6. AF Zirvesi Bahar Toplantısı
7 - 8 Nisan 2017 / Cornelia Hotel, Antalya

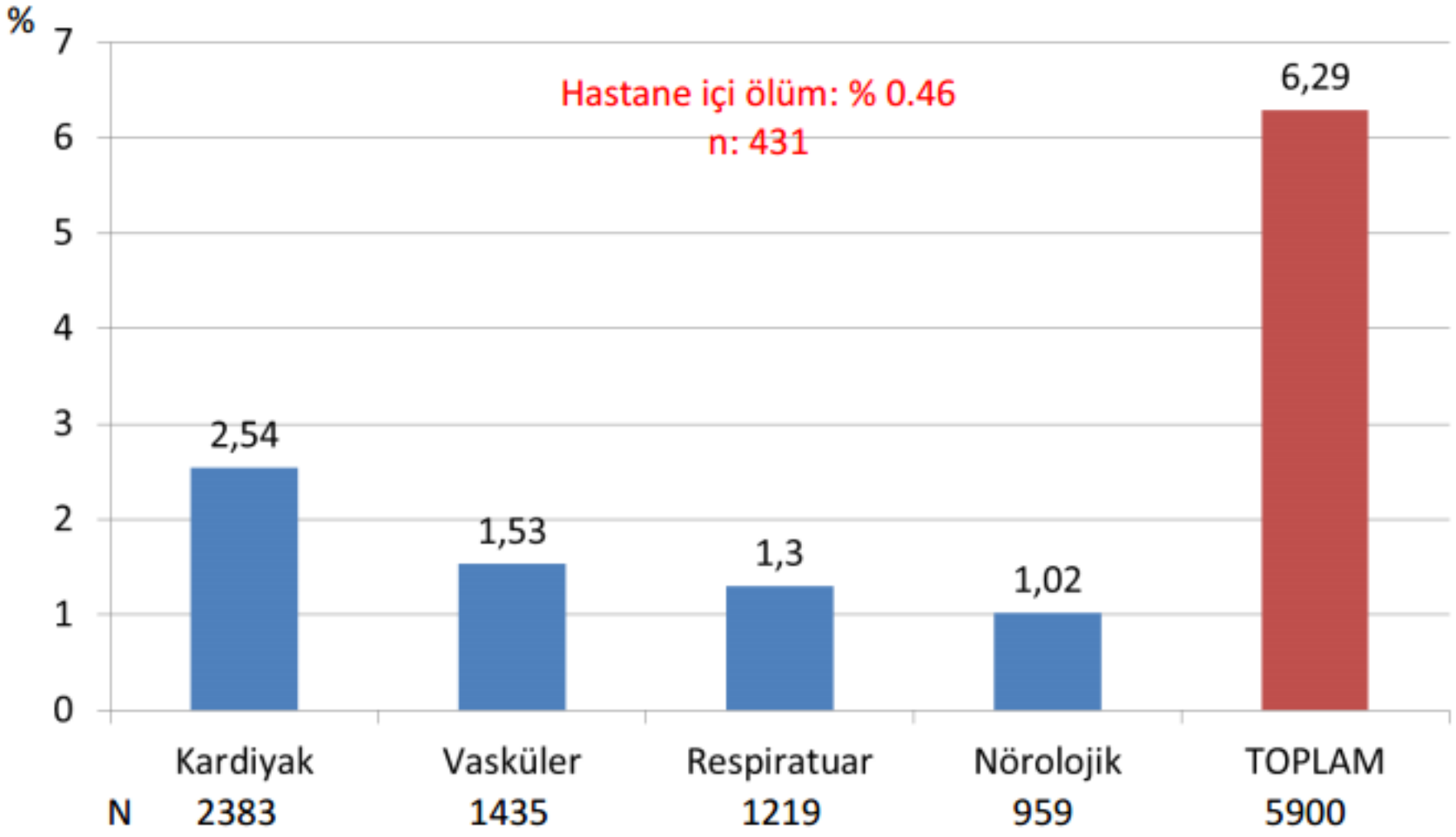
AF ABLASYONUNDA ANTİKOAGÜLASYON-PRATİK YAKLAŞIM OLARAK NE YAPALIM?

