Yeni Oral Antikoagülanların Kılavuzlardaki Endikasyonları

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Bülent Behlül Altunkeser

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EHRA PRACTICAL GUIDE

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

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Europace 2013

New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent [illegible] fibrillation (AF). Both physicians and patients will have to learn how to use these drugs effectively [illegible]ed questions on how to optimally use these drugs in specific clinical situations remain. The European Heart [illegible]o-ordinate a unified way of informing physicians on the use of the different NOACs. A writing group listed 1[illegible]pics [illegible]cre[illegible]tical sce[illegible]s and formulated as practical answers as possible based on available evidence. The 15 topics are: (1) Practical start-[illegible]d follo[illegible]o scheme fo[illegible] patients on NOACs; (2) How to measure the anticoagulant effect of NOACs; (3) Drug–drug interactions and phar[illegible]cokinetics of NOACs; (4) Switching between anticoagulant regimens; (5) Ensuring compliance of NOAC intake; (6) How to deal with dosi[illegible]g errors; (7) Patients with chronic kidney disease; (8) What to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding? (9) Management of bleeding complications; (10) Patients undergoing a planned surgical intervention or ablation; (11) Patients undergoing an urgent surgical intervention; (12) Patients with AF and coronary artery disease; (13) Cardioversion in a NOAC-treated patient; (14) Patients presenting with acute stroke while on NOACs; (15) NOACs vs. VKAs in AF patients with a malignancy. Since new information is becoming available at a rapid pace, an EHRA Web site with the latest updated information accompanies this text (www.NOACforAF.eu).

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

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JACC 2014

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This document was approved by the American College of Cardiology Board of Trustees, the American Heart Association Science Advisory and Coordinating Committee, and the Heart Rhythm Society Board of Trustees in March 2014.

AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Walter N. Kernan, MD, Chair; Bruce Ovbiagele, MD, MSc, MAS, Vice Chair; Henry R. Black, MD; Dawn M. Bravata, MD; Marc I. Chimowitz, MBChB, FAHA; Michael D. Ezekowitz, MBChB, PhD; Margaret C. Fang, MD, MPH; Marc Fisher, MD, FAHA; Karen L. Furie, MD, MPH, FAHA; Donald V. Heck, MD; S. Claiborne (Clay) Johnston, MD, PhD; Scott E. Kasner, MD, FAHA; Steven J. Kittner, MD, MPH, FAHA; Pamela H. Mitchell, PhD, RN, FAHA; Michael W. Rich, MD; DeJuran Richardson, PhD; Lee H. Schwamm, MD, FAHA; John A. Wilson, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vas

Abstract—The aim of this updated guideline is to provide comprehensive and t on the prevention of future stroke among survivors of ischemic stroke or transie addressed to all clinicians who manage secondary prevention for these patient are provided for control of risk factors, intervention for vascular obstruction, antithrombo m, and antiplatelet therapy for noncardioembolic stroke. Recommendations are also provid or t evel of recu t

Stroke 2014

CHA_2DS_2-VASc ve HAS-BLED

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure	1	Hypertension (systolic blood pressure >160 mm Hg)	1
Hypertension	1	Abnormal renal and liver function* (1 point each)	1 or 2
Age ≥75 y	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency/predisposition*	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)*	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Elderly (eg, age >65 y)	1
		Drugs or alcohol (1 point each)*	1 or 2
Aged 65 to 74 y	1		
Sex category (ie, female sex)	1		
Maximum score	9	Maximum score	9

HAS-BLED netleştirme

- **Anormal renal fonksiyon:** Kronik diyaliz, renal transplantasyon, serum kreatinin ≥ 2.26 mg/dL
- **Anormal KC fonksiyonu:** Kr KC hastalığı (siroz gb), KC enzimlerinde mühim yükseklik (bilirubin'de 2-3 kat yükseklik ile birlikte AST/ALT/ALP'de 3 kat yükseklik)
- **Kanamaya meyil/predispozisyon:** Kanama hikâyesi ve predispozisyonu (anemi)
- **Labil INR:** TTR < %60
- **İlaç veyâ alkol:** antiplatelet veyâ NSAID veyâ aşırı alkol kullanılması

R_2CHADS_2

R = GFR < 0.60 ml/dk

Renal Dysfunction as a Predictor of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation

Validation of the R_2CHADS_2 Index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) Study Cohorts

Jonathan P. Piccini, MD, MHS; Susanna R. Stevens, MS; YuChiao Chang, PhD; Daniel E. Singer, MD; Yuliya Lokhnygina, PhD; Alan S. Go, MD; Manesh R. Patel, MD; Kenneth W. Mahaffey, MD; Jonathan L. Halperin, MD; Günter Breithardt, MD; Graeme J. Hankey, MD; Werner Hacke, MD, PhD; Richard C. Becker, MD; Christopher C. Nessel, MD; Keith A.A. Fox, MB, ChB; Robert M. Califf, MD; for the ROCKET AF Steering Committee and Investigators

Background—We sought to define the factors associated with the occurrence of stroke and systemic embolism in a large, international atrial fibrillation (AF) trial.

Methods and Results—In ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), 14,264 patients with AF and creatinine clearance ≥30 mL/min were randomized to rivaroxaban or dose-adjusted warfarin. Cox modeling was used to identify factors at randomization independently associated with stroke and other systemic nervous system embolism based on intention-to-treat analysis. A risk score was developed and validated in ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation), an independent observational cohort. Over a median follow up of 1.94 years, 575 patients (4.0%) experienced primary end-point events. Prior stroke was the strongest, independent predictor of stroke and systemic embolism, second only to prior stroke or transient ischemic attack. Additional factors associated with stroke and systemic embolism included elevated diastolic blood pressure, diabetes mellitus, reduced glomerular filtration rate, as well as vascular disease of the heart and limbs (C-index 0.635). A model that included creatinine clearance (R_2CHADS_2) improved net reclassification index by 6.2% compared with CHA_2DS_2VASc (C statistic=0.578) and by 8.2% compared with $CHADS_2$ (C statistic=0.575). The inclusion of creatinine clearance <60 mL/min and prior stroke or transient ischemic attack in a model with no other covariates led to a C statistic of 0.590. Validation of R_2CHADS_2 in an external, separate population improved net reclassification index by 17.4% (95% confidence interval, 12.1%–22.5%) relative to $CHADS_2$.

Conclusions—In patients with nonvalvular AF at moderate to high risk of stroke, impaired renal function is a potent predictor of stroke and systemic embolism. Stroke risk stratification in patients with AF should include renal function.

Circulation 2013

R2 İşe Yaramıyor!

- 13400 böbrek ve AF hastası retrospektif inceleniyor.
- Böbrek yetersizliğinin riske dâhil edilmesi işe yaramıyor.
- Risk, böbrek yetersizliğine refâkat eden faktörler sebebiyle artıyor.

Friberg L et al. Eur Heart J 2015

Japonlar

Circ J 2014

mCHA$_2$DS$_2$-VASc score	
Congestive heart failure/left ventricular dysfunction	1
Hypertension (≥140 mmHg)	1
Age (≥75 years)	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease (coronary artery disease)	1
Age (65–74 years)	1
Sex category (female)	1
mHAS-BLED score	
Hypertension (≥140 mmHg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INR (≥3.5 episode(s))	1
Elderly (≥65 years)	1
Drugs (use of antiplatelets)	1

Japonlar

- Hedef INR = 1.6 – 2.6 (70 yaş üzeri)
- **CHA_2DS_2-VA** (kadını kaldırdık)
- **VA**; Sâdece KAH?

