Atriyal fibrilasyon – İnmenin Önlenmesi
Olgularla tartışalım

Dr. Özgür Aslan

Dokuz Eylül Üniversitesi Tıp Fakültesi

Kardiyoloji Anabilim Dalı, İzmir

Non-Valvüler AF için NOAK İlaçlar

	Dabigatran (RELY)[70,71]	Rivaroksaban (ROCKET-AF)3	Apiksaban (ARISTOTLE)4
İlaç özellikleri			
Mekanizma	Oral direkt trombin inhibitörü	Oral direkt faktör Xa inhibitörü	Oral direkt faktör Xa inhibitörü
Biyoyararlanım, %	6	60-80	50
Pik seviyelere ulaşma süresi, saat	3	3	3
Yarı ömür, saat	12-17	5-13	9-14
Atılım	%80 böbreklerle	2/3 karaciğer, 1/3 böbreklerle	%25 böbreklerle, %75 fekal
Doz	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.
Böbrek yetersizliğinde doz	110 mg b.i.d.	15 mg o.d. (eğer KrKl 30-49 mL/dk ise)	2.5 mg b.i.d.
Özel hususlar	Barsaklardan emilim pH'a bağımlıdır ve proton pompa inhibitörü alan hastalarda azalır	Börek veya karaciğer bozukluğu olan hastalarda daha yüksek seviyeler beklenir.	
	Verapamil/amiodaron/kinidin/ketokonazol alan hastalarda kanama riski artar	Aç hastalarda aktivite azalır, bu nedenle yemekten sonra alınmalıdır	

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Çalışma özellikleri			
Çalışma tasarımı	Randomize, açık etiketli	Randomize, çift kör	Randomize, çift kör
Hasta sayısı	18 111	14 264	18 201
İzlem süresi, yıl	2	1.9	1.8
Randomize gruplar	Dozu ayarlanmış varfarine karşı dabigatranın kör dozları (150 mg b.i.d., 110 mg b.i.d.)	Dozu ayarlanmış varfarine karşı rivaroksaban 20 mg o.d.	Dozu ayarlanmış varfarine karşı apiksaban 5 mg b.i.d.
Temel hasta özellikleri			
Yaş, yıl	71.5±8.7 (ort.±SD)	73 (65-78) [medyan (çeyrekler arası aralık)]	18 70 (63-76) [medyan (çeyrekler arası aralık)]
Erkek cinsiyet, %	63.6	61.3	64.5
$CHADS_2$ (ortalama)	2.1	3.5	2.1

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	Dabigatran (RELY)[70,71]			Rivaroksaban (ROCKET-AF)3		Apiksaban (ARISTOTLE)4	
Sonuçlar (% yıllık)							
	Varfarin	Dabigatran 150	Dabigatran 110	Varfarin	Rivaroksaban	Varfarin	Apiksaban
	(n=6022)	(n=6076)	(n=6015)	(n=7133)	(n= 7131)	(n=9081)	(n=9120)
		(RR, %95 CI; P değeri)	(RR, %95 CI; P değeri)		(HR, %95 CI; P değeri)		(HR, %95 CI; P değeri)
İnme/sistemik emboli	1.69	1.11 (0.66, 0.53-0.82; üstünlük için P <0.001)	1.53 (0.91, 0.74-1.11; Eşdeğerlik için P değeri <0.001)	2.4	2.1 (0.88, 0.75-1.03; Eşdeğerlik için P değeri <0.001, üstünlük için P=0.12) (ITT)	1.6	1.27 (0.79, 0.66-0.95; Eşdeğerlik için P<0.001, üstünlük için P=0.01
İskemik inme	1.2	0.92 (0.76, 0.60-0.98; P=0.03)	1.34 (1.11, 0.89-1.40; P=0.35)	1.42	1.34 (0.94; 0.75-1.17; P=0.581)	1.05	0.97 (0.92, 0.74-1.13; P=0.42)
Hemorajik inme	0.38	0.10 (0.26, 0.14-0.49; P <0.001)	0.12 (0.31, 0.17-0.56; P<0.001)	0.44	0.26 (0.59; 0.37-0.93; P=0.024)	0.47	0.24 (0.51, 0.35-0.75; P<0.001)
Majör kanama	3.36	3.11 (0.93, 0.81-1.07; P=0.31)	2.71 (0.80, 0.69-0.93; P=0.003)	3.4	3.6 (P=0.58)	3.09	2.13 (0.69, 0.60-0.80; P<0.001)
İntrakranyal kanama	0.74	0.30 (0.40, 0.27-0.60; P<0.001)	0.23 (0.31, 0.20-0.47; P<0.001)	0.7	0.5 (0.67; 0.47-0.93; P=0.02)	0.80	0.33 (0.42, 0.30-0.58; P<0.001)
Ekstrakranyal kanama	2.67	2.84 (1.07, 0.92-1.25; P=0.38)	2.51 (0.94, 0.80-1.10; P=0.45)	–	–	–	–