Prof. Dr. Murat SUCU
Gaziantep Üniversitesi Tıp Fakültesi
Kardiyoloji AD

AF Ablasyonu Komplikasyonları

ABD: 2000-2010

İşlem Sayısı: 93.801



Circulation 2013

AF Ablasyonu Sırasında Tromboembolizm Nedenleri

- Atriyal “stunning”
- Çok sayıda intraatriyal kateter ve sheatler
- Endoteliyal bozulma,fibrozis ,skar
- Koagulasyon faktörlerinin aktivasyonu

Pre-Postablasyon Tromboemboli

- CHADS2 skoru ≥ 2
- İnme öyküsü
- Persistan AF
- Sol Atriyal genişliği
- Sol Atriyal Apendiks dilatasyonu

% 0.5–2.8

Preablasyon Önerileri

- AF süresi 48 saatten uzun ise
- CHADS2 score ≥1
- CHADS2 score 0 fakat persistent AF var ise

3 hafta öncesinden warfarin (INR 2–3) başlanılmalıdır.

İşlem öncesi antikoagülasyon

- İşlem öncesi antikoagülasyon:
  - AF süresi >48 saat veya bilinmiyorsa en az 3 hafta terapötik seviyede antikoagülasyon veya (sınıf I)
  - İşlem öncesi en az 3 hafta antikoagülasyon söz konusu değilse TEE ile trombüsün dışlanması (sınıf I)
- İşlem öncesi TEE
  - 48 saattten uzun süreli veya süresi bilinmeyen AF'de işlemden önce en az 3 hafta terapötik seviyede antikoagülasyon yapılmamışsa (sınıf I)
  - İşlem sırasında sinüs ritmindeki hastalarda veya AF süresi 48 saatten daha kısa olanlarda TEE düşünülebilir (sınıf IIa)

İşlem öncesi antikoagülasyon-II

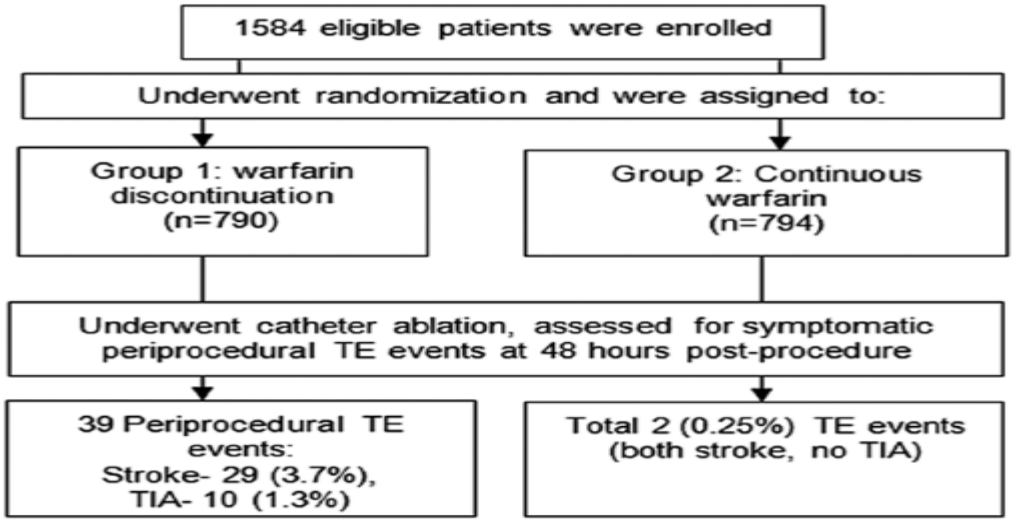
- Sol atriyumda trombüs varlığı kateter ablasyonu için kontrendikasyondur (sınıf III)
- Warfarinin işlem öncesi kesilip heparine geçilmesi, işlem sırası ve sonrasında heparin kullanılması (giriş yeri kanamasında artış !)
- İşlemin terapötik seviyede kullanılan warfarin altında yapılması (ACC/AHA/HRS 2014)
- Yeni OAK kullananlarda işlem öncesi dabigatran ve apixaban'ın 2 doz, rivaroxabanın 1 doz kesilerek yapılması
- İşlemin yeni OAK altında yapılması

Periprocedural Stroke and Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation With Different Anticoagulation Management

Results From the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) Randomized Trial