Okumura K et al. Circ J 2014

Kılavuzlarda her şey yok!

Hipertrofik KMP ve Hipertiroidi??

- Hipertrofik KMP'li hastalar (bi-l-hâssa sol atriyum büyük ve yaş ileri ise) ***warfarin almalıdır.***

Guttmann OP et al. Heart 2014

Hipertiroidi: Hâlâ muammâ?

Hipertrofik KMP Kılavuzu

- HKM'li bütün AF hastaları **sinüs ritmi sağlansa da** warfarin almalıdır.

Hipertrofik KMP Kılavuzu. Eur Heart J 2014

Circulation ve J Am Coll Cardiol Kılavuz 2014

CHA_2DS_2-VASc score recommended to assess stroke risk	I	B
Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis	I	B
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended. Options include:		
• Warfarin	I	A
• Dabigatran, rivaroxaban, or apixaban	I	B
With warfarin, determine INR at least weekly during initiation and monthly when stable	I	A
Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR	I	C
Re-evaluate the need for anticoagulation at periodic intervals	I	C
Bridging therapy with LMWH or UFH recommended with a mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks of stroke and bleeding	I	C
Without a mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated	I	C
Evaluate renal function prior to initiation of direct thrombin or factor Xa inhibitors, and re-evaluate when clinically indicated and at least annually	I	B

Circulation ve J Am Coll Cardiol Kılavuz 2014

With nonvalvular AF and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy	IIa	B
With CHA_2DS_2-VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation	IIa	B
With nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered	IIb	C
With moderate-to-severe CKD and CHA_2DS_2-VASc scores of ≥2, reduced doses of direct thrombin or factor Xa inhibitors may be considered	IIb	C
For PCI,* BMS may be considered to minimize duration of DAPT	IIb	C
Following coronary revascularization in patients with CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants, but without aspirin	IIb	B
Direct thrombin, dabigatran, and factor Xa inhibitor, rivaroxaban, are not recommended with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits	III: No Benefit	C
Direct thrombin inhibitor, dabigatran, should not be used with a mechanical heart valve	III: Harm	B

Nitekim

- 140000 hiç kumadin almamış non-valvüler AF hastası retrospektif olarak inceleniyor.
- CHA_2DS_2-VASc skoru 1 olanlarda inme riski % 0.5.
- Şu hâlde, **oral antikoagülanlardan fayda beklenmez.**
- *Avrupa kılavuzu abartılı.*

Friberg L et al. J Am Coll Cardiol 2015

KBY'de Güvenilir Antikoagulan yok mu?

KBY ve Warfarin

- **Diyalize giren,** 65 yaş üstü, 1600 AF hastası geriye dönük taranıyor.
- Warfarin kullananlarda kanama riski % 44 daha fazla.
- ***İnme riskinde azalma yok.***

Shah M et al. Circulation 2014

KBY ve Warfarin

- **Mİ geçiren** AF'li 24000 hasta.
- Warfarin Mİ ve iskemik inmeyi azaltıyor.
- ***Bu fayda GFR ≤ 15 ml/dk olan hastalarda da aynı.***

Carrero JJ et al. JAMA 2014

Apixaban için enteresan bir tavsiye

- ARISTOTLE çalışmasına kreatinin > 2.5 mg/dL ya da kreatinin klirensi < 25 mL/dk olan hastalar alınmadı.

Farmakokinetik husûsiyyetler değerlendirilerek;

> 80 yaş ya da < 60 kg olan ve diyalizle stabil olan hastalar apixaban 2.5 mg (2x1) alabilir. Diyalize girmeyen son dönem böbrek hastaları apixaban alamaz.

Böbrek ve YOAK

Kılavuz Circulation 2014

Renal Function	Warfarin (238)	Dabigatran† (177)	Rivaroxaban† (178)	Apixaban† (179)
Normal/Mild Impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	20 mg QD with the evening meal (CrCl >50 mL/min)	5.0 or 2.5 mg BID‡
Moderate Impairment	Dose adjusted for INR 2.0–3.0	150 mg BID or 75 mg BID§ (CrCl >30 mL/min)	15 mg QD with the evening meal (CrCl 30–50 mL/min)	5.0 or 2.5 mg BID‡
Severe Impairment	Dose adjusted for INR 2.0–3.0‖	75 mg BID§ (CrCl 15–30 mL/min)	15 mg QD with the evening meal (CrCl 15–30 mL/min)	No recommendation, See section 4.2.2.2.¶
End-Stage CKD Not on Dialysis	Dose adjusted for INR 2.0–3.0‖	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation, See section 4.2.2.2.¶
End-Stage CKD on Dialysis	Dose adjusted for INR 2.0–3.0‖	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation, See section 4.2.2.2.¶#

Böbrek ve YOAK

EHRA Kılavuzu Europace 2013

Table 7 NOACs in renal dysfunction: Approved European labels and dosing in chronic kidney disease

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%	50%[9]	35%
Bio-availability	3–7%	50%	62%[17]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	14%	37%[9]	33%
Approved for CrCl ≥ ...	≥30 ml/min	≥15 ml/min	Not available	≥15 ml/min
Dosing recommendation	CrCl ≥50 ml/min: no adjustment (i.e. 150 mg bid)	Serum creatinine ≥1.5 mg/dl: no adjustment (i.e. 5 mg bid)	Not available	CrCl ≥50 ml/min: no adjustment (i.e. 20 mg qd)
Dosing if CKD	When CrCl 30–49 ml/min, 150 mg bid is possible (SmPC) but 110 mg bid if 'high risk of bleeding' (SmPC) or 'recommended' (GL update)[2] Note: 75 mg bid approved in US only:[b] • if CrCl 15–30 ml/min • if CrCl 30–49 ml/min and other orange factor Table 5 (e.g. verapamil)	CrCl 15–29 ml/min: 2.5 mg bid Serum creatinine ≥1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg,[SmPC] or with other 'yellow' factor (Table 5): 2.5 mg bid	Not available	15 mg qd when CrCl 15–49 ml/min
Not recommended if	CrCl <30 ml/min	CrCl <15 ml/min	Not available	CrCl <15 ml/min

Orange, reduce dose (from 150 mg BID to 100 mg BID for dabigratran).
Yellow, consider dose reduction if another 'yellow' factor is present (from 20 mg to 15 mg QD for rivaroxaban; from 5 mg BID to 2.5 mg BID for apixaban).
Hatching, no data available yet.
[a]No EMA approval yet. Needs update after finalisation of SmPC.
[b]No EMA indication. FDA recommendation based on pharmacokinetics. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.
CKD, chronic kidney disease; CrCl, creatinine clearance; bid, twice daily; qd, once daily; SmPC, summary of product characteristics.

YOAK Alanlarda Böbrek Fonksiyonlarını Ne Sıklıkla Ta'kîp Edelim?