Non-Valvüler AF için NOAK İlaçlar

	Dabigatran (RELY)[70,71]			Rivaroksaban (ROCKET-AF)[3]		Apiksaban (ARISTOTLE)4	
Sonuçlar (% yıllık)							
Gastroentestinal kanama	1.02	1.51 (1.50, 1.19-1.89; P<0.001)	1.12 (1.10, 0.86-1.41; P=0.43)	2.2	3.2 (P <0.001)	0.86	0.76 (0.89, 0.70-1.15; P=0.37)
Miyokart enfarktüsü	0.64	0.81 (1.27, 0.94-1.71; P=0.12)	0.82 (1.29, 096-1.75; P=0.09)	1.1	0.9 (0.81; 0.63-1.06; P=0.12)	0.61	0.53 (0.88, 0.66-1.17; P=0.37)
Herhangi bir nedenle ölüm	4.13	3.64 (0.88, 0.77-1.00; P=0.051)	3.75 (0.91, 0.80-1.03; P=0.13)	2.2	1.9 (0.85; 0.70-1.02; P=0.07)	3.94	3.52 (0.89, 0.80-0.99; P=0.047)
İzlem sonunda devam etmeme %	10.2	15.5	14.5	22.2	23.7	27.5	25.3
Devam etmeme % / yıl	5.1	7.8	7.3	11.7	12.5	15.3	14.1

Olgu 1

Hasta: Cemile hanım

Kişisel Bilgiler	
Cinsiyet	Bayan
Yaş	74 y
Ağırlık	71 kg
Kan Basıncı	118/78 mmHg
Kalp Hızı	120 bpm, düzensiz
Böbrek fonksiyonu	Bozulmamış
Kişisel	• Ev hanımı • Aile üyeleri hareket etmesine yardımcı oluyorlar

Hastanın öyküsü	
Tıbbi hikaye	• Romatizmal kapak hastalığı • Çarpıntı ve nefes darlığı nedeniyle 6 ay içinde 3 kez hastaneye yatırılmış. • Coumadin başlanmış. 1 kez gözünde kanama olması nedeniyle ilaca ara verilmiş. Tekrar başlanmış ancak INR takibi yaptıramıyor. • YOAK önerilmiş
İlaçlar	• Furosemid • Digoksin • Warfarin + ASA