Luigi Di Biase, MD, PhD; J. David Burkhardt, MD; Pasquale Santangeli, MD; Prasant Mohanty, MPH, MBBS; Javier E. Sanchez, MD; Rodney Horton, MD; G. Joseph Gallinghouse, MD; Sakis Themistoclakis, MD; Antonio Rossillo, MD; Dhanunjaya Lakkireddy, MD; Madhu Reddy, MD; Steven Hao, MD; Richard Hongo, MD; Salwa Beheiry, RN, Jason Zagrodzky, MD; Bai Rong, MD; Sanghamitra Mohanty, MD; Claude S. Elayi, MD; Giovanni Forleo, MD; Gemma Pelargonio, MD; Maria Lucia Narducci, MD; Antonio Dello Russo, MD; Michela Casella, MD; Gaetano Fassini, MD; Claudio Tondo, MD; Robert A. Schweikert, MD; Andrea Natale, MD

Methods and Results—This was a prospective, open-label, randomized, parallel-group, multicenter study assessing the role of continuous warfarin therapy in preventing periprocedural thromboembolic and hemorrhagic events after radiofrequency catheter ablation. Patients with $CHADS_2$ score ≥1 were included. Patients were randomly assigned in a 1:1 ratio to the off-warfarin or on-warfarin arm. The incidence of thromboembolic events in the 48 hours after ablation was the primary end point of the study. The study enrolled 1584 patients: 790 assigned to discontinue warfarin (group 1) and 794 assigned to continuous warfarin (group 2). No statistical difference in baseline characteristics was observed. There were 39 thromboembolic events (3.7% strokes [n=29] and 1.3% transient ischemic attacks [n=10]) in group 1: two events (0.87%) in patients with paroxysmal AF, 4 (2.3%) in patients with persistent AF, and 33 (8.5%) in patients with long-standing persistent AF. Only 2 strokes (0.25%) in patients with long-standing persistent AF were observed in group 2 (P<0.001). Warfarin discontinuation emerged as a strong predictor of periprocedural thromboembolism (odds ratio, 13; 95% confidence interval, 3.1–55.6; P<0.001).



Feasibility and Safety of Uninterrupted Dabigatran Therapy in Patients Undergoing Ablation for Atrial Fibrillation

Tomoyuki Nagao[1], Yasuya Inden[1], Masayuki Shimano[1], Masaya Fujita[1], Satoshi Yanagisawa[1], Hiroyuki Kato[1], Shinji Ishikawa[1], Aya Miyoshi[1], Satoshi Okumura[1], Shiou Ohguchi[1], Toshihiko Yamamoto[1], Naoki Yoshida[1,2], Makoto Hirai[3] and Toyoaki Murohara[1]

Table 3. Complications.

	Dabigatran n=173	Warfarin n=190	p value
Total bleeding complications	12 (7)	14(7)	0.89
Major bleeding complications			
Cardiac tamponade	2 (1)	2 (1)	0.93
Vascular complication	0 (0)	0 (0)	N/A
Minor bleeding complications			
Groin hematoma	8 (5)	9 (5)	0.96
Pericardial effusion without tamponade	1 (1)	3 (2)	0.36
Thromboembolic complications			
Stroke or TIA	0 (0)	1 (1)	0.34
Total complications	12 (7)	15 (8)	0.75

