

YOAK KULLANIMINDA GÜNCEL DEĞİŞİKLİKLER

Uzm Dr HANDE ERMAN

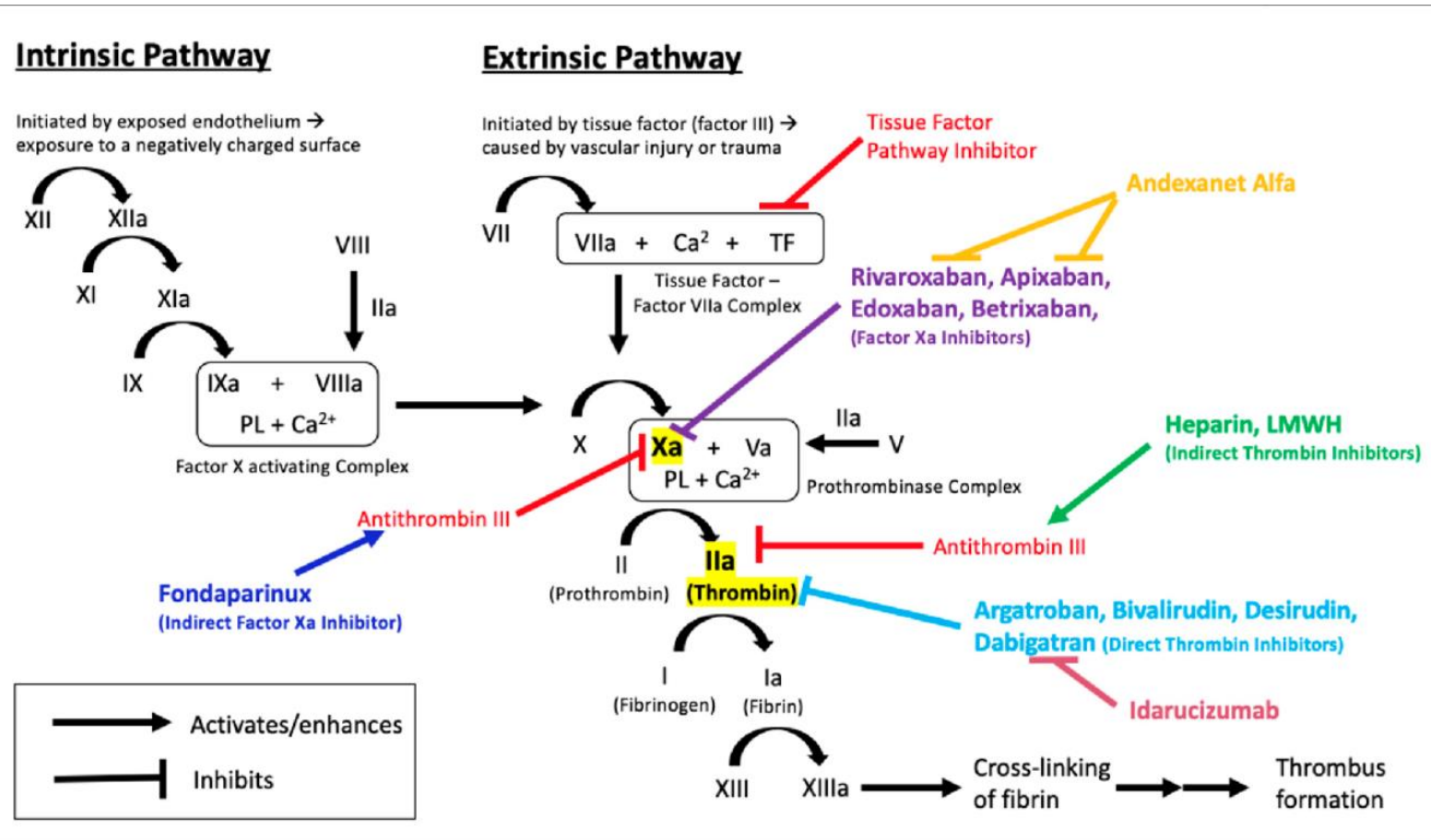
SBÜ. İSTANBUL KARTAL DR LÜTFİ KIRDAR ŞEHİR HASTANESİ

İÇ HASTALIKLARI KLİNİĞİ

YOAK: Yeni oral antikoagülanlar

NOAK: non-vitamin K antagonist oral anticoagulants

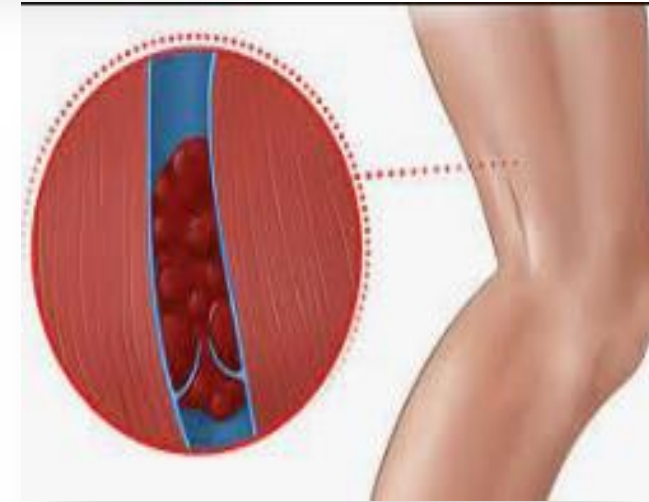
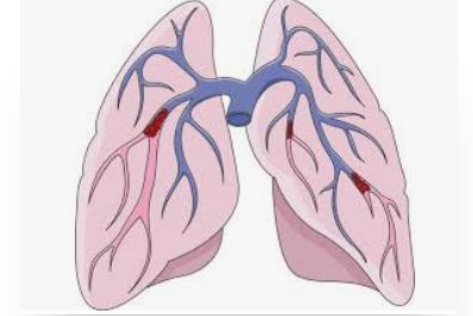
DOAC: Direct oral anticoagulants



YOAK: Yeni oral antikoagülanlar

Oral antikoagülan tedavi endikasyonu olan, uygun hasta gruplarında yeni oral antikoagülanların kullanımı tromboemboli riskini azaltmada oldukça önemlidir.

Varfarin kullanımındaki zorluklar (labil INR, dar terapötik aralık, çoklu diyet ve ilaç etkileşimi, sık izlem gerekliliği, kanama korkusu) nedeni ile YOAK kullanımı uygun hastalarda tercih sebebidir.



Yeni oral antikoagülanlar: Dabigatran

- Direk trombin (faktör IIa) inhibitörüdür.
- Dabigatran eteksilatin aktif halidir. Karaciğerde aktif metabolite dönüşür ve eliminasyon %80 renal yoldadır.
- GFR' ye göre doz ayarı gerekir
- Yarılanma süresi 14-17 saat.
- Non-valvular atrial fibrilasyonda 2x150mg olarak alınmalıdır (>80 yaş, beraberinde verapamil kullanımı ve GIS kanamada 110mg bid)

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

Yeni oral antikoagülanlar: Rivaroksaban

- Yarışmalı ve geri dönüşlü olarak serbest ve trombosit bağı FXa'yı inhibe eder.
- Yarı ömrü 7-11 saattir.
- Eliminasyonu %60 oranında karaciğerden gerçekleşir
- Kanama riski ile seyreden karaciğer hastalıklarında, Child-b, Child-C sirozda kontraendikedir.,
- Nonvalvular AF tanılı hastalarda 20mg önerilmektedir.