- Kre klirensi ≥ 60 mL/dk olanlarda yılda bir.
- Kre klirensi ≈ 30-60 mL/dk olanlarda 6 ayda bir.
- Kre klirensi ≤ 30 mL/dk olanlarda 3 ayda bir.

EHRA Kılavuz Europace 2013

RELY

- 18.100 hasta
- Warfarin, dabigatran 110 mg (2x1) ve 150 mg (2x1)
- Ort. $CHADS_2$ skoru ≈ 2.1
- TTR nisbeti = % 64 (warfarin alanlarda)
- Kre klirensi ≥ 30 mL/dk (dabigatran dozu klirense bağlı değil)
- 2 yıl ta'kîp

Warfarine göre genel sonuçlar

Dabigatran 110mg

- Non-inferior
- Hemorajik inme daha az
- Majör kanama daha az
- İKK ve hayâtı tehdîd edici kanama daha az
- GİS kanaması benzer
- Dispeptik şikâyetler daha fazla
- Sekonder korunma sonuçları primer korunma sonuçlarıyla benzer

Dabigatran 150 mg

- Üstün
- Hemorajik inme daha az
- Majör kanama aynı
- İKK ve hayâtı tehdîd edici kanama daha az
- GİS kanaması daha fazla
- Dispeptik şikâyetler daha fazla
- Sekonder korunma sonuçları primer korunma sonuçlarıyla benzer

Warfarine göre alt grup

Dabigatran 110mg

- < 75 yaş için İKK ve EKK kanama daha az
- > 75 yaş için İKK daha az EKK benzer
- Sonuçlar paroksismal, persistan ve permanent AF için aynı
- Her $CHADS_2$ skoru (0, 1, 2 ve daha fazla) için sonuçlar aynı
- KV yapılan hastalarda (1900 hasta) inme riski ve LAA'da trombüs görünme nisbeti aynı
- Mİ biraz fazla (% 0.8 x % 0.6; p=0.09)

Dabigatran 150 mg

- < 75 yaş için İKK ve EKK kanama daha az
- > 75 yaş için İKK daha az EKK benzer
- Sonuçlar paroksismal, persistan ve permanent AF için aynı
- Her $CHADS_2$ skoru (0, 1, 2 ve daha fazla) için sonuçlar aynı
- KV yapılan hastalarda (1900 hasta) inme riski ve LAA'da trombüs görünme nisbeti aynı
- Mİ biraz fazla (% 0.8 x % 0.6; p=0.09)

Dabigatran ve Mİ mes'elesi

- Bir meta-analizde dabigatran'ın warfarine göre Mİ sıklığını arttırdığı görüldü[1].
- ≈ 14000 hastalık bir "gerçek dünyâ" analizinde dabigatran warfarine göre Mİ sıklığını azalttı (Danimarka tecrübesi)[2].
- EHRA'ya göre Mİ sonrası YOAK başlanması gerekirse FXa inh. tercîh edilsin[3].

[1]Uchino K et al. Arch Intern Med 2012

[2]Larsen TB et al. J Am Coll Cardiol 2013

[3]EHRA kılavuz Europace 2013

Dabigatran ve Pazar Sonrası Yeni Veriler

- 135000 AF hastası dabigatran ya da kumadin kullanıyor.
- İskemik inme, beyin kanaması ve **ölüm** dabigatran kolunda daha az.
- **Mİ oranları benzer.**
- Majör ve GİS kanama dabigatran kolunda daha fazla.
- **Dabigatran 2x75 mg** kullananlarda beyin kanaması daha az, **diğer sonlanma noktaları benzer.**

Graham DJ et al. Circulatin 2014

ROCKET-AF

- 14200 hasta, ort $CHADS_2$ skoru ≈ 3.47
- Warfarin, Rivaroxaban 20 (tek doz) ve 15 mg (30 ml/dk < Kr klirensi < 50 ml/dk) (tek doz, akşam yemeğiyle birlikte)
- TTR nisbeti = % 55
- Rivaroxaban warfarin'e non-inferior
- Major kanama nisbetleri benzer
- Fatal ve İKK daha az
- GİS kanaması daha fazla
- KV sonrası inme ve sistemik emboli nisbetleri benzer (285 hasta)

Kılavuz Circulation 2014

Sekonder İnmeden Korunma Kılavuzu Stroke 2014

EHRA Kılavuz Europace 2013

ARISTOTLE

- 18200 hasta
- Warfarin, apixaban 5 mg 2x1, apixaban 2.5 mg 2x1 (yaş ≥ 80, ağırlık ≤ 60 kg, kreatinin ≥ 1.5 mg/mL; üçünden herhangi ikisi varsa)
- Ort $CHADS_2$ skoru ≈ 2.1
- TTR nisbeti = % 62
- 1.8 yıl ta'kîp

Kılavuz Circulation 2014

Warfarine göre apixaban

- Hemorajik ve iskemik inmeyi
- Sistemik emboliyi
- Majör kanamaları
- İKK'yı azalttı.
- GİS kanamaları benzerdi.

- Sonuçlar AF tipine, $CHADS_2$ ve CHA_2DS_2-VASc skor indeksine göre değişmiyordu.
- KV sonrası her iki tedâvîde de tromboembolik hâdise görülmedi (577 hasta).

Sekonder İnmeden Korunma Kılavuzu

Stroke 2014

VKA therapy *(Class I; Level of Evidence A)*, apixaban *(Class I; Level of Evidence A)*, and dabigatran *(Class I; Level of Evidence B)* are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.

Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF *(Class IIa; Level of Evidence B)*.

YOAK'lar ile yapılan üç çalışma

Dâhil Edilenler

- Çalışma müddetince operasyon ihtiyâcı olmayacağı düşünülen aort darlığı ve yetersizliği hastaları

Hâriç Tutulanlar

- Mekanik kapak hastaları
- Ciddî Mitral darlığı
- Gebeler
- Emzirenler
- Ciddî HT (> 180 mmHg ve > 100 mmHg)
- Biyoprotez kapak hastaları
- Yeni inme geçirenler (7-14 gün içinde)
- Ciddî K.C hastalığı olanlar

YOAK Alan Hastalarda Antikoagulan Te'sîri Nasıl Ölçelim?

- Ciddî kanama
- Trombotik hâdise geçirilmesi
- Âcil cerrâhî gerekliliği
- Yüksek doz şüphesi
- Böbrek veyâ KC yetmezliği
- YOAK'ların kan seviyelerini arttıran ilaç kullanılması

EHRA Kılavuz
Europace 2013

YOAK'ların antikoagulan te'sîrini ölçmek gerekir!

Ölçerken Nelere Dikkat Edelim?

- İlacın alındığı sa'at ile testin yapıldığı sa'at arasında geçen zamân çok mühim!!!

İlaç alındıktan 3 sa'at sonra yapılan ölçmeler maksimum antikoagulan te'sîr gösterirken, 12-24 sa'at sonra yapılan ölçmeler düşük çıkacaktır!!

