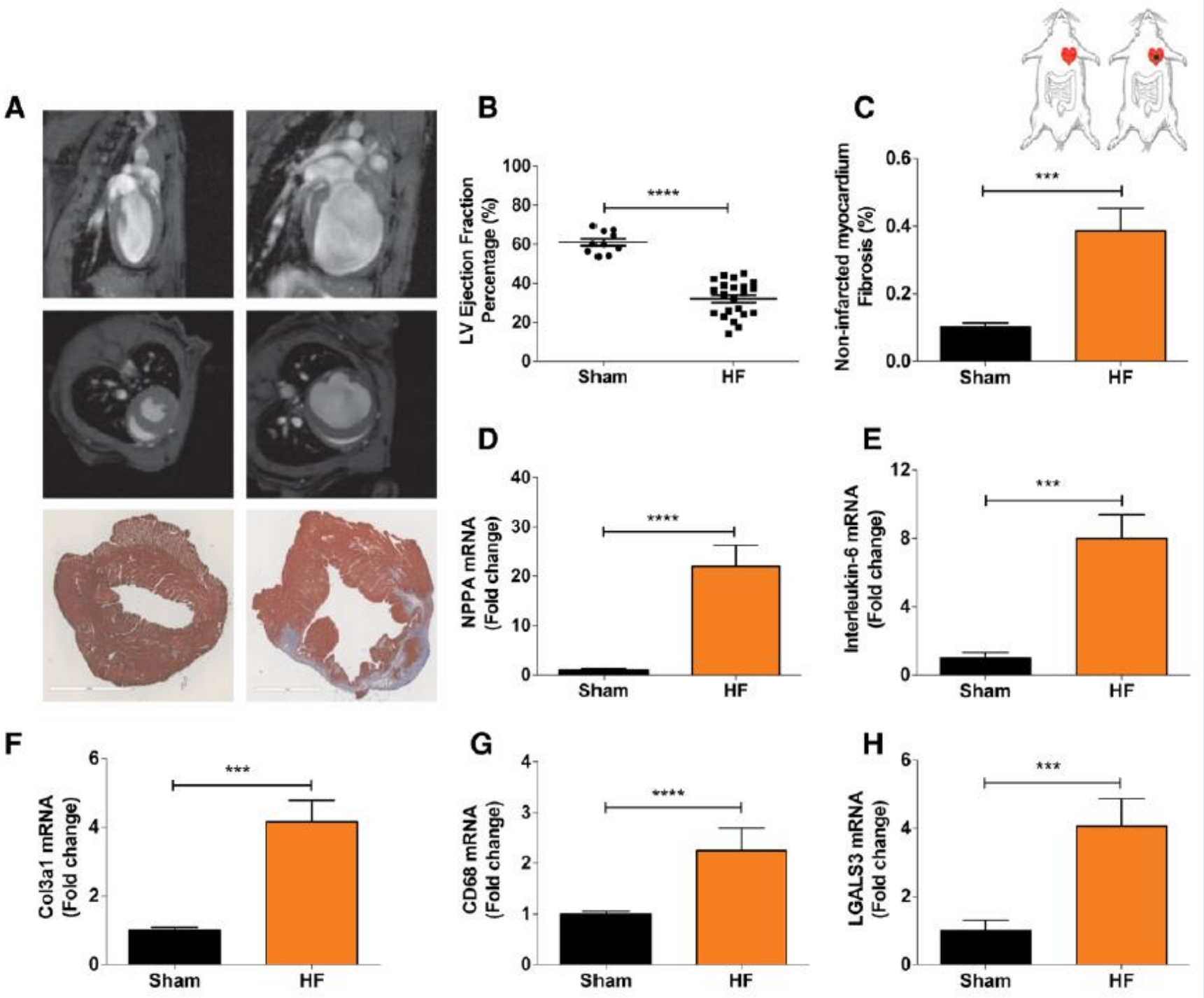
Figure 2 Cumulative incidence of cancer in the heart failure (HF) cohort and the background population adjusted for death from all causes.