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Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

CONCLUSIONS

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)

Yeni oral antikoagülanlar: Apiksaban

- Oral direkt Faktör Xa inhibitörüdür.
- %70 oranında fekal yolla elimine olur.
- Yarı ömrü 10-14 saattir.
- Nonvalvuler AF tanılı hastalarda apiksaban 5mg bid kullanımı önerilmektedir (kreatinin>1.5, <60kg, >80yaş → 2.5mg/bid)

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Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Gernaldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)

Yeni oral antikoagülanlar: Edoksaban

- Faktör Xa'nın direkt ve geri dönüşümlü inhibitörüdür.
- Yarı ömrü 8-10 saattir
- Eliminasyon büyük oranda renal yolla gerçekleşir.
- Nonvalvular atrial fibrilasyonda 60mg tek doz kullanımı önerilmektedir.

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiko Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

CONCLUSIONS

Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. (Funded by Daiichi Sankyo Pharma Development; ENGAGE AF-TIMI 48 ClinicalTrials.gov number, NCT00781391.)

Non-valvular AF de inme önlemede

Stroke prevention in atrial fibrillation (SPAF)

	Standard dose	Comments/dose reduction
Apixaban ⁴⁷	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤ 60 kg, age ≥ 80 years, serum creatinine ≥ 133 $\mu\text{mol/L}$ (1.5 mg/dL) (or single criterion: if CrCl 15–29 mL/min)
Dabigatran ⁴⁸	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase III trial ^a
Edoxaban ⁴⁹	60 mg QD	30 mg QD if: weight ≤ 60 kg or CrCl 15–49 mL/min or concomitant therapy with strong P-Gp inhibitor (see 'Pharmacokinetics and drug-drug interactions of NOACs' section)
Rivaroxaban ⁴⁶	20 mg QD	15 mg QD if CrCl ≤ 15 –49 mL/min

SmPc' refers to European SmPc.

BID, twice daily; CrCl, creatinine clearance; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily.

^aSmPC: 110 mg BID if age ≥ 80 years, concomitant verapamil, increased risk of GI bleeding.

Nonvalvular AF ve Akut koroner sendrom

	Standard dose	Comments/dose reduction
Apixaban ²⁴⁴	5 mg BID	Dose reduction as for SPAF
Dabigatran ²⁴⁷	150 mg BID or 110 mg BID	110mg as for SPAF ⁴⁰³
Edoxaban ²⁴⁵	60 mg QD	Dose reduction as for SPAF
Rivaroxaban ²⁴⁶	15 mg QD	Dose reduction to 10 mg QD if CrCl 30–49 mL/min

In addition to single/dual antiplatelet therapy, where applicable. See 'Patients with atrial fibrillation and coronary artery disease' section for details.
BID, twice daily; CrCl, creatinine clearance; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

DVT ve Pulmoner emboli tedavisinde

Recommendations	Class ^a	Level ^b
Therapeutic anticoagulation for ≥ 3 months is recommended for all patients with PE. ³⁴⁷	I	A

Treatment of DVT/PE

	Initial therapy	Remainder of treatment phase
Apixaban ⁴⁹⁸	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran ⁴⁹⁹	Heparin/LMWH	150 mg BID, no dose reduction ^a
Edoxaban ⁵⁰⁰	Heparin/LMWH	60 mg QD, same dose reduction as for SPAF (see above)
Rivaroxaban ^{501,502}	15 mg BID, 21 days	20 mg QD, no dose reduction ^b

BID, twice daily; GI, gastrointestinal; LMWH, low molecular weight heparin; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

^aPer SmPC: 110 mg BID if age ≥ 80 years, concomitant verapamil, increased risk of GI bleeding [based on pharmacokinetic/pharmacodynamic (PK/PD) analyses; not studied in this setting].

^bPer SmPC: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting).

DVT ve Pulmoner emboli tedavisinde

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

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

Long-term prevention of recurrent DVT/PE

	Standard dose	Comments/dose adjustment
Apixaban ⁵⁰³	2.5 mg BID	No pre-specified dose-reduction criteria in clinical trial ^a
Dabigatran ⁵⁰⁴	150 mg BID	
Edoxaban ^{473,500,505}	60 mg QD ^b	
Rivaroxaban ⁵⁰⁶	10 mg QD	

c

Post-majör ortopedi cerrahisi sonrası VTE önlemede

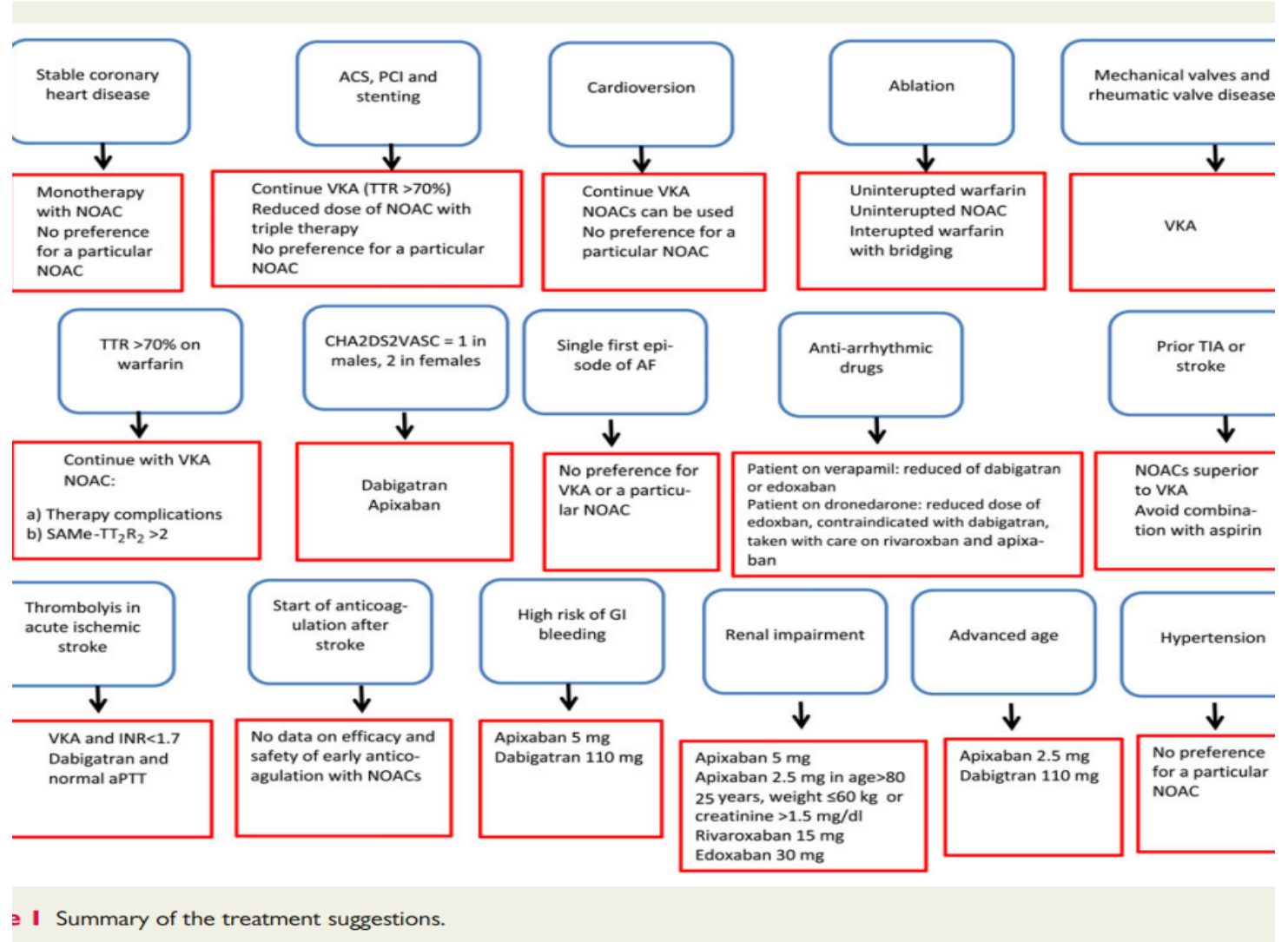
VTE prevention post-major orthopaedic surgery

	Standard dose	Comments/dose reduction
Apixaban ⁵⁰⁷	2.5 mg BID	
Dabigatran ^{508,509}	220 mg QD/150 mg QD	^a
Edoxaban ^{510,511}	30 mg QD	Not approved in Europe (only studied in Asia)
Rivaroxaban ⁵¹²⁻⁵¹⁵	10 mg QD	

BID, twice daily; QD, once daily.