Olgu 1

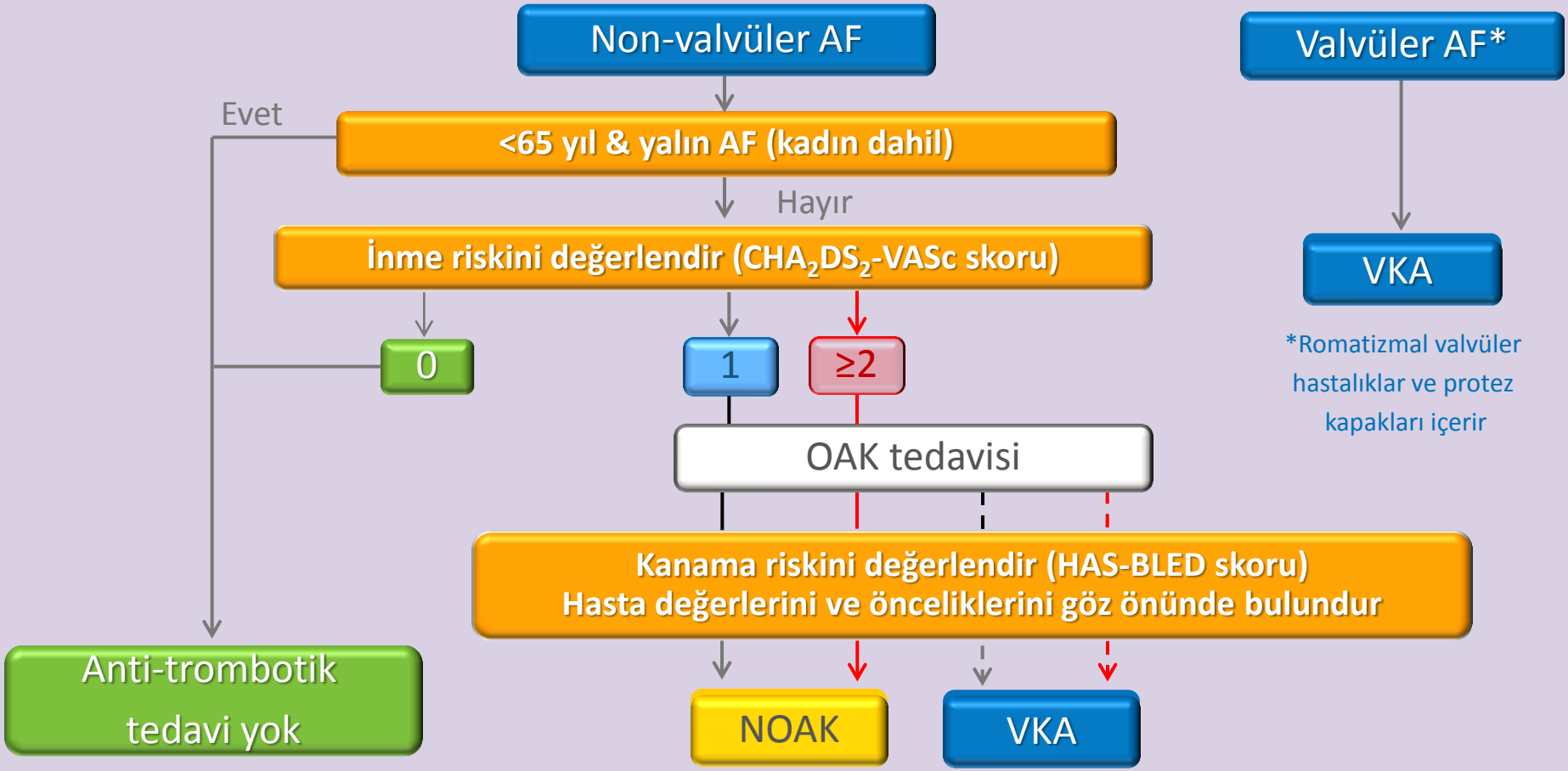
Hasta: Cemile hanım

Başvuru ve Bulgular

- Rahatsız edici çarpıntı atakları ve nefes darlığı
- EKG: AF – 130-140/dk
- EKO: Sol atriyum dilate (4.6x4.8cm), EF %50, Mitral kapaklar fibrotik, açılımı iyi, 3.derece MY…

→ **Kapak hastalığı öyküsü olan AF olgusu**

Antikoagülan seçimi



AF: atriyal fibrilasyon; OAC: oral antikoagülant; VKA: vitamin K antagonisti; YOAK: yeni oral antikoagülan

Renk: CHA_2DS_2-VASc; yeşil = 0; mavi = 1; kırmızı ≥ 2

çizgi; devamlı = en iyi seçenek; kesik = alternatif seçenek

Camm et al. *Europace* 2012;14:1385–1413.

REVIEW

How to define valvular atrial fibrillation?

Comment définir la fibrillation atriale valvulaire ?

Laurent Fauchier*, Raphael Philippart, Nicolas Clementy, Thierry Bourguignon, Denis Angoulvant, Fabrice Ivanes, Dominique Babuty, Anne Bernard

Table 1 Exclusion criteria related to valve disease in phase II and III trials with the new anticoagulants in atrial fibrillation.

Study drug	Study acronym/name	Year of publication	Atrial fibrillation exclusion criteria related to valve disease
Apixaban	AVERROES [5,7]	2011	Valvular disease requiring surgery, prosthetic mechanical heart valve
Apixaban	ARISTOTLE [11,14]	2011	Clinically significant (moderate or severe) mitral stenosis, prosthetic mechanical heart valve
Apixaban	ARISTOTLE-J [15]	2011	Valvular heart disease
Betrixaban	EXPLORE-Xa [4]	2013	Prosthetic mechanical heart valve
Dabigatran	PETRO [9]	2007	Mitral stenosis, prosthetic valves
Dabigatran	RE-LY [6,8]	2009	History of heart valve disorder (including haemodynamically relevant valve disease and prosthetic valve)
Edoxaban	Edoxaban phase II study [19]	2012	Comorbid rheumatic valvular disease, history of valvular surgery, infective endocarditis
Edoxaban	ENGAGE-AF-TIMI 48 [10,18]	2013	Moderate or severe mitral stenosis, unresected atrial myxoma, mechanical heart valve
Rivaroxaban	ROCKET-AF [17]	2011	Haemodynamically significant mitral valve stenosis, prosthetic heart valve
Rivaroxaban	J-ROCKET-AF [13]	2012	Haemodynamically significant mitral valve stenosis, prosthetic heart valve
Ximelagatran	SPORTIF III [12,16]	2003	Mitral stenosis, previous valvular heart surgery, active infective endocarditis
Ximelagatran	SPORTIF V [3,12]	2005	Mitral stenosis, previous valvular heart surgery, active infective endocarditis

Intern Emerg Med (2015) 10:21–24
DOI 10.1007/s11739-014-1181-5

IM - REVIEW

Novel oral anticoagulants and valvular atrial fibrillation: are they always contraindicated?