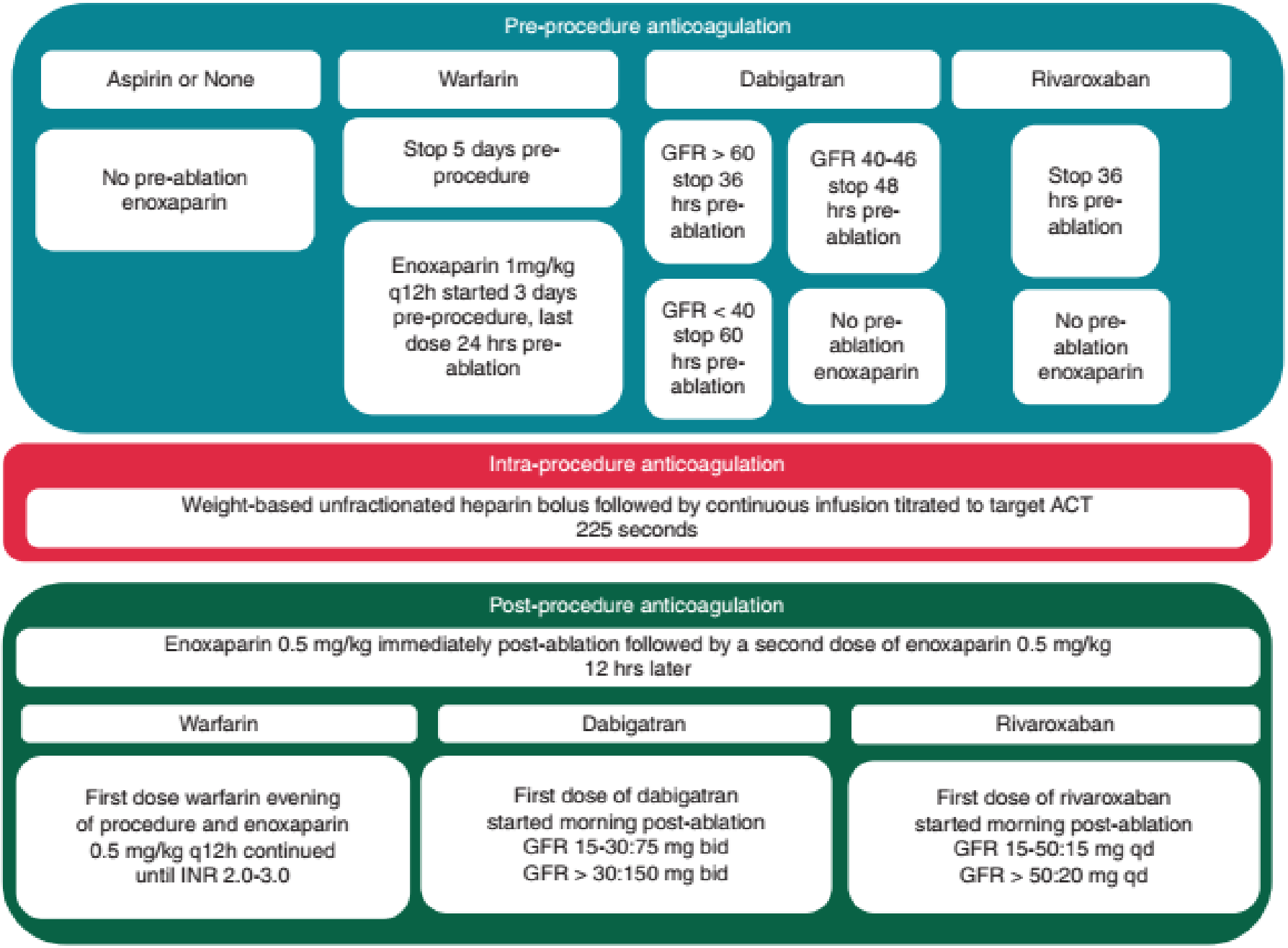
- FDA invaziv yada cerrahi girişimden önce dabigatranın
  - *CrCl ≥50 mL/min 1 yada 2 gün öncesinden*
  - *CrCl ≤50 mL/min) ise işlemden 3-5 gün önce*

kesilmesini önermektedir.