^aSmPc: 1 × 150 mg if CrCl 30–50 mL/min; concomitant verapamil, amiodarone, quinidine; age >75 years.

Hangi YOAK ne zaman?



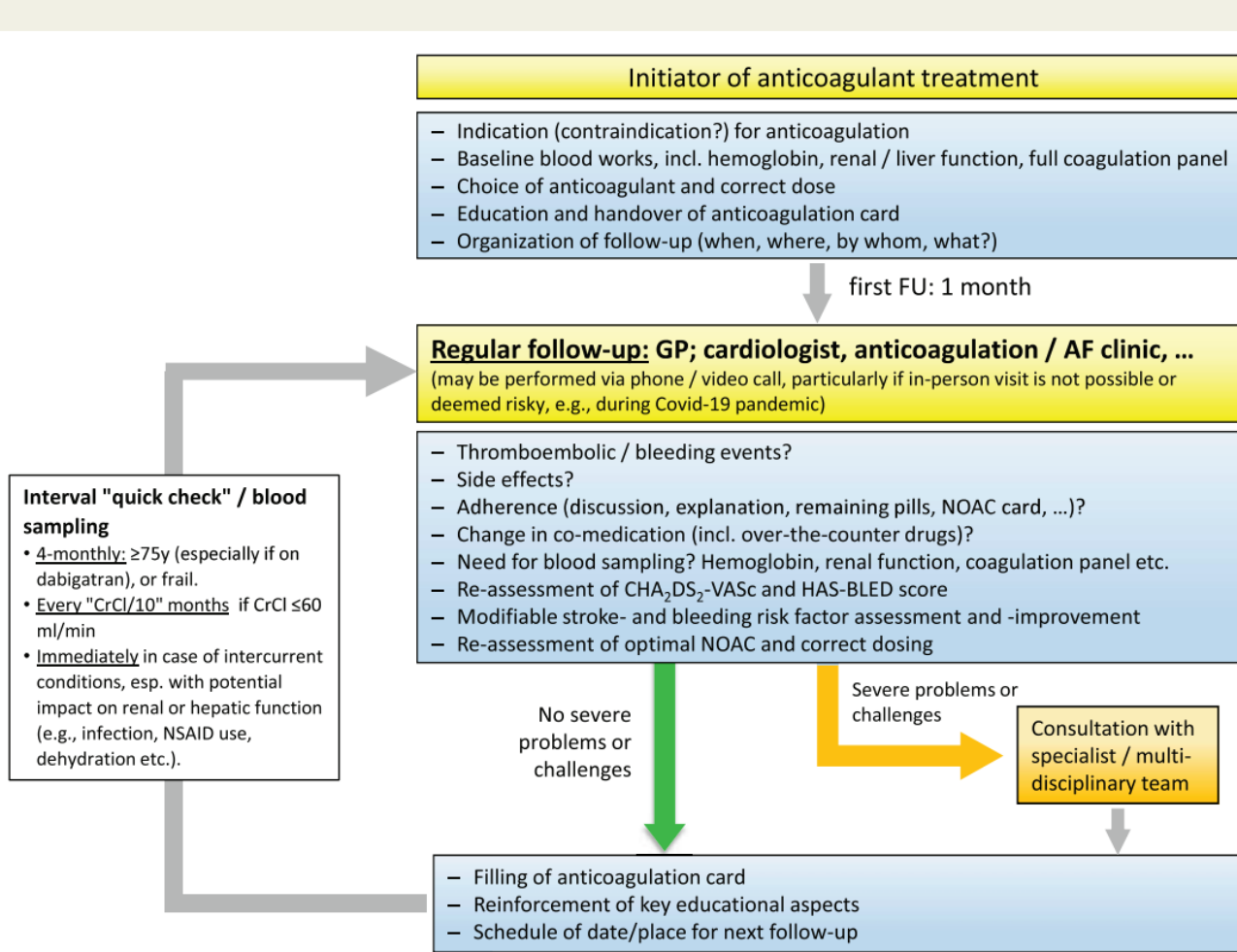
Diener HC, Aisenberg J, Ansell J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. Eur Heart J. 2017 Mar 21;38(12):860-868. doi: 10.1093/eurheartj/ehw069.

Kontraendikasyonlar

- Orta-ciddi MD
- Mekanik protez kapak
- Aktif kanama
- Gebelik
- Koagülopati+KC ciddi yetmezliği
- CCl<30ml/dk (dabigatran)
CCI < 15ml/dk rivaroksaban ve apiksaban

Endikasyonlar

- Nonvalvular AF
- DVT Tedavi ve Önlemede
- PE tedavisinde
- Majör ortopedi operasyonu sonrasında VTE önlemede



CHA ₂ DS ₂ -VASc Score	
CHF (heart failure)	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke	2
Vascular Disease	1
Age 65-74	1
Sex Category (female)	1

Condition	Points
H – Hypertension	1
A – Ab(N) liver/renal	1 point each
S – Stroke	1
B – Bleeding	1
L – Labile INRs	1
E – Elderly (>65)	1
D – Drugs or ETOH	1 point each

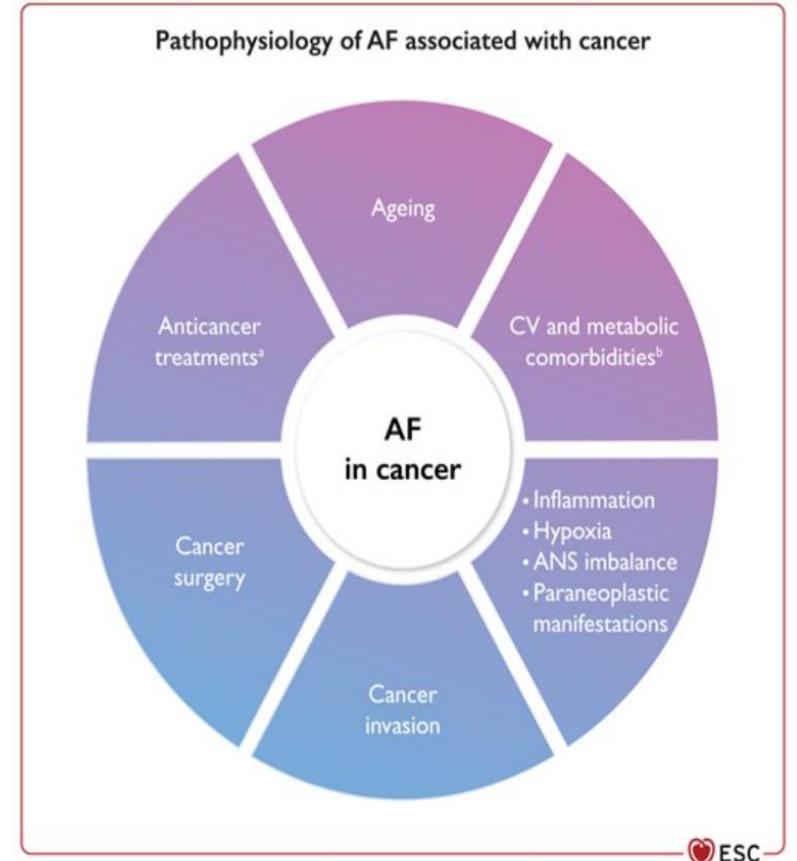
Figure 3 Initiation and structured follow-up of patients on NOACs. It is crucial to ensure a structured follow-up of patients on NOACs. The anticoagulation card, as proposed in Figure 2, is intended to document each visit so that every person following up on the patient is well-informed. Moreover, written communication between different healthcare providers is required to inform them about the follow-up plan and execution. AF, atrial fibrillation; CrCl, creatinine clearance; GP, General Practitioner; NOAC, non-vitamin K antagonist oral anticoagulant.