Giuseppe Di Pasquale · Silvia Zagnoni · Letizia Riva

Table 2 Type of valvular disease among patients enrolled in NOACs trials

Trial	VHD patients (%)	Type of VHD	
RE-LY [12]	3.950 (21 %)	MR	3.101 (17.1 %)[b]
		AR	817 (4.5 %)
		AS	471 (2.6 %)
		TR	1.179 (6.5 %)
		MS (Mild)	193 (1.1 %)
ROCKET-AF [13]	1.992 (14 %)[a]	MR	1.756 (89.6 %)[c]
		AR	486 (24.8 %)
		AS	215 (11 %)
		Other	11 (0.6 %)
		Prior cardiac procedure: 106 (5.3 %)	
		Valvuloplasty: 64 (60.4 %)	
		Other: 42 (39.6 %)	
ARISTOTLE [15]	4.808 (26.4 %)[a]	MR	3.526
		AR	887
		AS	384
		TR	2.124
		MS	131
ENGAGE AF [16]	N/A	N/A	

MR mitral regurgitation, *MS* mitral stenosis, *AR* aortic regurgitation, *AS* aortic stenosis, *TR* tricuspid regurgitation

[a] Patients with single VHD or combination of VHD

[b] Percentage of overall population

[c] Percentage among patients with VHD

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Apixaban Compared with Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the ARISTOTLE Trial

Alvaro Avezum, Renato D. Lopes, Phillip J. Schulte, Fernando Lanas, Bernard J. Gersh, Michael Hanna, Prem Pais, Cetin Erol, Rafael Diaz, M. Cecilia Bahit, Jozef Bartunek, Raffaele De Caterina, Shinya Goto, Witold Ruzyllo, Jun Zhu, Christopher B. Granger and John H. Alexander

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Table 1. Types of valvular heart disease.

	Overall		Apixaban		Warfarin		
Any VHD*	**N=4808**	**%**	**N=2438**	**%**	**N=2370**	**%**	***P* value**
Any mitral valve disease	3578	74.4%	1801	73.9	1777	75.0	0.38
Mitral regurgitation	3526	73.3%	1778	72.9	1748	73.8	0.52
Mitral stenosis	131	2.7%	69	2.8	62	2.6	0.65
Any aortic valve disease	1150	23.9%	604	24.8	546	23.0	0.16
Aortic regurgitation	887	18.4%	462	19.0	425	17.9	0.36
Aortic stenosis	384	8.0%	208	8.5	176	7.4	0.16
Tricuspid regurgitation	2124	44.2%	1082	44.4	1042	44.0	0.77
Prior valve surgery	251	5.2%	132	5.4	119	5.0	0.54

*Patients may have more than one type of valvular heart disease.
VHD indicates valvular heart disease.