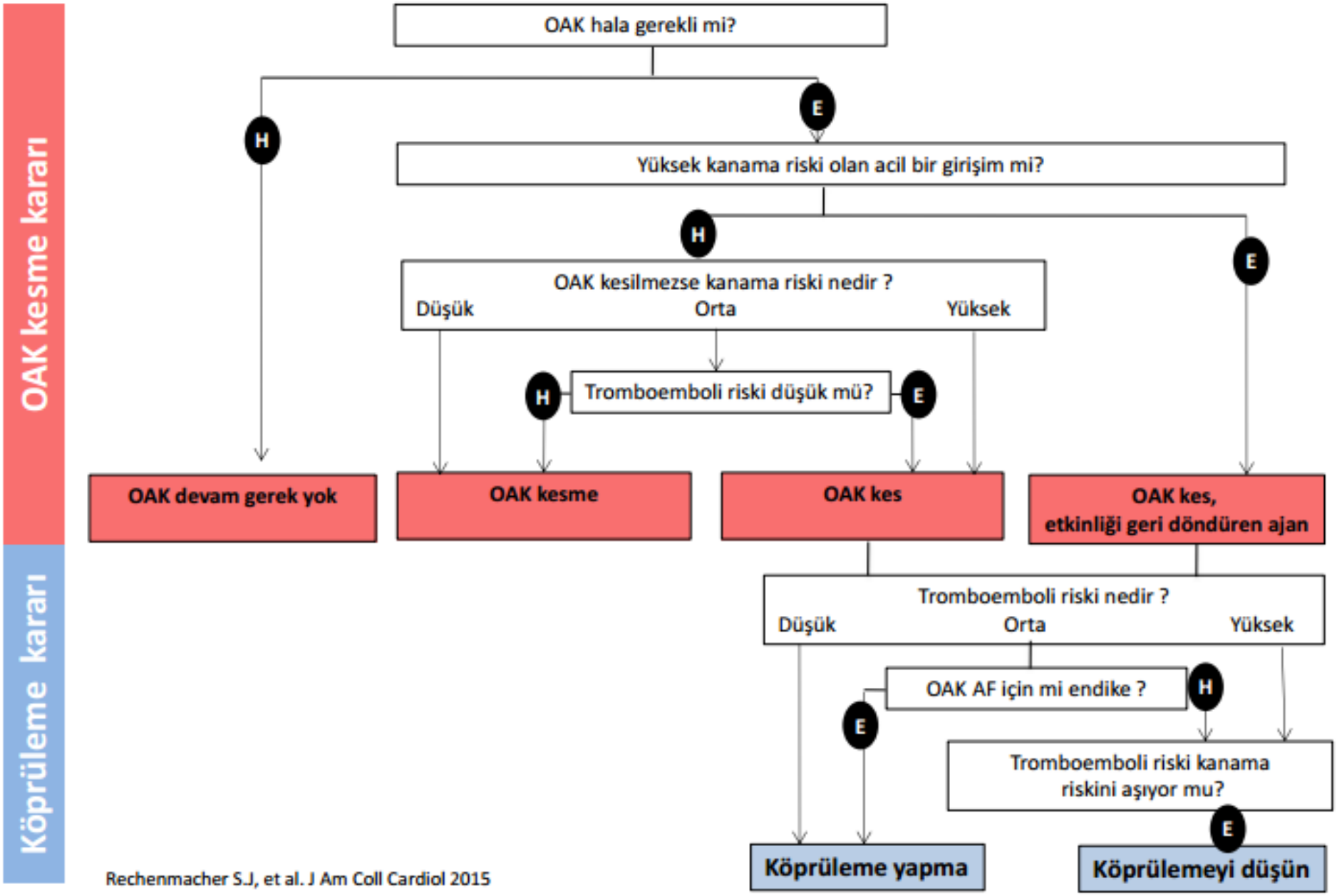
Snipelisky *et al. Heparin dabigatran etkileşimi*

- FDA elektif invaziv yada cerrahi girişimden önce apiksabanın
  - Kanama riski açısından orta yada yüksek riskli hastalarda 48 saat öncesinden

kesilmesini önermektedir.


Pre-procedure anticoagulation
Aspirin or None
No pre-ablation enoxaparin
Warfarin
Stop 5 days pre-procedure
Enoxaparin 1mg/kg q12h started 3 days pre-procedure, last dose 24 hrs pre-ablation
Dabigatran
GFR > 60 stop 36 hrs pre-ablation
GFR 40-46 stop 48 hrs pre-ablation
GFR < 40 stop 60 hrs pre-ablation
No pre-ablation enoxaparin
Rivaroxaban
Stop 36 hrs pre-ablation
No pre-ablation enoxaparin
Intra-procedure anticoagulation
Weight-based unfractionated heparin bolus followed by continuous infusion titrated to target ACT 225 seconds
Post-procedure anticoagulation
Enoxaparin 0.5 mg/kg immediately post-ablation followed by a second dose of enoxaparin 0.5 mg/kg 12 hrs later
Warfarin
First dose warfarin evening of procedure and enoxaparin 0.5 mg/kg q12h continued until INR 2.0-3.0
Dabigatran
First dose of dabigatran started morning post-ablation
GFR 15-30:75 mg bid
GFR > 30:150 mg bid
Rivaroxaban
First dose of rivaroxaban started morning post-ablation
GFR 15-50:15 mg qd
GFR > 50:20 mg qd