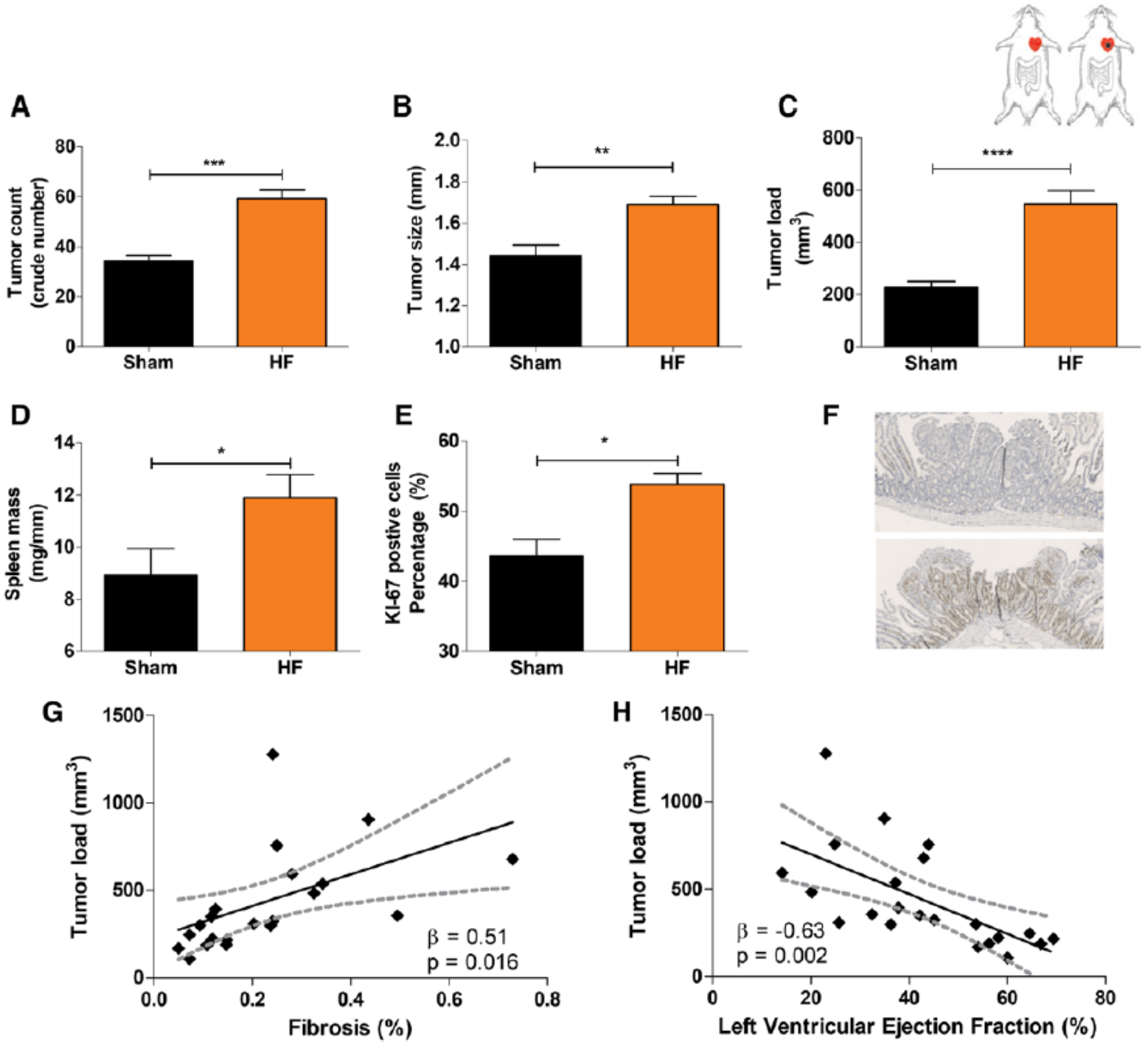
SZE-ben növekvő rák rizikó okai

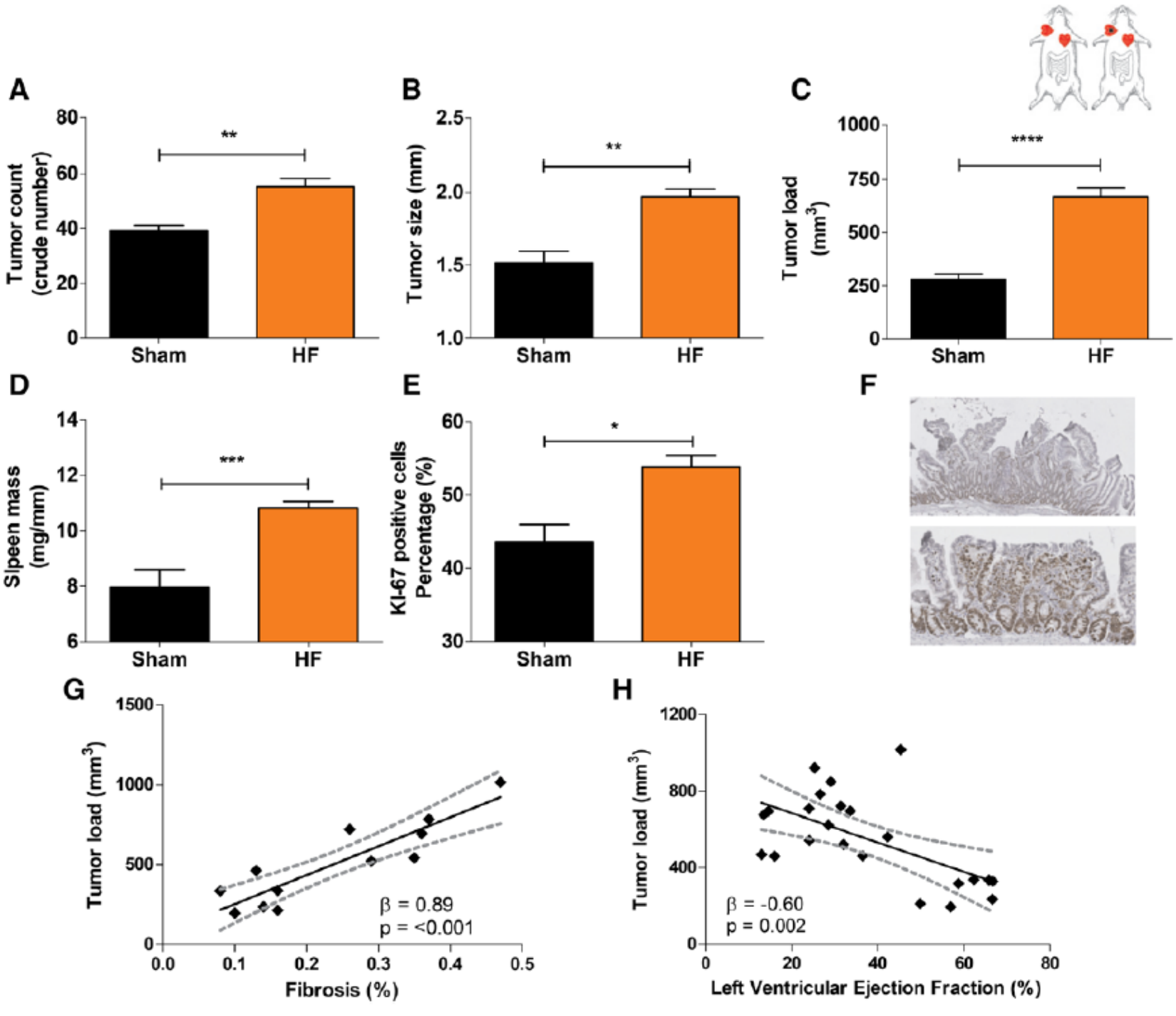
- Közös rizikófaktorok
  - Dohányzás, elhízás, diéta, ülő életmód, légszennyezés
- Neuroendokrín faktorok
  - Pl RAAS
- **SZE-ben vérben emelkedő különböző faktorok**



Meijers et al, Circulation, 2018


A
B
C
LV Ejection Fraction Percentage (%)
100
80
60
40
20
0
****
Sham
HF
Non-infarcted myocardium Fibrosis (%)
0.6
0.4
0.2
0.0
***
Sham
HF
D
NPPA mRNA (Fold change)
40
30
20
10
0
****
Sham
HF
E
Interleukin-6 mRNA (Fold change)
12
8
4
0
***
Sham
HF
F
Col3a1 mRNA (Fold change)
6
4
2
0
***
Sham
HF
G
CD68 mRNA (Fold change)
4
3
2
1
0
****
Sham
HF
H
LGALS3 mRNA (Fold change)
6
4
2
0
***
Sham
HF


A
Tumor count (crude number)
80
60
40
20
0
***
Sham
HF
B
Tumor size (mm)
2.0
1.8
1.6
1.4
1.2
1.0
**
Sham