AF ve Kalp yetersizliğinde YOAK kullanımı

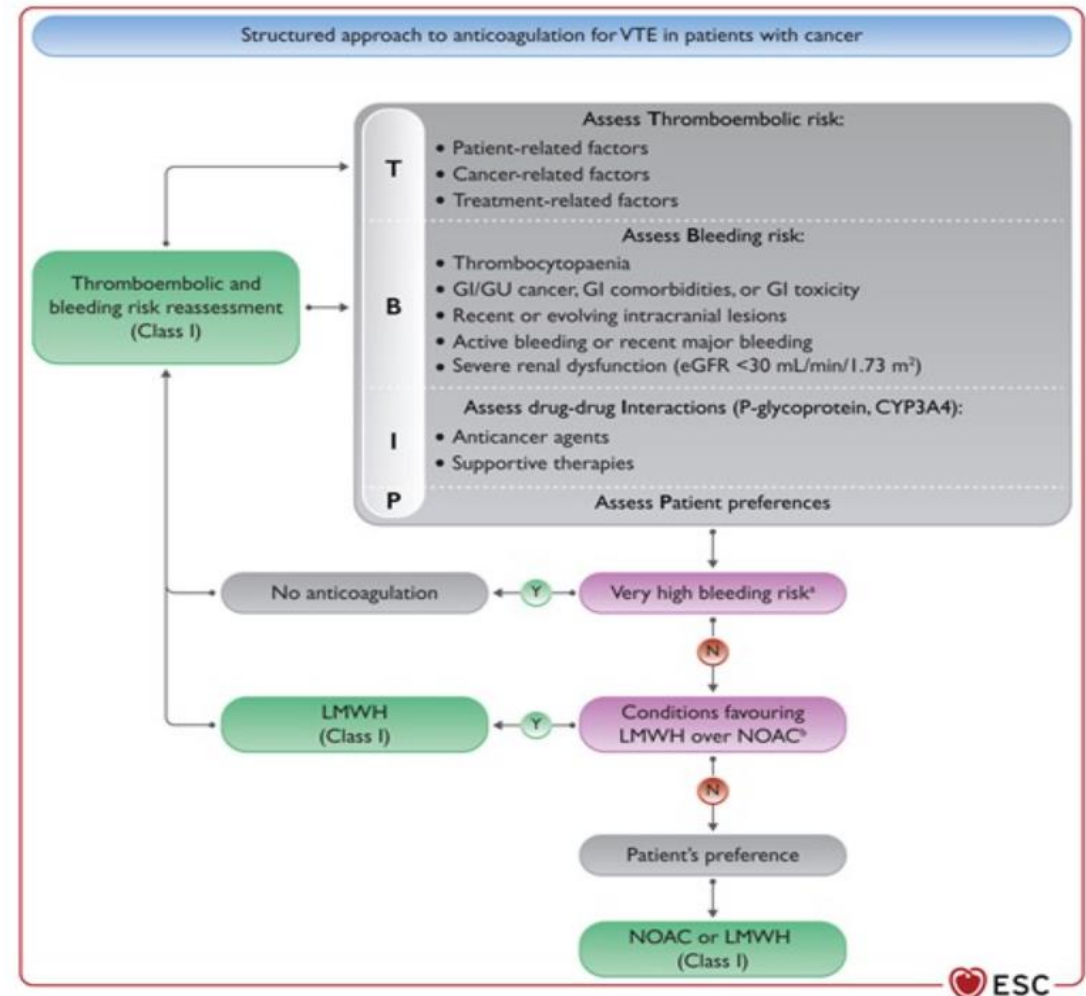
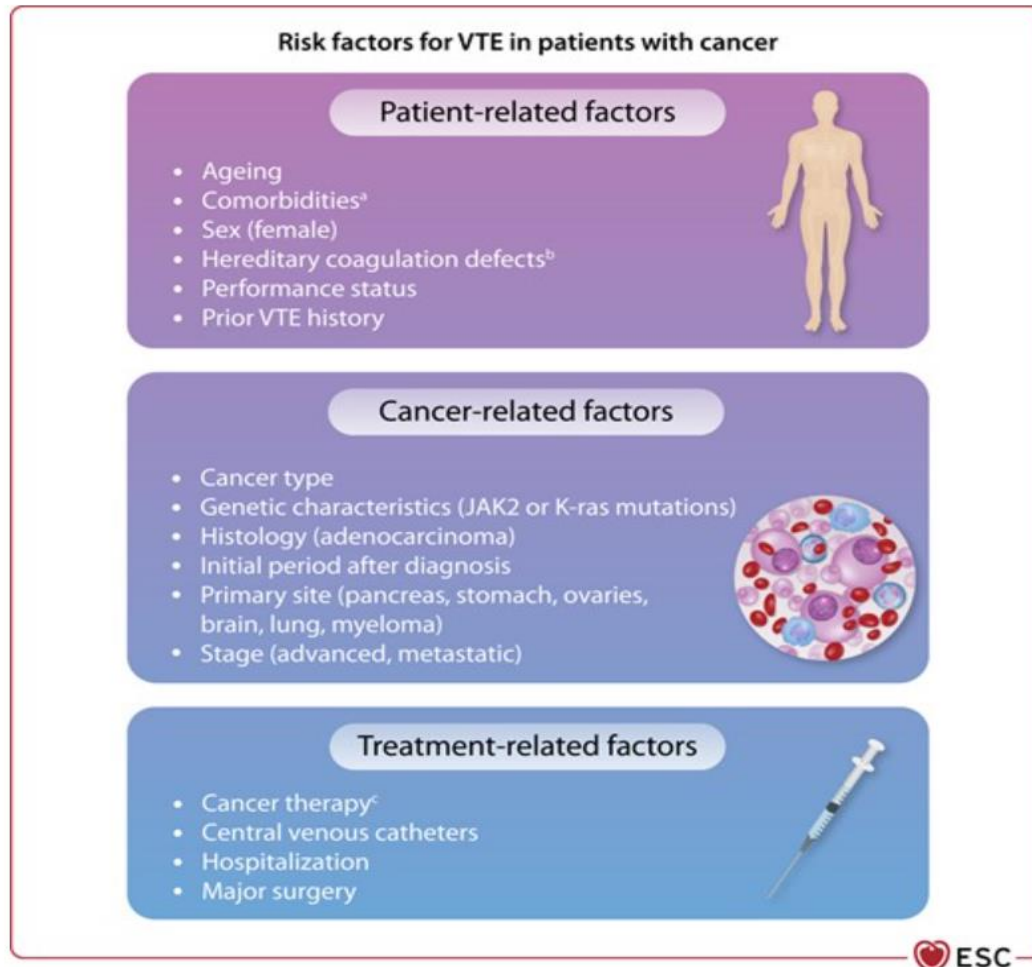
- Avrupa Kardiyoloji Derneği Kalp Yetersizliği 2016 kılavuzunda kalp yetersizliği ve AF 'si olan hastalarda YOAK kullanımı varfarine kıyasla gastrointestinal kanama riskini artırsa da inme ve intrakranial kanama ve mortalite riskini daha fazla düşürdüğü için sınıf IIa düzeyinde önerilmekteydi.
- 2021 kılavuzunda ise orta-ciddi mitral darlığı ve ya mekanik protez kalp kapağı olan hastalar haricinde YOAK'lar sınıf Ia olarak önerilmektedir.