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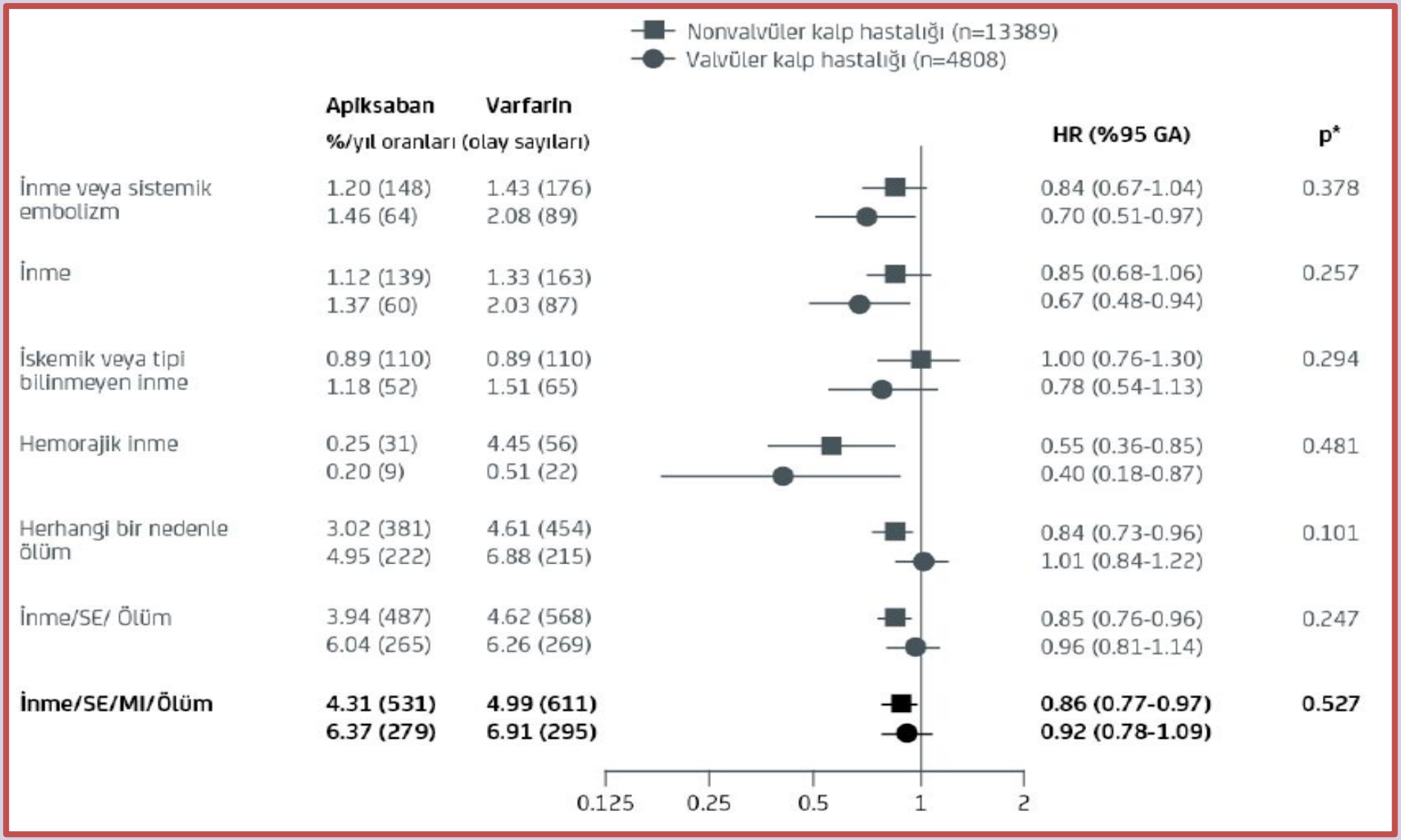

Apixaban Compared with Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the ARISTOTLE Trial

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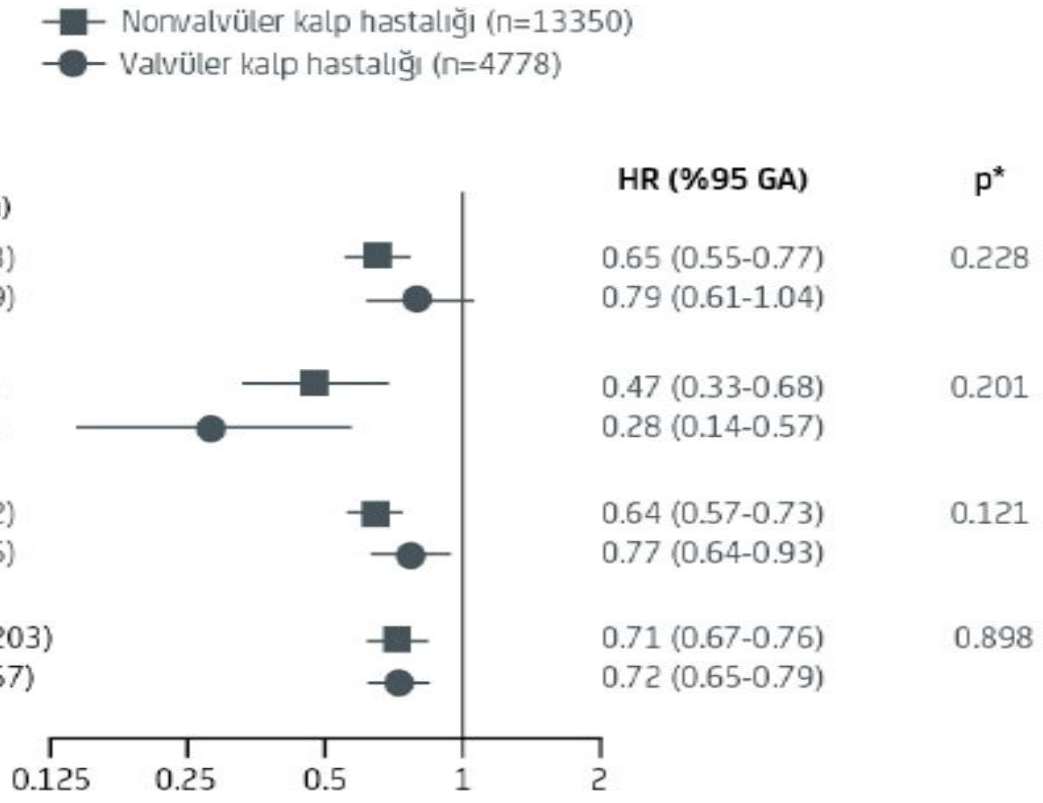