Antikoagülasyon köprülemede algoritma



Rechenmacher S.J, et al. J Am Coll Cardiol 2015

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REVIEW TOPIC OF THE WEEK

Bridging Anticoagulation

Stephen J. Rechenmacher, MD, James C. Fang, MD

TABLE 1 Risk Stratification for Perioperative Thromboembolism as Suggested by ACCP

	Indication for Anticoagulation		
Risk Group	**Mechanical Heart Valve**	**Atrial Fibrillation**	**VTE**
High*	• Mitral valve prosthesis • Cage-ball or tilting disc aortic valve prosthesis • CVA/TIA <6 months prior	• $CHADS_2$ score 5 or 6 • CVA/TIA <3 months prior • Rheumatic valvular heart disease	• VTE <3 months prior • Severe thrombophilia†
Moderate	• Bileaflet aortic valve and other risk factors‡	• $CHADS_2$ score 3 or 4	• VTE 3-12 months prior • Nonsevere thrombophilia§ • Recurrent VTE • Active cancer
Low	• Bileaflet aortic valve *without* other risk factors	• $CHADS_2$ score 2 or less without prior CVA/TIA	• VTE >12 months prior without other risk factors

Data from the American College of Chest Physicians (ACCP) guidelines (5). *A true high-risk category may be difficult to objectively define in the absence of trials demonstrating benefit of heparin bridging in such patients. †Deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities. ‡CVA risk factors include: atrial fibrillation, prior CVA/TIA, hypertension, diabetes, congestive heart failure, age >75 years. §Heterozygous factor V Leiden or prothrombin gene mutation.

$CHADS_2$ = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and stroke; CVA = cerebrovascular accident; TIA = transient ischemic attack; VTE = venous thromboembolism.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O., Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D., David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A., David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B., Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D., for the BRIDGE Investigators*

Table 3. Study Outcomes.

Outcome	No Bridging (N = 918)	Bridging (N = 895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

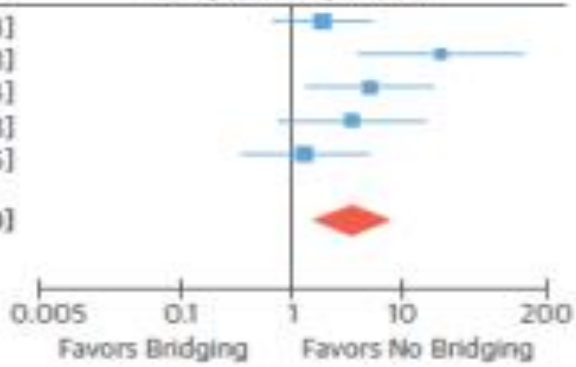
* P value for noninferiority.
† P value for superiority.

Köprülemede major kanama ve tromboembolik olay odds ratios

A Major Bleeding

Study or Subgroup	Bridging Events	Bridging Total	No Bridging Events	No Bridging Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	15	342	5	213	24.9%	1.91 [0.68, 5.33]
Garcia et al., 2008	4	108	2	1185	15.3%	22.75 [4.12, 125.68]
Jaffer et al., 2010	13	229	3	263	21.0%	5.22 [1.47, 18.54]
McBane et al., 2010	14	514	2	261	17.9%	3.63 [0.82, 16.08]
Wysokinski et al., 2008	6	204	4	182	20.8%	1.35 [0.37, 4.86]
Total (95% CI)		**1397**		**2104**	**100.0%**	**3.60 [1.52, 8.50]**
Total events	52		16			

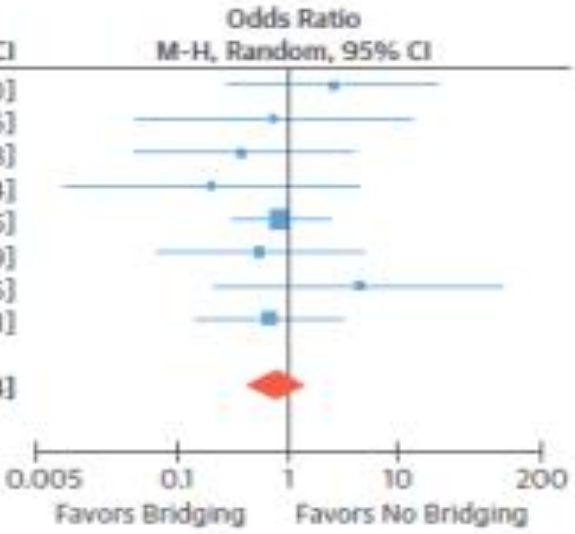
Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 8.41$, df = 4 (P = 0.08); $I^2 = 52\%$
Test for overall effect: Z = 2.92 (P = 0.004)