EHRA Kılavuz Europace 2013

Dabigatran (aPTT, dTT, ECT)

- *Günde iki kez 150 mg alan bir hastada*

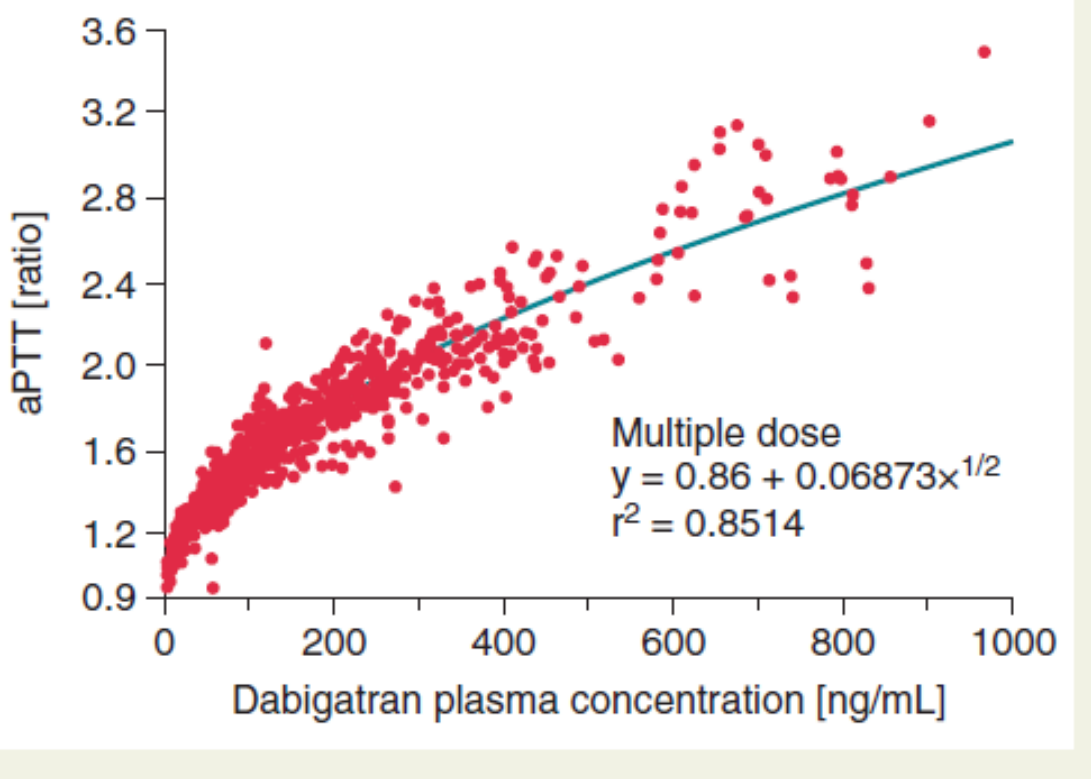
2-3 sa'at sonra ölçülen aPTT, üst limitin 2 katı

12 sa'at sonra ölçülen aPTT üst limitin 1.5 katı olması beklenir.

12 sa'at sonra ölçülen aPTT'nin üst limitin > 2 katı olması yüksek kanama riskini gösterir.

EHRA Kılavuz Europace 2013

Dabigatran dozu ile aPTT münâsebeti



Dabigatran (aPTT, dTT, ECT)

- *dTT, kanda ölçülebilir dabigatran valığında bile normalin üstünde çıkar.*
- *Normal dTT kanda ölçülebilir dabigatran olmadığını gösterir.*
- > 65 s olması kanama riskini gösterir.
- ECT > üst limitin 3 katı olması artmış kanama riskini gösterir.

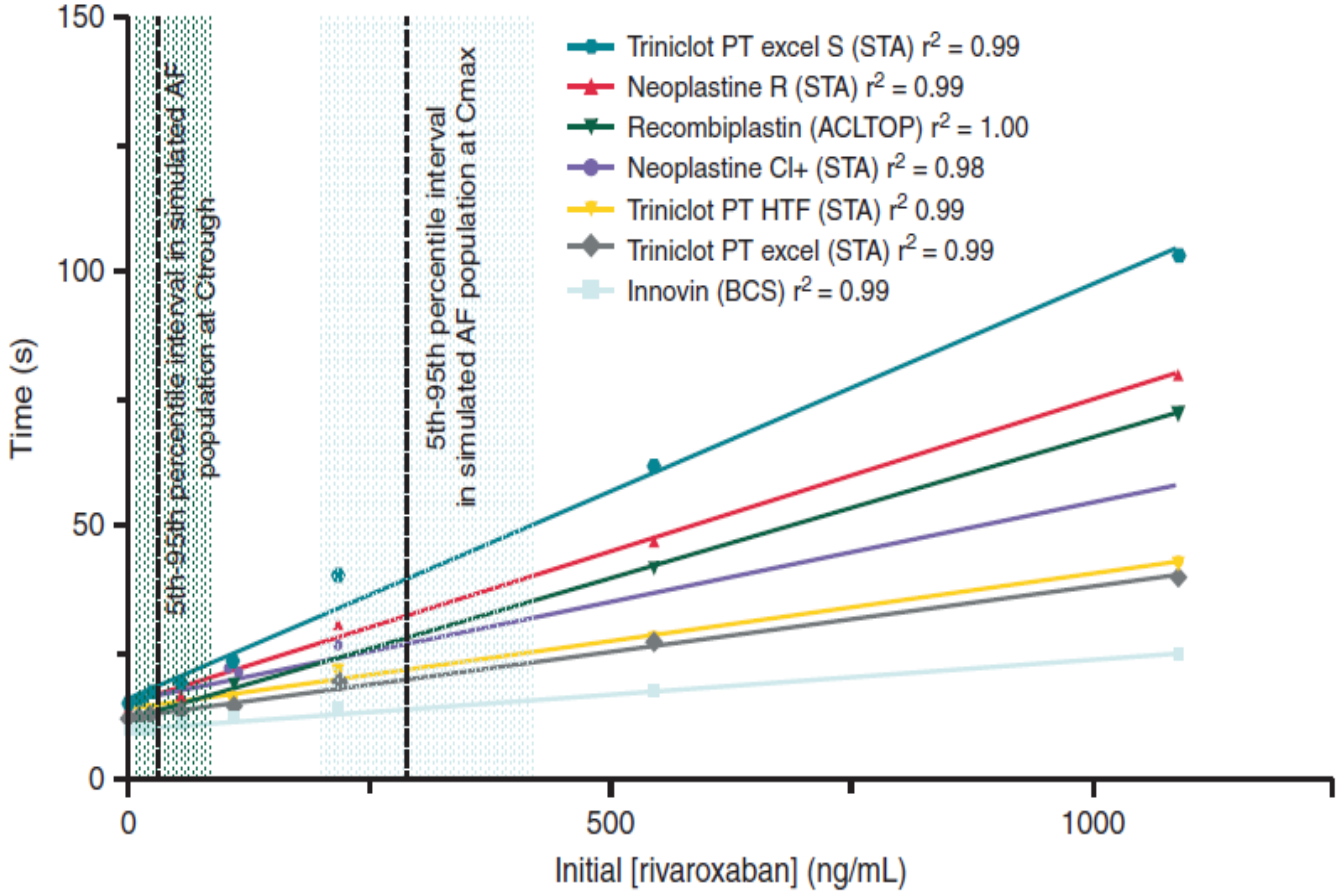
EHRA Kılavuz Europace 2013

Rivaroxaban PT

- **Faktör Xa inh.'lerinin te'sîrini ölçmek için INR kullanılamaz!**
- Rivaroxaban için PT fikir verebilir, fakat tavsiye edilebilecek değer aralıkları yok.
- PT ölçmede kullanılan tromboplastin türü değerleri etkiliyor.