Kanser ve AF

- Tüm kanser tiplerinde AF oluşum riskinin kanser olmayan kişilere göre artmış olduğu ifade edilmektedir.
- Kanser tedavisi sırasında AF gelişim oranı %2-16 arasında değişmektedir.
- YOAK'lar (mekanik kalp kapağı ve orta-ciddi mitral yetersizlik haricinde) kanama riski yüksek olmayan ve önemli ilaç etkileşim olmayan AF tanılı hastalarda DMAH ve VKA 'ya alternatif olarak değerlendirilmelidir (Sınıf IIa, Düzey: B).



Kanser, VTE ve YOAK'lar



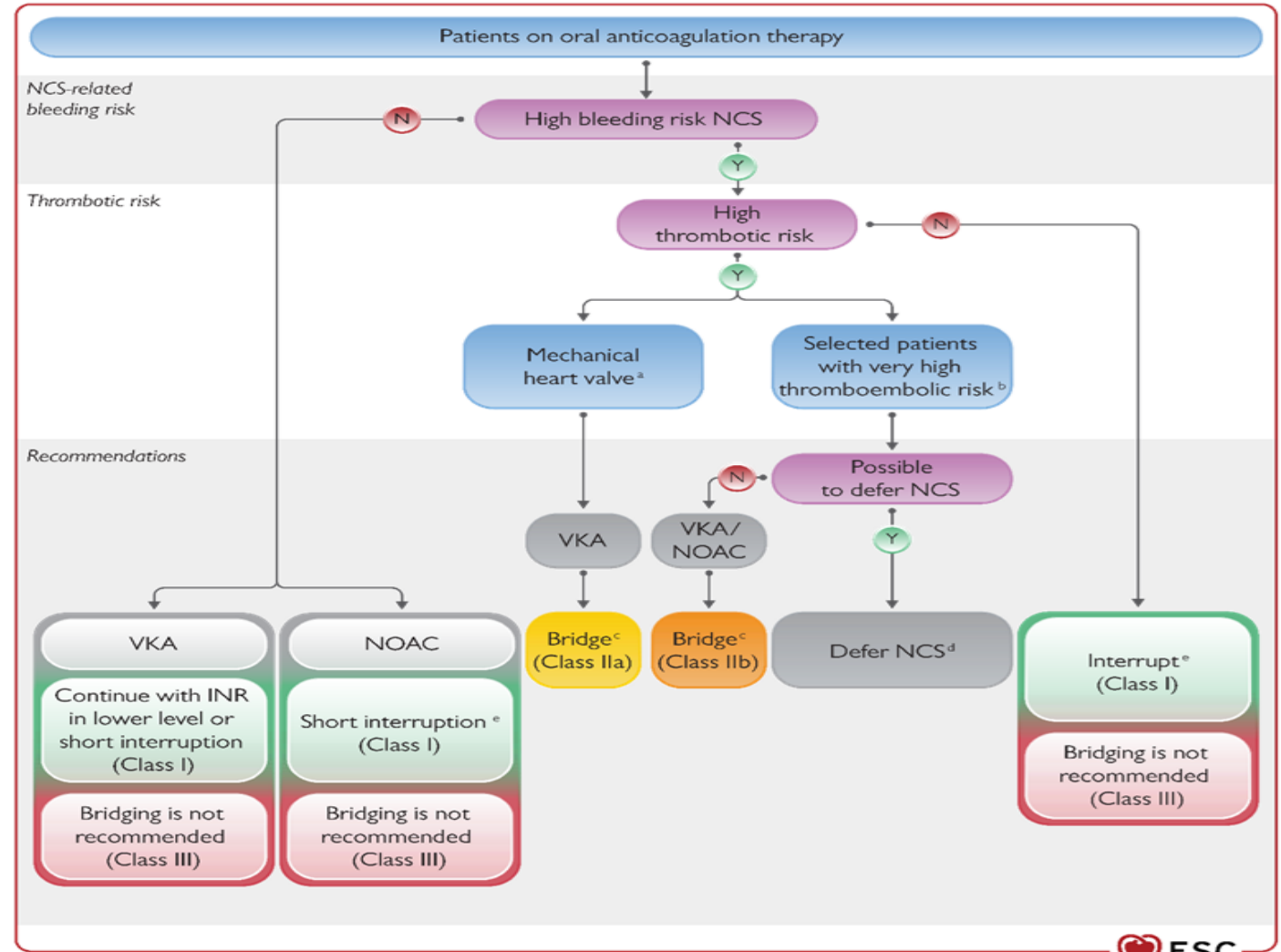
Kanser, VTE ve YOAK'lar

- Kanser hastalarında semptomatik veya insidental VTE gelişmesi durumunda eğer kontraendikasyon yoksa apiksaban, edoksaban veya rivaroksaban kullanımını önerilmektedir. Sınıf I, Düzey A.
- Kateter ilişkili VTE de antikoagülan kullanım süresi 3 ay olarak önerilmektedir. Sınıf I, Düzey C.
- Yüksek tromboz riski olan (Khorana ya da COMPASS-CAT) kanser hastalarına primer profilaksi amaçlı YOAK (apiksaban veya rivaroksaban) veya DMAH kullanımını önerilebilir (Sınıf IIB, Düzey B).
- VTE risk faktörleri olan Multipl Myelom tanılı hastalarda DMAH ve aspirine alternatif olarak düşük doz apiksaban veya rivaroksaban kullanılabilir (Sınıf IIB, Düzey C).