B Thromboembolic Events

Study or Subgroup	Bridging Events	Bridging Total	No Bridging Events	No Bridging Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	4	342	1	213	8.8%	2.51 [0.28, 22.60]
Garcia et al., 2008	0	108	7	1185	5.2%	0.72 [0.04, 12.76]
Jaffer et al., 2010	1	229	3	263	8.2%	0.38 [0.04, 3.68]
Marquie et al., 2006	0	114	2	114	4.6%	0.20 [0.01, 4.14]
McBane et al., 2010	10	514	6	261	40.5%	0.84 [0.30, 2.35]
Tompkins et al., 2010	1	155	6	513	9.4%	0.55 [0.07, 4.59]
Varkarakis et al., 2005	0	25	3	762	4.7%	4.25 [0.21, 84.56]
Wysokinski et al., 2008	3	204	4	182	18.6%	0.66 [0.15, 3.01]
Total (95% CI)		**1691**		**3493**	**100.0%**	**0.80 [0.42, 1.54]**
Total events	19		32			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.68$, df = 7 (P = 0.82); $I^2 = 0\%$
Test for overall effect: Z = 0.67 (P = 0.50)



Forest plot for major bleeding from Siegal et al. (10) demonstrates a significant odds ratio of 3.6 for patients receiving bridging anticoagulation **(A)**. There is no significant difference in thromboembolic events between bridging and nonbridging **(B)**. CI = confidence interval; M-H = Mantel-Haenszel. Reprinted with permission from Siegal et al. (10).

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	Synthesis of vitamin K-dependent clotting factors (factors II, VII, IX, and X)	Thrombin	Factor Xa	Factor Xa
Bioavailability	>95%	~6%	>80%	>50%
Time to peak activity	72–96 hours	2 hours	2.5–4 hours	3 hours
Half-life	40 hours	14–17 hours	5–9 hours (young healthy patients),11–13 hours (elderly patients)	8–15 hours
Dosing frequency in patients with AF	Once daily	Twice daily	Once daily	Twice daily
Interactions	Numerous drugs including substrates of CYP2C9, CYP3A4, and CYP1A2; various foods	Strong P-gp inhibitors and inducers	Strong CYP3A4 inducers, strong inhibitors of both CYP3A4 and P-gp	Strong inhibitors/inducers of both CYP3A4 and P-gp
Renal elimination (absorbed active drug)	<1%	~80%	~33%[a]	~27%

Abbreviations: AF, atrial fibrillation; CYP, cytochrome P450; P-gp, P-glycoprotein.

[a]An additional 33% of the absorbed rivaroxaban dose inactivated in the liver is also eliminated renally.

İşlem sırasında antikoagülasyon-I

- Transseptal ponksiyonundan hemen önce veya hemen sonra heparin (ACT 300-400 sn olacak şekilde) uygulanması
- İşlemin warfarin ile sistemik antikoagülasyon altında yapılması işlem sırasında (terapötik ACT seviyelerinde) heparin kulllanım ihtiyacını değiştirmez
- ACT seviyesinin terapötik antikoagülasyon sağlanıncaya kadar 10-15 dk'da bir ; daha sonra 15-30 dk'da bir monitörizasyonu

Increased anticoagulation intensity reduces thrombus risk during AF ablation

Ren et al, J Cardiovasc electrophysiol 2005

Incidence of ICE detected mobile thrombus
(on sheath/catheter after T/septal)

	ACT 250-300	ACT >300	p
All pts (n=511)	11.2%	2.8%	<0.05
Pts with SEC (n=179)	44.9%	4.6%	<0.0001