EHRA Kılavuz Europace 2013

Rivaroxaban PT



YOAK Kullananlarda Hematoloji Laboratuarı

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12–24 h after ingestion	12–24 h after ingestion	12–24 h after ingestion[9]	16–24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk[5,9]	Prolonged: may indicate excess bleeding risk but local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	At trough: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk[9]	Cannot be used
dTT	At trough: >200 ng/ml or >65 s: excess bleeding risk	Cannot be used	Cannot be used[10]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative;[10] no data on threshold values for bleeding or thrombosis	Quantitative; no data on threshold values for bleeding or thrombosis
ECT	At trough: ≥3 x ULN: excess bleeding risk	Not affected	Not affected	Not affected

YOAK ve Diğer İlaçlar

	Via	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (reduce dose by 50%)[a]	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[24]	+40%[SmPC]	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%)[a]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[SmPC]	No data yet	Up to +160%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	No data yet	+30–54%[26,27]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	−66%[34]	−54%[SmPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%[22–24]	No data yet	No effect	No effect[21,25]
Other factors					
Age ≥80 years	Increased plasma level	No data yet			
Age ≥75 years	Increased plasma level	No data yet			
Weight ≤60 kg	Increased plasma level				
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Antikoagulan Rejimlerde İlaç Değiştirmek

- Warfarin → YOAK
- Parenteral → YOAK
- YOAK → Warfarin
- YOAK → Parenteral
- YOAK → YOAK

Warfarin'den YOAK'ya

- INR < 2 olur olmaz başlanır.
- INR = 2-2.5 arasında olduğu zamân da aynı gün ya da ertesi gün başlanır.
- INR > 2.5 olduğunda YOAK'ya geçerken karışıklıklar olabilir (INR uzaması YOAK'dan da kaynaklanabilir).

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Parenteral'den YOAK'ya

- Heparin kesilir kesilmez başlanabilir. (Böbrek hastalığında dikkat! Heparin eliminasyonu gecikir).
- Enoxaparin'in gün içindeki ikinci doz vakti geldiğinde başlanabilir.

EHRA Kılavuz Europace 2013

YOAK'dan Warfarin'e

- **Parenteral'den warfarin'e geçer gibi.**
- INR terapötik seviyeye gelinceye kadar iki ilaç birlikte kullanılır.
- *FXa inh ile örtüşme fazına dikkat!*
- INR, YOAK'nın sonraki dozu verilmeden hemen önce ve son dozdan 24 sa'at sonra ölçülmelidir (sâdece warfarin'in uzattığı düşünülen INR).

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YOAK'dan Warfarin'e Geçerken Dikkat!

- ROCKET-AF ve ARISTOTLE çalışmalarında, çalışma bittiğinde YOAK'dan warfarine geçilenlerde, warfarine devâm edilenlere göre hem kanama hem de inmede artış görülüyor.

Granger CB et al. Am Heart J 2015

YOAK'dan Parenteral'e

YOAK'dan YOAK'a

- Heparin ya da enoxaparin, YOAK verme vakti geldiğinde başlanabilir.
- YOAK'dan YOAK'a geçerken de aynı kâide geçerlidir.
- **Hepsi için böbrek fonksiyonlarının normal olduğundan emîn ol!**

EHRA Kılavuz Europace 2013

Doz Hatâları

- **Dabigatran ve apixaban**: Hasta ilacını almayı unutursa ve 6 sa'atten fazla süre geçmemişse unuttuğu dozu alabilir. Eğer daha uzun süre geçmişse doz atlanır. Fazladan ilaç almışsa (2 doz) bir sonraki doz atlanır.
- **Rivaroxaban:** 12 sa'atten fazla süre geçmemişse unuttuğu dozu alabilir. Daha uzun süre geçmişse doz atlanır. Fazladan ilaç almışsa doz atlanmaz.

EHRA Kılavuz Europace 2013

Kanama Şüphesi veyâ Overdose

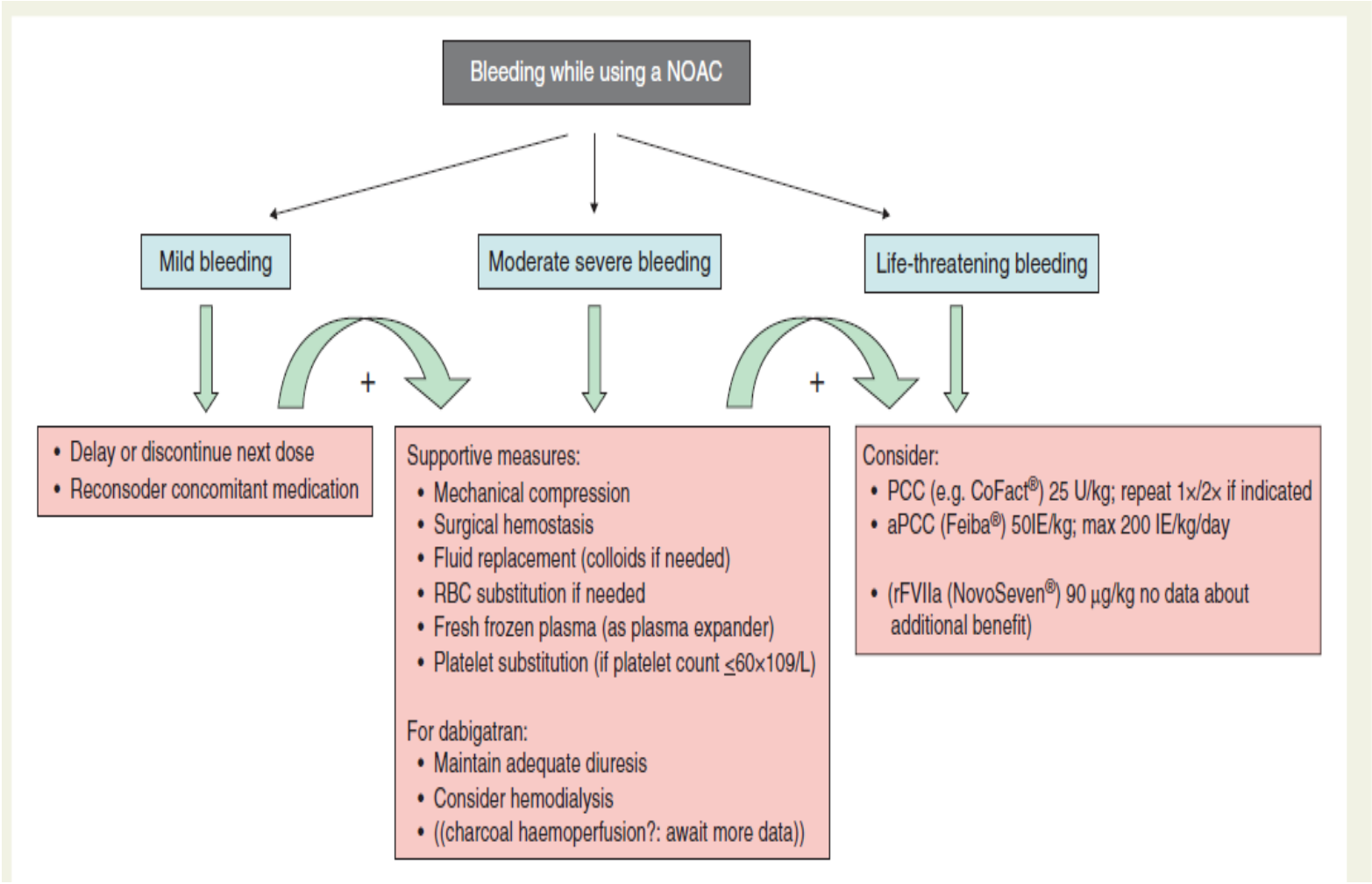
- YOAK'ların bir seferde aşırı miktârda alınması hâlinde emilmeyi azaltmak için charcoal (30-50 g) verilebilir.
- Doz aşımı ve kanamalarda en iyi (hattâ tek) antidot zamân! (bekle-gör)
- **YOAK'larla yapılan çalışmalarda İKK ve fatal kanamalar warfarine göre daha iyi seyirli.**