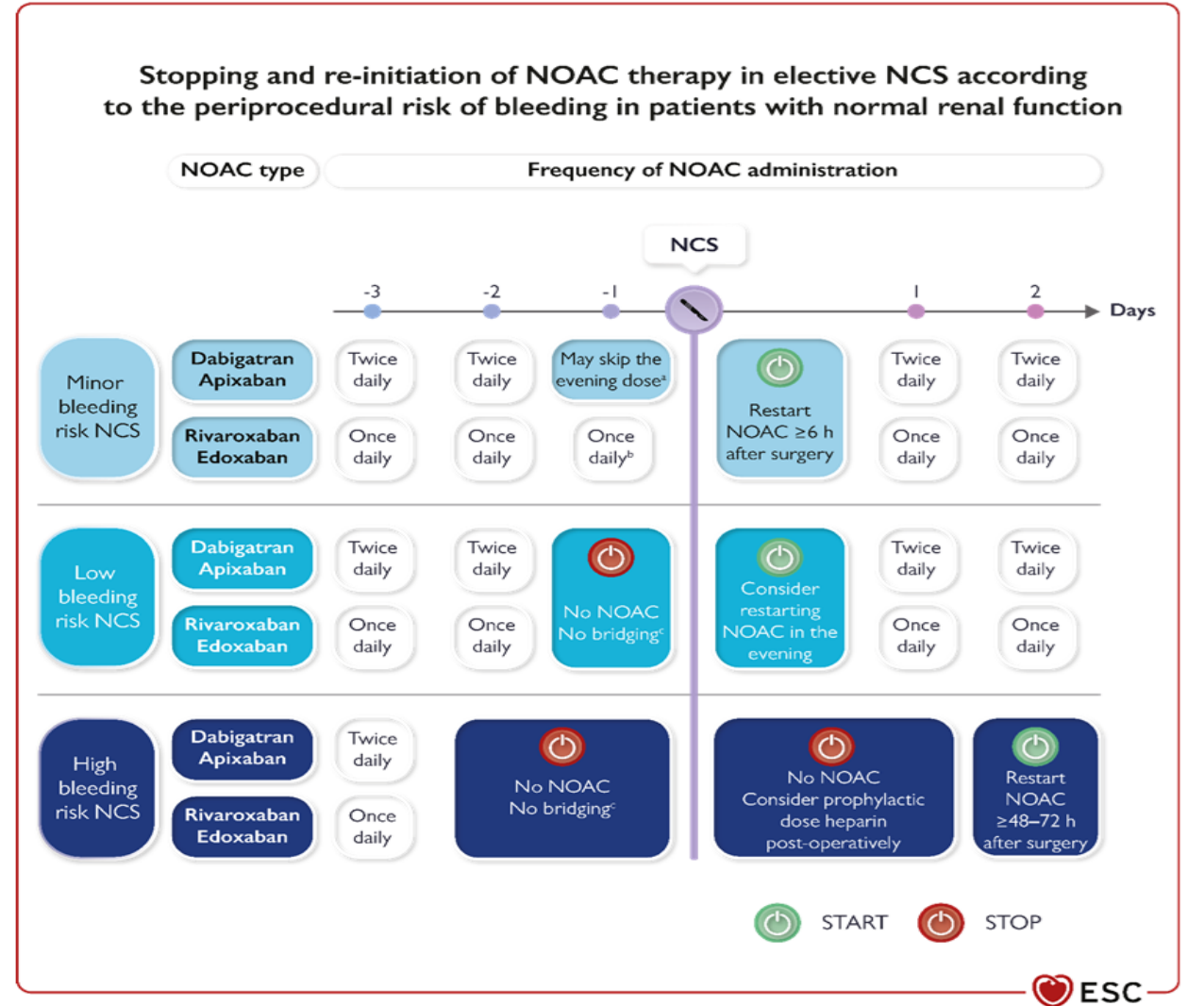
Kalp dışı cerrahi planlanırken YOAK'lar

- Acil cerrahi girişim gerektiğinde YOAK tedavisi kesilmelidir (Sınıf I, Düzey C).
- Minör kanama riski olan veya kanam kontrolü kolaylıkla sağlanabilecek cerrahi işlemlerde YOAK'ların kesilmemesi önerilebilir (Sınıf I, Düzey B).
- Minör kanama riski dışındaki kanama risklerinde, hangi YOAK kullanıldığı, renal fonksiyon ve kanama riskine göre ara verme rejimi planlanmalıdır (Sınıf I, Düzey B),
- YOAK kullanan hastalarda kanama riski düşük olan prosedürler tercih edilmelidir. Bu durumda en son YOAK dozundan 12-24 saat sonra cerrahi işlem planlanabilir (Sınıf I, Düzey C).
- Düşük-orta trombotik riski içeren cerrahi işlemlerde YOAK tedavisi için köprü antikoagülan önerilmemektedir (Sınıf III, Düzey B). Operasyon sonrası kanama riskini azaltmak amacı ile YOAK dozunun azaltılması önerilmemektedir (Sınıf III, Düzey C)

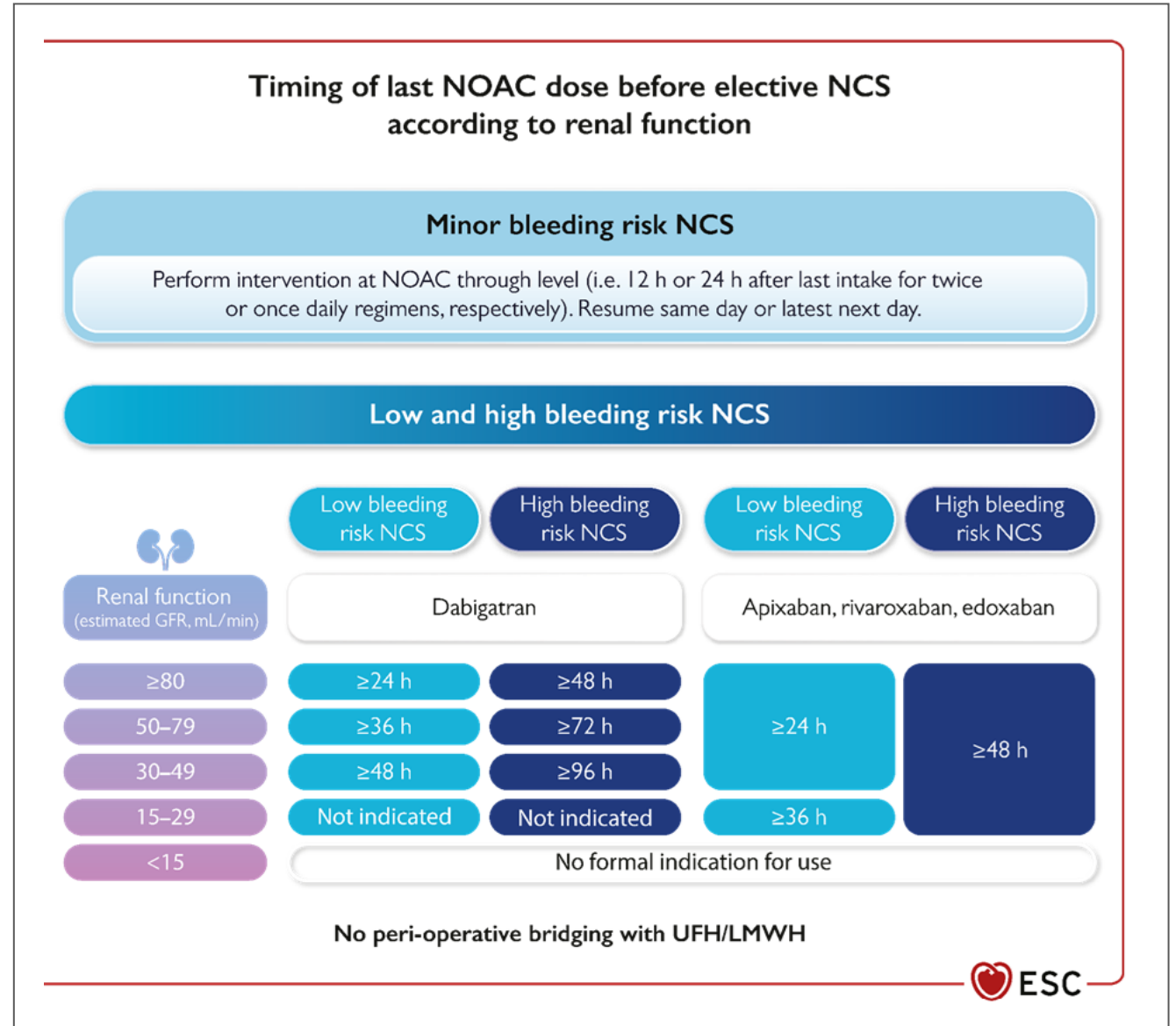
Kalp dışı cerrahi planı ve YOAK kullanımı



Kalp dışı cerrahide YOAK tedavi planı



Elektif cerrahi planında YOAK tedavi planı



Kalp dışı cerrahi planlanırken YOAK'lar

<i>Interruption of anticoagulation</i>		
When an urgent surgical intervention is required, it is recommended that NOAC therapy is immediately interrupted.	I	C
Idarucizumab should be considered in patients on dabigatran and requiring urgent surgical intervention with intermediate to high bleeding risk.	IIa	B
In non-minor bleeding risk procedures in patients using a NOAC, it is recommended to use an interruption regimen based on the NOAC compound, renal function, and bleeding risk.	I	B
For interventions with a very high risk of bleeding, such as spinal or epidural anaesthesia, interruption of NOACs for up to five half-lives and re-initiation after 24 h should be considered.	IIa	C
When specific reversal agents are not available, PCC or activated PCC should be considered for reversing NOAC effects.	IIa	C
If an urgent surgical intervention is required, specific coagulation tests and assessment of NOAC plasma levels should be considered to interpret routine coagulation tests and waning of anticoagulant effect.	IIa	C