HF
C
Tumor load (mm3)
800
600
400
200
0
****
Sham
HF
D
Spleen mass (mg/mm)
14
12
10
8
6
*
Sham
HF
E
KI-67 postive cells Percentage (%)
60
50
40
30
*
Sham
HF
F
G
Tumor load (mm3)
1500
1000
500
0
β = 0.51
p = 0.016
0.0
0.2
0.4
0.6
0.8
Fibrosis (%)
H
Tumor load (mm3)
1500
1000
500
0
β = -0.63
p = 0.002
0
20
40
60
80
Left Ventricular Ejection Fraction (%)


A
Tumor count (crude number)
80
60
40
20
0
**
Sham
HF
B
Tumor size (mm)
2.5
2.0
1.5
1.0
**
Sham
HF
C
Tumor load (mm3)
1000
750
500
250
0
****
Sham
HF
D
Spleen mass (mg/mm)
14
12
10
8
6
***
Sham
HF
E
KI-67 positive cells Percentage (%)
60
50
40
30
*
Sham
HF
F
G
Tumor load (mm3)
1500
1000
500
0
β = 0.89
p = <0.001
0.0
0.1
0.2
0.3
0.4
0.5
Fibrosis (%)
H
Tumor load (mm3)
1200
800
400
0
β = -0.60
p = 0.002
0
20
40
60
80
Left Ventricular Ejection Fraction (%)