EHRA Kılavuz Europace 2013

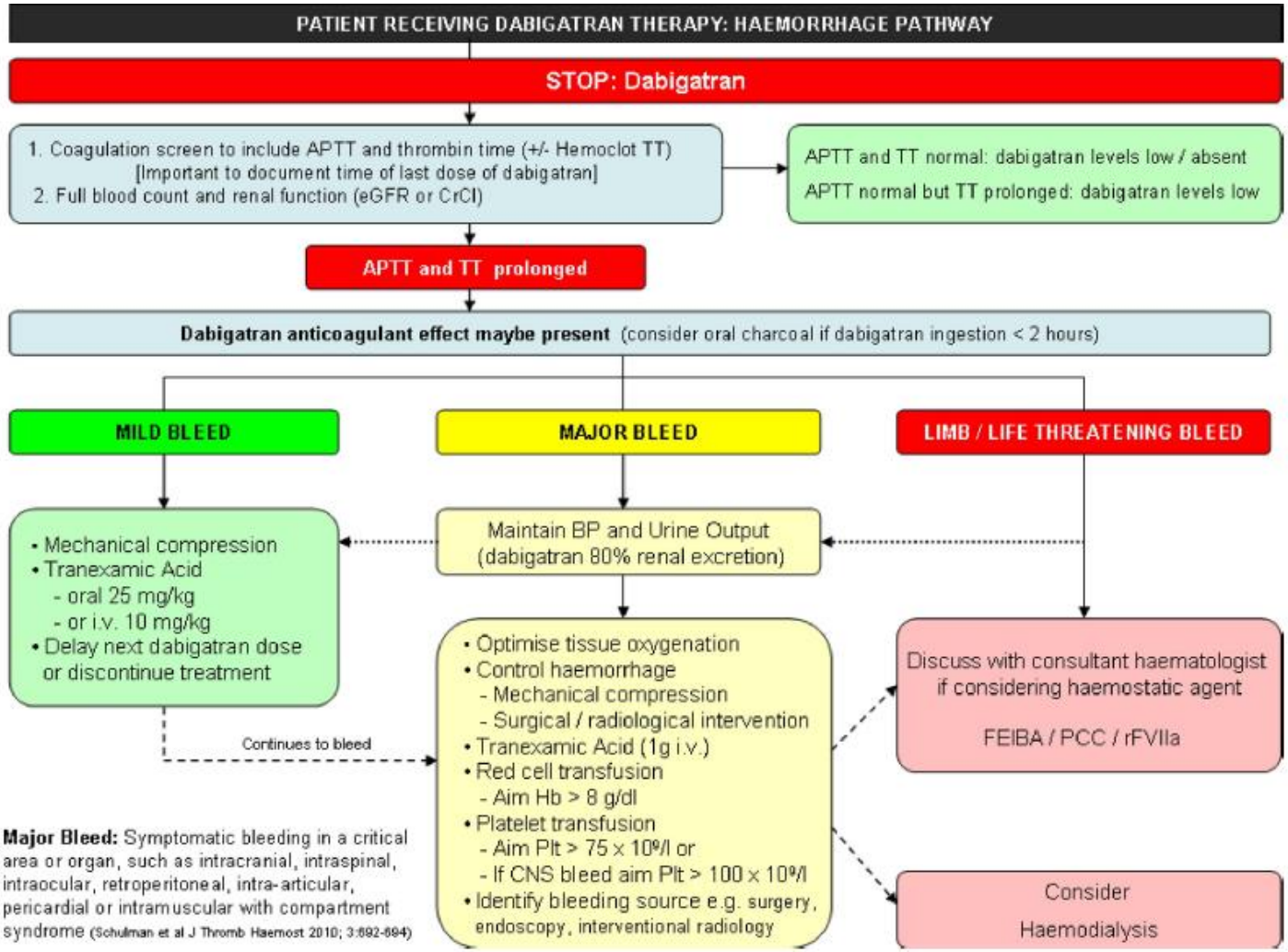
Kanama (hayâtı tehdîd eden veyâ etmeyen)

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening bleeding	Inquire last intake + dosing regimen Estimate normalization of haemostasis: Normal renal function: 12–24 h CrCl 50–80 ml/min: 24–36 h CrCl 30–50 ml/min: 36–48 h CrCl <30 ml/min: ≥48 h Maintain diuresis Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: -65% after 4 h)[48] Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization of haemostasis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit + expensive (only animal evidence)	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max. 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit + expensive (only animal evidence)

YOAK ve Kanama



YOAK ve Kanama



Alikhan R et al. Emerg Med J 2014

AF ve KAH

- Warfarin alan hastalarda heparin yapmaksızın PTCA yapılabilir.
- YOAK, PTCA yapılan hastalarda, çalışma protokolü gereği kesildiği için delil yok.
- Fondaparinux tecrübesini de unutmamak lâzım.

EHRA Kılavuz Europace 2013

YOAK Tedâvîsi Altında STYMİ Primer PTCA

- İlacı kes.
- Primer PTCA'yı (radiyal) fibrinolizis'e tercîh et.
- YOAK'un son alınma vaktine bakmadan parenteral antikoagulan ver.
- Düşük kanama riskinden dolayı bivalirudin tercîh et ve müdâheleden sonra hemen kes.
- Glp IIb/IIIa inh kullanma!

EHRA Kılavuz Europace 2013

YOAK Tedâvîsi Altında STYMİ Fibrinolitik Tedâvî

- dTT, ECT, aPTT (dabigatran için) ya da PT (FXa inh için) normalin üst limitlerini aşmıyorsa düşünülebilir.
- İlâve heparin v.b., YOAK te'sîri geçmeden evvel (ilacı son aldığı zamândan en az 12 sa'at geçene kadar) aslâ verilmez!

EHRA Kılavuz Europace 2013

YOAK Tedâvîsi Altında non-STYMİ

- İlacı kes.
- En az 12 sa'at geçtikten sonra fondaparinux (tercîhen), heparin veyâ enoxaparin başlanabilir.
- PTCA yapılacaksa BMS'ler düşünülebilir, hattâ balon ile iktifâ edilebilir (dual ve triple tedâvî süresini azaltmak için).