Perioperatif trombofilaksi ve YOAK'lar

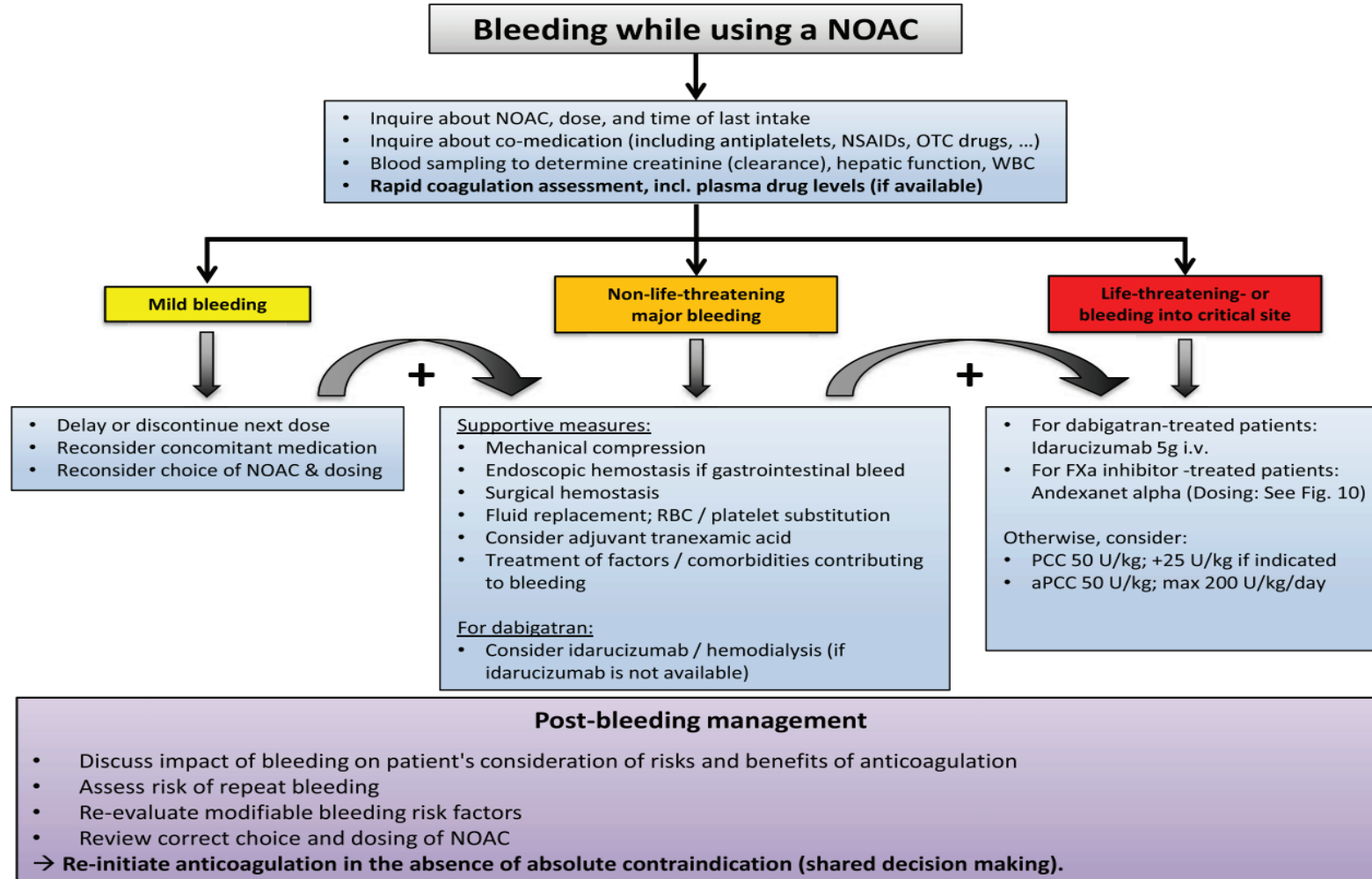
- Perioperatif trombofilaksi cerrahinin şekline ve hastaya göre karar verilmelidir. Sınıf I, Düzey A.
- Trombofilaksi gerektiği düşünülüyorsa cerrahi prosedür, immobilizasyon süresi ve hasta ilişkili faktörler değerlendirilerek antikoagülan tercih edilmelidir (DMAH, YOAK veya fondaparinuks) (Sınıf I, Düzey A)
- Postoperatif dönemde oral antikoagülan kullanımı gereken hastalarda YOAK genellikle VKA'ya tercih edilmesi önerilir (Sınıf I, Düzey A).

YOAK kullanımında klinisyeni zorlayan durumlar

- KANAMA
- TROMBOSİTOPENİ



YOAK kullanımı sırasında kanama



YOAK ve Trombositopeni

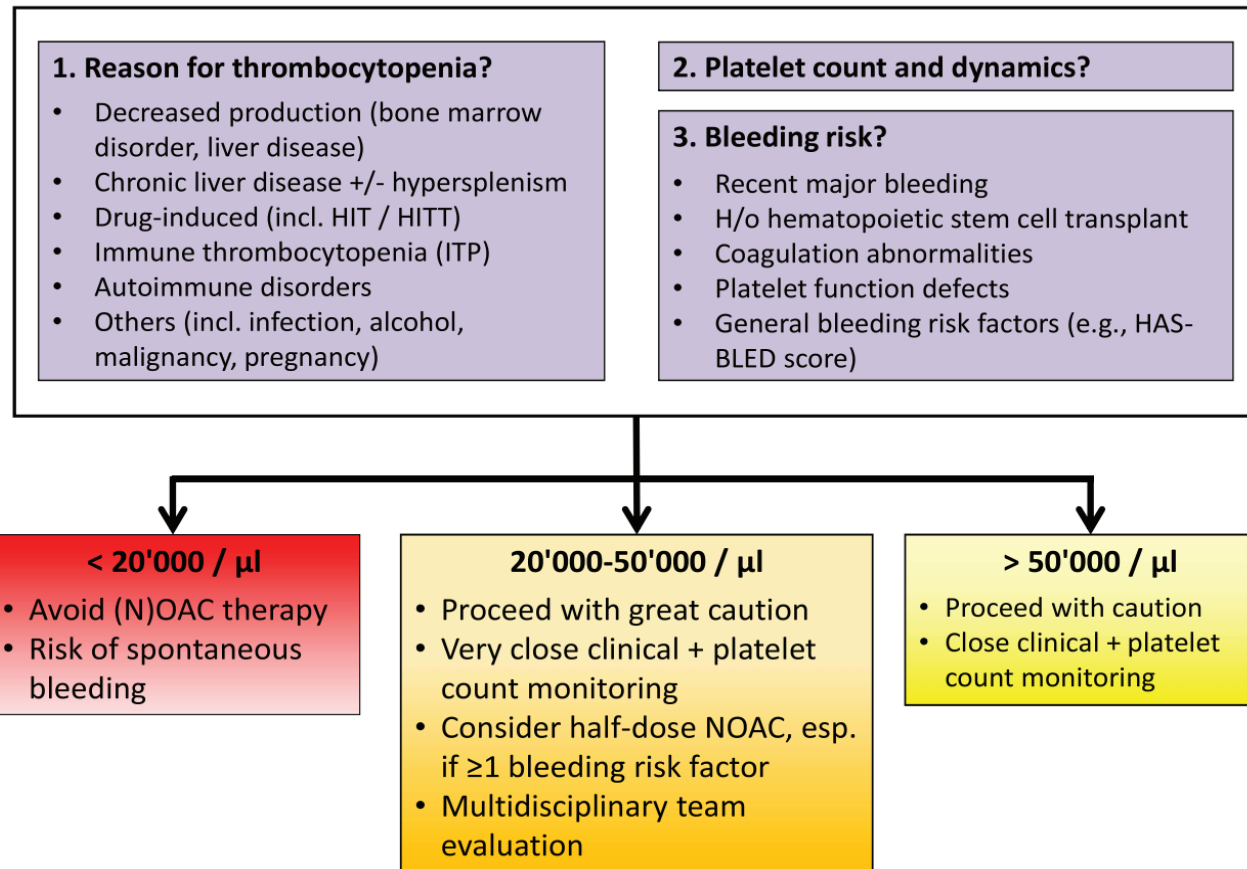


Figure 24 NOACs in patients with thrombocytopenia. NOAC, non-vitamin K antagonist oral anticoagulant.