ISTH, Uluslararası Tromboz ve Hemostaz Derneği; CRNM, klinik olarak ilişkili majör olmayan.
* Valvüler kalp hastalığı durumunda etkileşim ile randomize tedavi için p değeri.

AF - Trombojenez

Kapak hastalığının rolü ?

Trombojenez mekanizması ?

- **Virchow Üçlüsü**
  - Damar duvarı hasarı (Endotel Disf.)
  - Hiperkoagülabilite (Trombosit disf.)
  - Kan akımında staz
- **LA içinde yavaş akım ?**
  - Orta-ciddi mitral darlığı ?
    - Hemen her zaman romatizmal !
      - 'Romatizmal AF' ? Vs 'Valvüler AF' ?
- **Mekanik kapak yüzeyine temas ?**
  - 'Protez kapaklı AF'

- *''mechanical and rheumatic mitral valvular AF''* (MARM-AF)
  - [De Caterina and Camm]
- *''Mekanik Kapaklı AF''* ve *''Mitral darlık ile AF''*
  - [Breithardt and Baumgartner]

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Europace
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REVIEW

Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial

Raffaele De Caterina[1,2]* and A. John Camm[3]

[1]Institute of Cardiology and Center of Excellence on Aging, G. d'Annunzio University—Chieti-Pescara, C/o Ospedale SS. Annunziata, Via dei Vestini, 31, Chieti 66031, Italy; [2]G. Monasterio Foundation, Pisa, Italy; and [3]Division of Clinical Sciences, St George's University of London, London, UK