EHRA Kılavuz Europace 2013

AKS Sonrası

- Parenteral tedâvî bittikten sonra YOAK başlanabilir.
- Hasta en az 1 antiplatelet alacağı için düşük dozlar tercîh edilmelidir.
- HAS-BLED'e muhakkak bak!

EHRA Kılavuz Europace 2013

Planlı Cerrâhî Müdâhele ve YOAK

- **Operasyon öncesi ve sonrası köprülemeye gerek yok.** (kısa yarı ömür ve belirlenebilir antikoagulan te'sîr).
- Kanama riski düşük müdâhelelerde YOAK alındıktan 12-24 sa'at sonra **(kesilmeden)** operasyon yapılabilir ve **6 sa'at sonra** tekrâr başlanabilir.
- Dental prosedürler için tranexamik asit (%5) ile birkaç kez ağız çalkalanabilir.

EHRA Kılavuz Europace 2013

Cerrâhî Risk Sınıflaması

Interventions not necessarily requiring discontinuation of anticoagulation

- Dental interventions
  - Extraction of 1 to 3 teeth
  - Paradontal surgery
  - Incision of abscess
  - Implant positioning
- Ophthalmology
  - Cataract or glaucoma intervention
- Endoscopy without surgery
- Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)

Interventions with low bleeding risk

- Endoscopy with biopsy
- Prostate or bladder biopsy
- Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
- Angiography
- Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)

Interventions with high bleeding risk

- Complex left-sided ablation (pulmonary vein isolation; VT ablation)
- Spinal or epidural anaesthesia; lumbar diagnostic puncture
- Thoracic surgery
- Abdominal surgery
- Major orthopedic surgery
- Liver biopsy
- Transurethral prostate resection
- Kidney biopsy

ACC/AHA Kılavuzundan farklı

EHRA Kılavuz Europace 2013

Elektif Cerrâhî Öncesi Son YOAK Dozunu Ne Zamân Verelim?

	Dabigatran		Apixaban		Edoxaban[a]		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	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

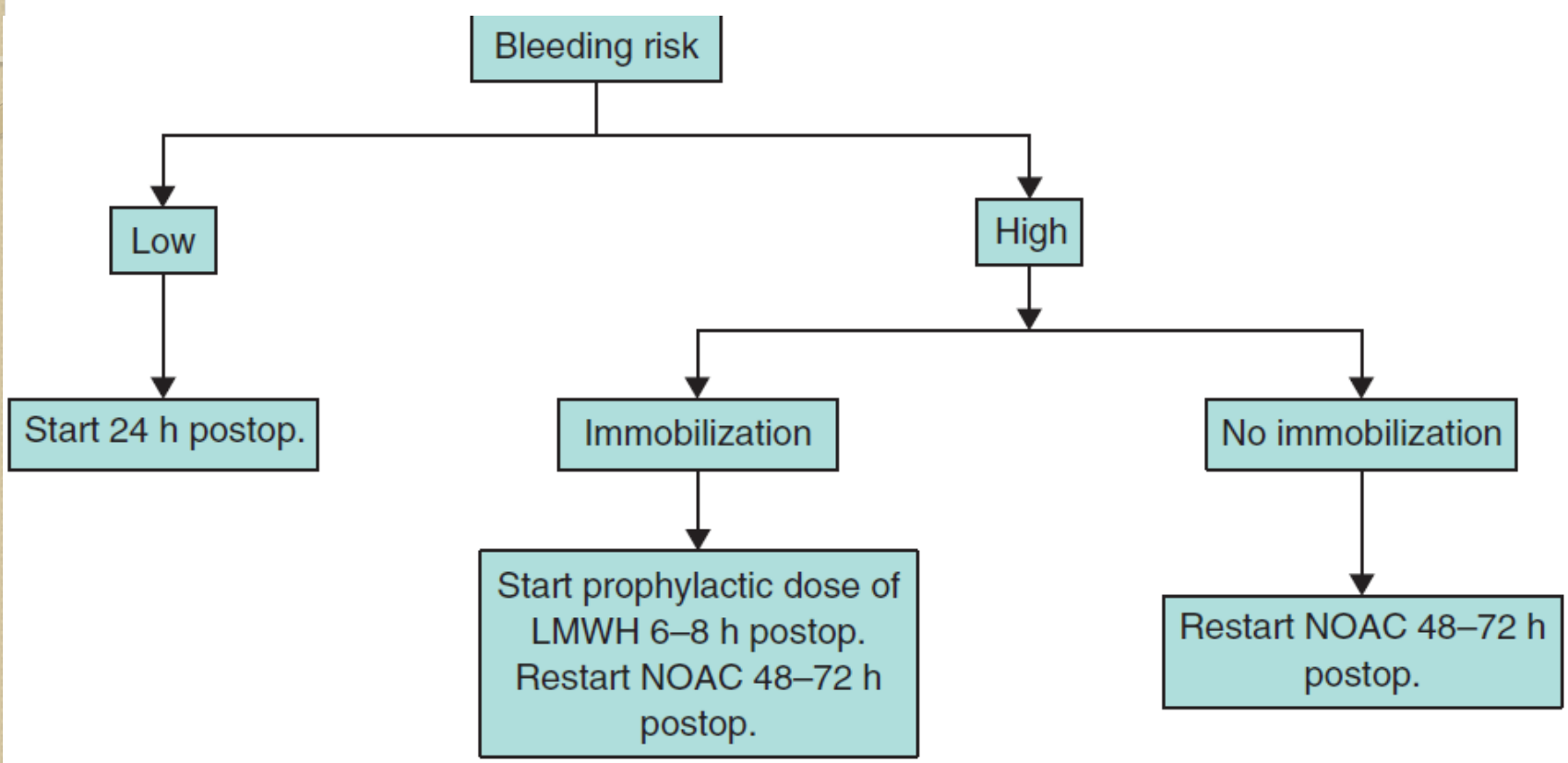
EHRA Kılavuz Europace 2013

Operasyon Sonrası Ne Zamân Başlayalım?

- Hemostazın sağlandığı müdâhelelerde (atravmatik spinal-epidural anestezi dâhil) 6-8 sa'at sonra başlanabilir.
- İmmobilizasyon gereken operasyonlarda cerrâhîden 6-8 sa'at sonra koruma dozunda LMWH başlanabilir.
- İnvazif prosedürlerden 48-72 sa'at sonra YOAK başlanabilir.

EHRA Kılavuz Europace 2013

Operasyon Sonrası Ne Zamân Başlayalım?



Lai A et al. BJS 2014

Dikkat!