SerpinA3
SerpinA1
Fibronectin
Coruloplasmin
Paraoxonáz1

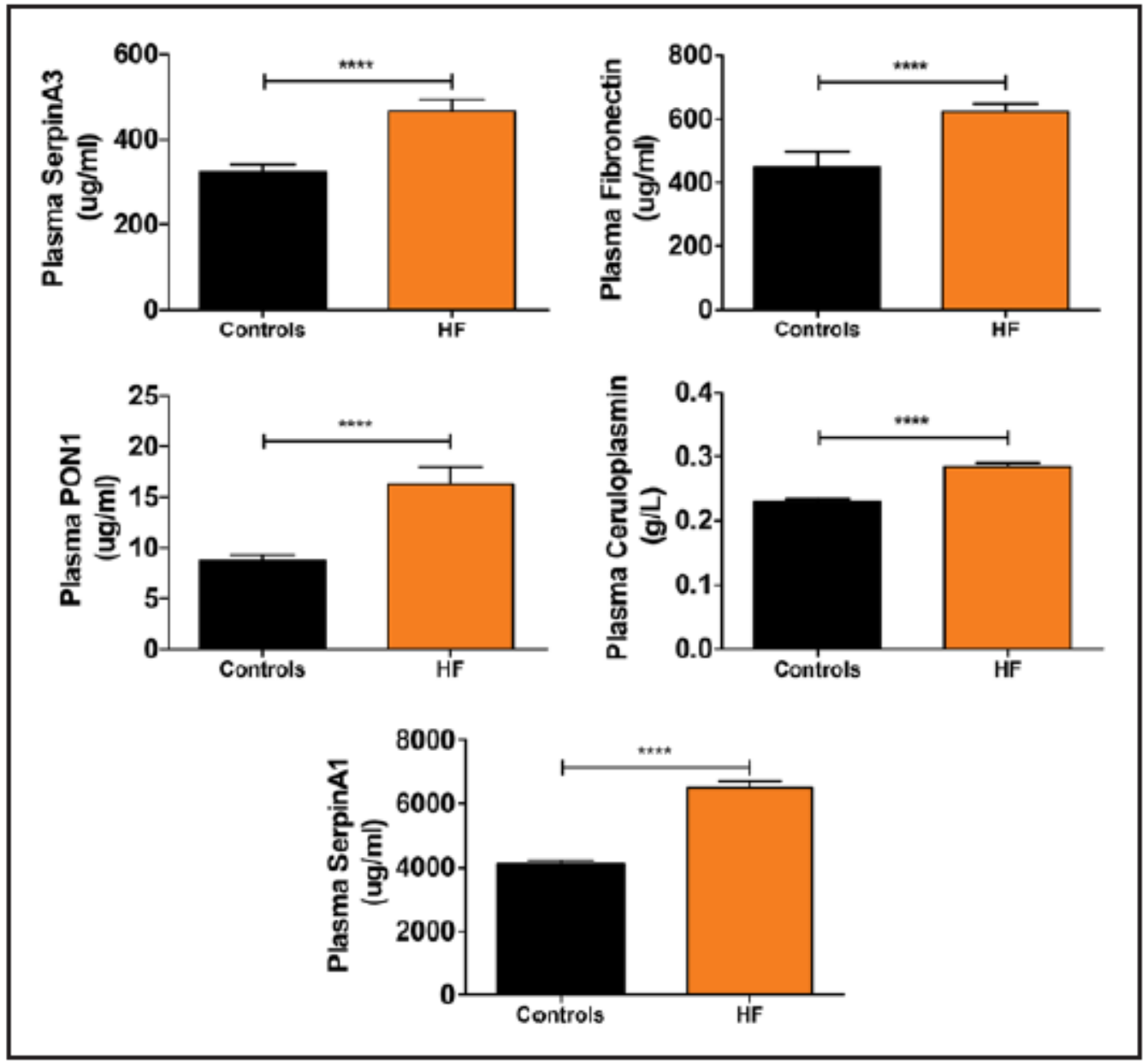


Figure 6. Human plasma levels of the identified candidate proteins.

Összefoglalás

- Daganatos betegek perioperatív ellátása interdiszciplináris megközelítést igényel
- Daganatos betegek nem csak a thrombózisra, de több mechanizmuson keresztül a vérzésre is hajlamosabbak
- A NOAC-ok terjedésével ismerni kell azok pharmakodinámiáját és használatukat műtétek idején
- NOAC antidotumok a piacra kerültek
- Szívelégtelenségben sokkal több a daganat, ez egészen új utat nyit a kardio-onkológia számára a kutatásban