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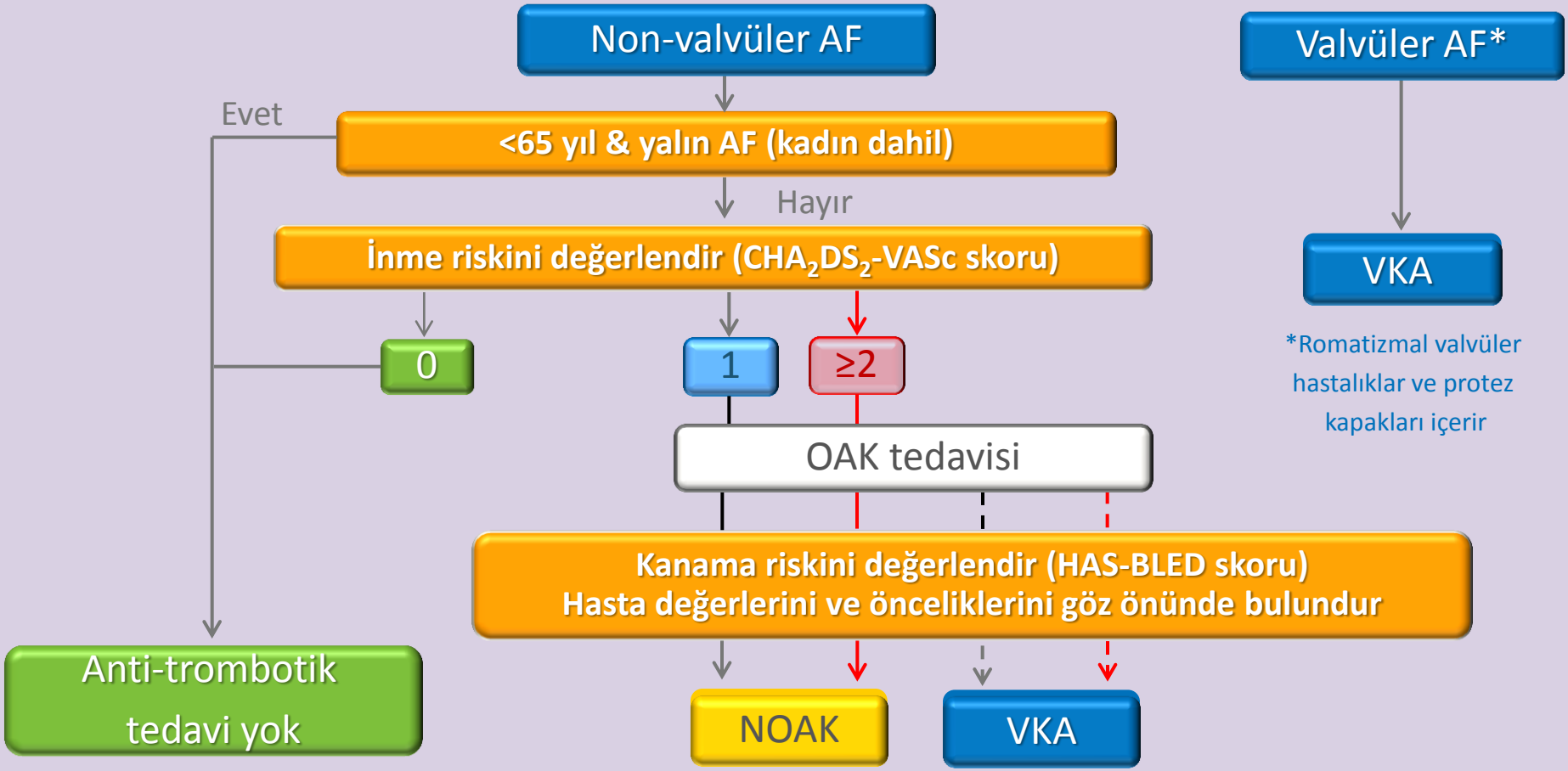
Patients at thromboembolic risk with non-valvular atrial fibrillation (AF) can now be managed either with a vitamin K antagonist (VKA) or with a fixed dose of a non-VKA oral anticoagulant (NOAC), while patients with valvular AF have been restricted to VKAs on the basis of a potentially higher risk and different mechanism of thrombosis, and the lack of sufficient data on the efficacy of NOACs. The terms 'non-valvular AF' and 'valvular AF' have not been however consistently defined. 'Valvular' AF has included any valvular disorder, including valve replacement and repair. In AF with rheumatic mitral disease, observational studies strongly suggest that VKA treatment is valuable. These patients have not been included in NOAC trials, but there is also no stringent argument to have excluded them. This is at sharp variance from patients with mechanical valves, also excluded from the pivotal Phase III trial comparing warfarin with NOACs, but in whom a single Phase II trial of dabigatran etexilate against VKA treatment was stopped prematurely because of increased rates of thromboembolism as well as increased bleeding associated with dabigatran. Until more data are available, such patients should be therefore managed with VKAs. We here propose an open-label randomized trial of one of the NOACs against the best of treatment available in regions of the world in which rheumatic heart disease is still highly prevalent, aiming at showing the superiority of the NOAC used against current standard treatment.

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

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

Antikoagülan seçimi



AF: atriyal fibrilasyon; OAC: oral antikoagülant; VKA: vitamin K antagonisti; YOAK: yeni oral antikoagülan

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çizgi; devamlı = en iyi seçenek; kesik = alternatif seçenek

Camm et al. *Europace* 2012;14:1385–1413.

Kadın hasta	Böbrek fonksiyonları korunmuş
Ağırlık: 71 kg	Sol atriyum dilate
Kan basıncı: 118/78 mmHg	‘Orta-ciddi MD ve Mekanik Kapak OLMAYAN’ AF
Kalp hızı yüksek	74 yaşında

Risk factors		
C	Congestive Heart Failure	+1 point
H	Hypertension	+1 point
A_2	Age ≥75	+2 point
D	Diabetes	+1 point
S_2	Stroke/TIA History	+2 point
V	Vascular Disease	+1 point
A	Age 65-74	+1 point
S	Sex (Female)	+1 point

Stroke risk per year	
SCORE	% RATE PER YEAR
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Reference: European Heart Rhythm Association. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31(19):2369-2429.

Kadın hasta	Böbrek fonksiyonları korunmuş
Ağırlık: 71 kg	Sol atriyum dilate
Kan basıncı: 118/78 mmHg	‘Orta-ciddi MD ve Mekanik Kapak OLMAYAN’ KRONİK AF
Kalp hızı yüksek / gözde kanama / INR izlemi ?	74 yaşında

- Kronik AF olmanın hiç etkisi yok mu ?