- **YOAK'ların emilmesini bozan, post op. ileus geliştiğinde ya da gastrik rezeksiyon yapıldığında terapötik dozda DMWH kullan!!!**

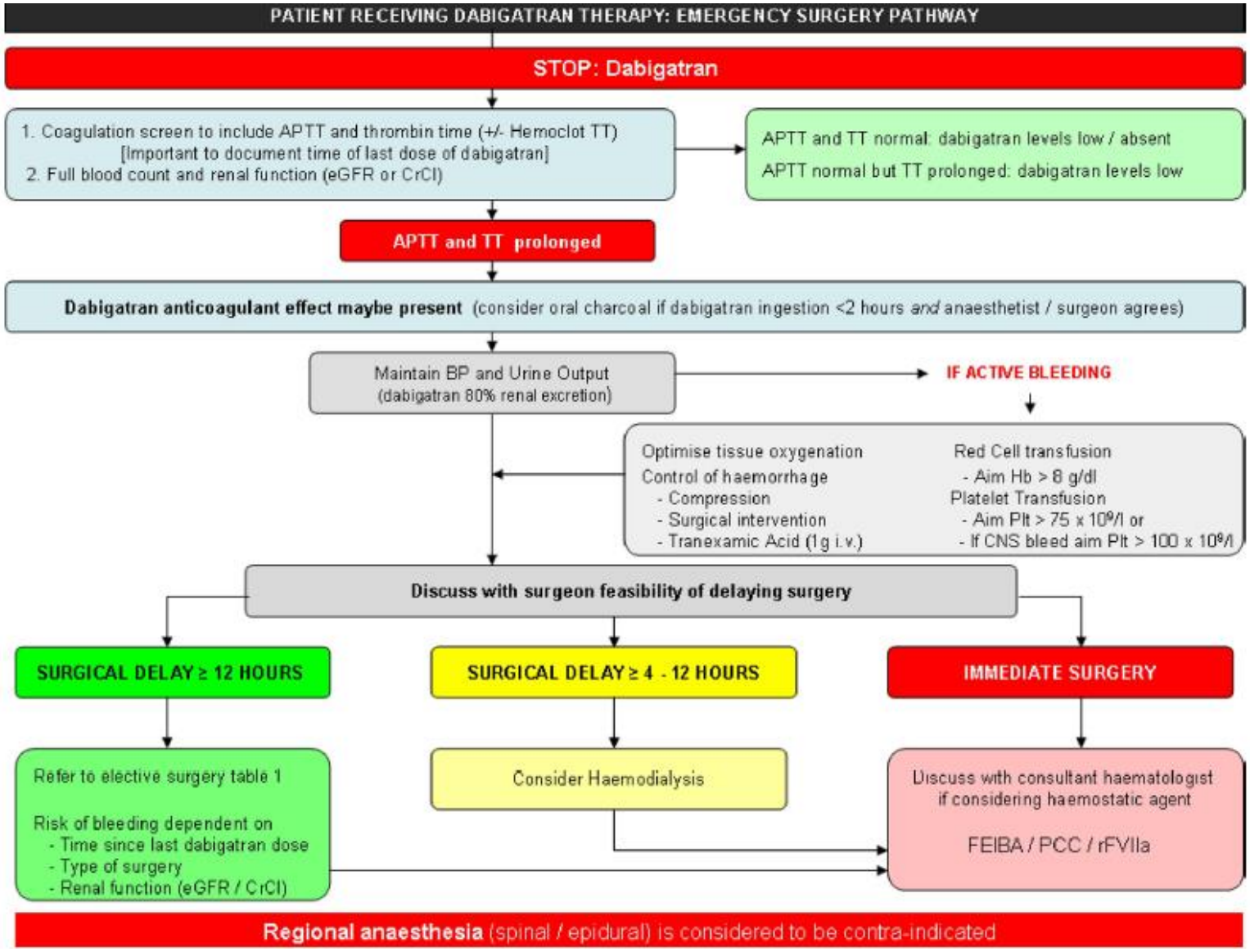
Lai A et al. BJS 2014

YOAK Altında Âcil Cerrâhî

- En az 12, mümkünse 24 sa'at geciktirilmelidir (YOAK'ların te'sîri bitene kadar).
- **Rely(alt grup):** Âcil cerrâhî gereken çalışma hastalarında **warfarine göre dabigatran'la daha az kanama meyli.**
- Kanama testlerine (aPTT, dTT, PT) göre de karâr verilebilir, fakat rutin olarak kullanılmamalıdır (veri az).

EHRA Kılavuz Europace 2013

Dabigatran Altında Âcil Cerrâhî



Alikhan R et al. Emerg Med J 2014

Antikoagulan Altında İskemik İnme

- Antikoagulan altında iskemik inme geçirenlerde **fibrinolitik tedâvî yapılamaz!**
- Son dozun alınma vakti bilinemeyenlerde uzamış aPTT (dabigatran için) ve uzamış PT (FXa inh için**), fibrinolitik tedâvî için kontraendikasyondur.**
- Mekanik rekanalizasyon düşünülebilir.

EHRA Kılavuz Europace 2013

Antikoagulan Altında İskemik İnme

Tedâvî: 1-3-6-12 gün kâidesi

- GİA'dan 1 gün sonra (warfarin, YOAK)
- Küçük infarkt'tan 3 gün sonra
- Orta büyüklükteki infarkt'tan 6 gün sonra (warfarin)
- Büyük infarkt'tan 2-3 hafta sonra (warfarin)

antikoagulan başlanabilir.

EHRA Kılavuz Europace 2013

İskemik İnme:Tedâvî

For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms *(Class IIa; Level of Evidence B).* (New recommendation)

In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days *(Class IIa; Level of Evidence B).* (New recommendation)

Sekonder İnmeden Korunma Kılavuzu Stroke 2014

Sekonder İnmeden Korunma Kılavuzu

Stroke 2014

The combination of oral anticoagulation (ie, warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement *(Class IIb; Level of Evidence C)*.

Terapötik antikoagulasyona rağmen GİA veyâ inme geçiren AF hastalarında warfarin dozunu arttırmanın ilâve fayda sağladığına dâir delil yok.

Hemorajik İnme

1. The decision to restart antithrombotic therapy after ICH related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH, and the overall status of the patient and must therefore be individualized to each patient. For patients with a comparatively lower risk of cerebral infarction (eg, AF without prior ischemic stroke) and a higher risk of recurrent ICH (eg, elderly patients with lobar ICH or presumed amyloid angiopathy) or with very poor overall neurological function, an antiplatelet agent may be considered for prevention of ischemic stroke *(Class IIb; Level of Evidence B)*.
2. For patients who require resumption or initiation of anticoagulation after an acute ICH, subarachnoid hemorrhage, or subdural hematoma, the optimal timing is uncertain. For most patients, however, it might be reasonable to wait ≥1 week *(Class IIb; Level of Evidence B)*.
3. For patients with hemorrhagic cerebral infarction, continuation of anticoagulation may be considered, depending on the specific clinical scenario and underlying indication for anticoagulant therapy (*Class IIb; Level of Evidence C*).

Sekonder İnmeden Korunma Kılavuzu Stroke 2014

Hemorajik İnme: Yeni Veri

- 1176 hasta, retrospektif analiz.
- Kumadine bağlı beyin kanaması.
- Medyan İNR: 2.77
- Dört sa'at içinde İNR 1.3'ün altına ve sistolik kan basıncı 160 mm Hg'nin altına düşürülenlerde hematom büyümesi ve hastahâne içi mortalite daha düşük.
- Medyan 31gün içinde kumadin tekrâr başlananlarda başlanmayanlara göre iskemik inme ve ölüm daha az, kanama nisbetleri benzer.

Kurumatsu JB et al. JAMA 2015

SON SÖZ!

- Atriyal fibrilasyonda inmeye karşı korumaya dâir, ülkemize âit verilerin tesbît edilip kılavuz yazılmasının zamânı gelmiş, hattâ geçmektedir.