COVID-19 pandemisinde YOAK kullanımı

- YOAK'ların monitörizasyon gerektirmemesi pandemi sırasında avantaj sağlamıştır.
- Fakat bununla birlikte atrial fibrilasyonlu hastalar COVID-19 enfeksiyonu varlığında yüksek risk grubunda oldukları unutulmamalıdır. Bu nedenle YOAK dozu ve takip aralığı hastaya göre planlanmalı ve hastaların takip şemasına uyumu sağlanmalıdır.
- YOAK kullanmakta olan hastaların COVID-19 enfeksiyonu nedeni ile hastane yatışı gerekmesi durumunda antikoagülan tedavinin devamı önerilir. Fakat klinik bozulma (özellikle renal disfonksiyon) ve beraberinde verilen tedaviler göz önünde bulundurularak tedavi devamı değerlendirilmelidir.
- YOAK kullanan hastalarda COVID-19 aşısı yapılması durumunda ise, enjeksiyon öncesi dozun enjeksiyondan 3 saat sonrasına ertelenmesi, günde iki sefer kullanılan YOAK'larda bir sonraki dozun zamanında alınması önerilmektedir.



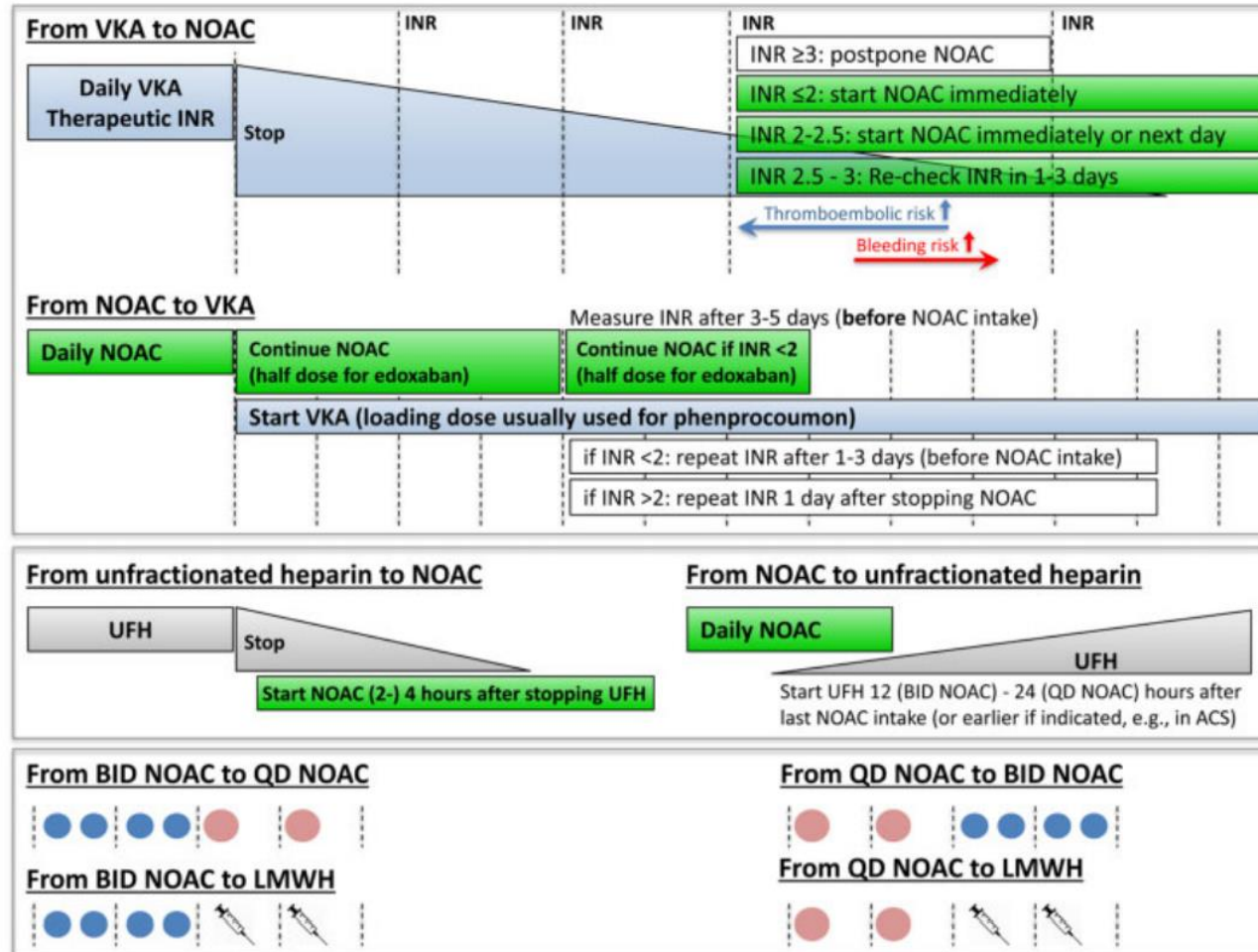
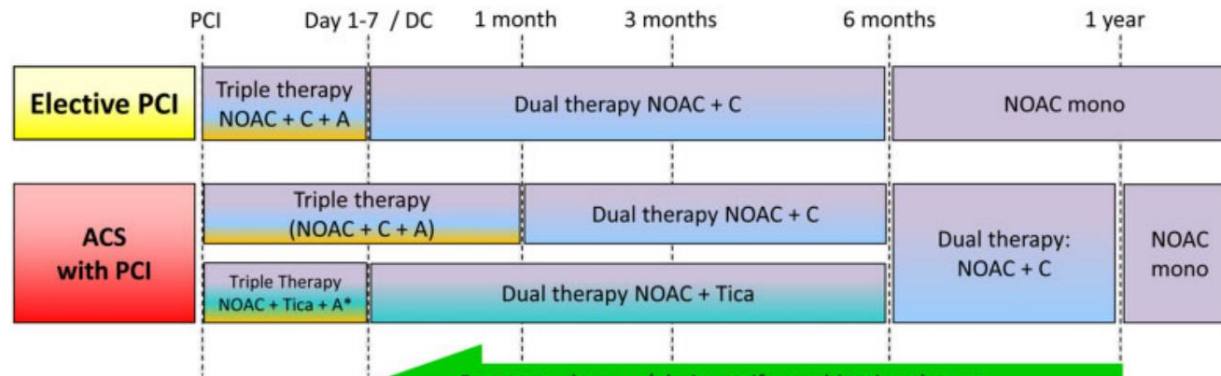


Figure 4 Switching between NOACs and other anticoagulants. ACS, acute coronary syndrome; BID, twice daily; INR, international normalized ratio; LMWH, low molecular weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily; UFH, unfractionated heparin; VKA, vitamin K antagonist



Factors to shorten / de-intensify combination therapy

- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective; GRACE < 140 if ACS)

Factors to lengthen / intensify combination therapy

- High atherothrombotic risk (scores as above; stenting of left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk

In all patients:

- Avoid use of BMS / first generation DES
- Use PPI if on triple / dual therapy
- Minimize bleeding risk by assessing and treating modifiable bleeding risk factors (e.g., hypertension, etc.)
- Close follow-up; check for signs of (occult) bleeding

Table 1

Doses of the different NOACs in the four large comparative trials in AF patients

NOAC	Dose
Dabigatran (RELY)	150 mg twice daily 110 mg twice daily
Rivaroxaban (ROCKAT-AF)	20 mg once daily, protocol-mandated dose reduction to 15 mg
Apixaban (ARISTOTLE)	5 mg twice daily, protocol-mandated dose reduction to 2.5 mg
Edoxaban (ENGAGE-AF)	60 mg once daily, protocol-mandated dose reduction to 30 mg 30 mg once daily, protocol-mandated dose reduction to 15 mg

[Open in a separate window](#)

Study acronyms in brackets.