İşlem sırasında antikoagülasyon-II

- Terapötik ACT en az 300-350 sn olmalı
- Yükleme 60 IU/kg (max 4000 IU), 12 IU/kg/h (max 1000 IU/h)
- Kateter sol atriyuma ilerletildiğinde kılıfın sağ atriyuma çekilmesi
- Transseptal kılıfdan devamlı heparinize izotonik infüzyonu
- İşlem sonunda tüm kateterler sol atriyumdan alındığında heparin infüzyonunun kesilmesi
- ACT ≤200-250 olduğunda kasık kılıflarının çekilmesi veya ablasyonu takiben heparinin etkisini ortadan kaldıran protaminin kullanımı (sınıf IIa)

Calkins et al. HRS/EHRA/ECAS Catheter and Surgical Ablation, Heart Rhythm 2012

İşlemi takiben antikoagülasyon

- Kasık kılıflarının çekilmesinden sonra 4-6 saat içinde warfarine tekrar başlanır veya işlem warfarin altında yapıldıysa devam edilir
- Warfarine tekrar başlanan hastalarda LMWH (enoxaparin 0.5-1.0 mg/kg 2x1) veya IV regüler heparin ile INR 2-3 oluncaya kadar köprüleme
- İşlem sonrası yüksek kanama riski sebebiyle LMWH dozu azaltılabilir (2X0.5mg/kg)
- Warfarine alternatif olarak direkt trombin inhibitörleri veya faktör Xa inhibitörlerinin başlanması

AF Ablasyon Sonrası Tromboemboli

- RF enerjisi verilen lezyon tam endotelizasyonuna kadar koagülasyon kaynağı
  - Tam süresi bilinmemekle beraber 3 ay yeterli bir süre olarak değerlendirilebilir
- Atriyumların mekanik kontraktilitesini kazanması
  - Oluşan fibrozis ve yaralanan atriyal dokunun iyileşmesi (3 ay yeterli süre)
- Atriyal kontraktilitenin taşikardi sonlanmasından sonra azalması (atrial stunning) haftalar veya aylar sürebilir
  - Atrimi nüks ederse “atrial stunning” uzun sürebilir

AF Ablasyonu sırası/sonrasında antikoagülasyon rejimleri

-5	-4	-3	-2	-1	0	1	2	3	4	5
W	-	-	-	-	W H (L)	W L	W L	W L	W L	W L
W	-	-	-	-	W H(L)	W $L^{1/2}$	W $L^{1/2}$	W $L^{1/2}$	W $L^{1/2}$	W $L^{1/2}$
W	W	W	W	W	W (H)	W	W	W	W	W
D	D	D	D	D	D (H)	D	D	D	D	D
D	D	D			D (H)	D	D	D	D	D
R	R	R	R	R	R (H)	R	R	R	R	R
A	A	A	A	A	A (H)	A	A	A	A	A

Ablasyon Tedavisinde Kanama ile ilgili Yaklaşım

- Prothrombin complex concentrate (PCC),
- Factor VII
- Factor VIII inhibitor bypass activity(FEIBA)

- Rivaroxaban ve dabigatran.
  - ANTİKOAGÜLAN AKTİVİTELERİ düzeltebilir.

Marlu *et al.*

Company	Compound	Mechanism of action	Reversal for:			Status
			Factor Xa inhibitors	Dabigatran	LMWH/ Fondaparinux	
Portola Pharmaceuticals	PRT064445/ (andexanet alfa)	Recombinant factor Xa analogue that binds to direct factor Xa inhibitors and antithrombin	Yes	No	Yes (antithrombin-mediated factor Xa inhibition)	Phase II completed for rivaroxaban (104), apixaban (105) and enoxaparin (120) (ongoing for edoxaban) Phase III started (apixaban [clinicaltrials.gov NCT02207725]/rivaroxaban [clinicaltrials.gov NCT02220725]) (106, 107) or planned (edoxaban)
Boehringer Ingelheim	BI 655075 (idarucizumab)	Antibody fragment that binds specifically to dabigatran	No	Yes	No	Phase I completed (109, 110) Phase III completed (clinicaltrials.gov NCT02104947) (111)
Perosphere, Inc.	PER977 (aripazine)	Small molecule that binds to heparins, fondaparinux and NOACs	Yes	Yes	Yes	Phase I completed (edoxaban) (112)

LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant.

Teşekkür Ederim