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Effect of Atrial Fibrillation on Atrial Thrombogenesis in Humans: Impact of Rate and Rhythm

Han S. Lim, MBBS, PHD,* Scott R. Willoughby, PHD,* Carlee Schultz, BHLTHSC(Hons),* Cheryl Gan, BSC,* Muayad Alasady, MBCHB,* Dennis H. Lau, MBBS, PHD,* Darryl P. Leong, MBBS, MPH, PHD,* Anthony G. Brooks, PHD,* Glenn D. Young, MBBS,* Peter M. Kistler, MBBS, PHD,† Jonathan M. Kalman, MBBS, PHD,‡ Matthew I. Worthley, MBBS, PHD,* Prashanthan Sanders, MBBS, PHD*

Adelaide and Melbourne, Australia

Objectives We sought to assess the effect of atrial fibrillation (AF) on atrial thrombogenesis in humans by determining the impact of rate and rhythm.

Background Although AF is known to increase the risk of thromboembolic stroke from the left atrium (LA), the exact mechanisms remain poorly understood.

Methods We studied 55 patients with AF who underwent catheter ablation while in sinus rhythm; 20 patients were induced into AF, 20 patients were atrial paced at 150 beats/min, and 15 were control patients. Blood samples were taken from the LA, right atrium, and femoral vein at baseline and at 15 min in all 3 groups. Platelet activation (P-selectin) was measured by flow cytometry. Thrombin generation (thrombin-antithrombin [TAT] complex), endothelial dysfunction (asymmetric dimethylarginine [ADMA]), and platelet-derived inflammation (soluble CD40 ligand [sCD40L]) were measured using enzyme-linked immunosorbent assay.

Results Platelet activation increased significantly in both the AF ($p < 0.001$) and pacing ($p < 0.05$) groups, but decreased in control patients ($p < 0.001$). Thrombin generation increased specifically in the LA compared with the periphery in both the AF ($p < 0.01$) and pacing ($p < 0.01$) groups, but decreased in control patients ($p < 0.001$). With AF, ADMA ($p < 0.01$) and sCD40L ($p < 0.001$) levels increased significantly at all sites, but were unchanged with pacing (ADMA, $p = 0.5$; sCD40L, $p = 0.8$) or in control patients (ADMA, $p = 0.6$; sCD40L, $p = 0.9$).

Conclusions Rapid atrial rates and AF in humans both result in increased platelet activation and thrombin generation. Prothrombotic activation occurs to a greater extent in the human LA compared with systemic circulation. AF additionally induces endothelial dysfunction and inflammation. These findings suggest that although rapid atrial rates increase the thrombogenic risk, AF may further potentiate this risk. (J Am Coll Cardiol 2013;61:852–60)

Role of Atrial Fibrillation Burden in Assessing Thromboembolic Risk

Peter Zimetbaum, MD; Jonathan W. Waks, MD; Ethan R. Ellis, MD; Taya V. Glotzer, MD; Rod S. Passman, MD, MSCE

Circ Arrhythm Electrophysiol December 2014

Table. Studies Showing A Correlation Between AF Burden and Stroke or Systemic Embolism

Author (year)	Patients (n)	Study Type	AF Monitoring	Follow-Up	Outcome
Glotzer et al (2003)[5]	312	Secondary analysis of multicenter RCT (MOST)	Dual-chamber PPM	Median 27 mo	10 patients (3.2%) developed stroke AHRE lasting ≥5 min associated with HR of 2.79 for death or nonfatal stroke (P=0.0011)
Capucci et al (2005)[7]	725	Prospective registry (AT500 Registry)	Dual-chamber PPM	Median 22 mo	14 patients (1.9%) developed a thromboembolic event (11 were stroke or TIA) AF episodes lasting >24 h associated with adjusted HR of 3.1 for thromboembolic event (P=0.044) AF episodes lasting between 5 min and 24 h were not associated with a significant increase in thromboembolic risk
Botto et al (2009)[33]	568	Prospective observational study	Dual-chamber PPM	1 y	14 patients (2.5%) developed stroke or systemic embolism When patients were stratified into multiple groups based on $CHADS_2$ score (0, 1, 2, or ≥3) and duration of AF episodes over 24 h (<5 min, 5 min to 24 h, and 24 h continuously), this allowed selection of 2 patient populations with significantly different annual rates of thromboembolic events (0.8% vs 5%) Patients with a high $CHADS_2$ score and any burden of AF and patients with a low $CHADS_2$ score and a high burden of AF had increased rates of thromboembolism.
Glotzer et al (2009)[3]	2486	Prospective observational study (TRENDS)	Dual-chamber PPM or ICD	Mean 1.4 y	Annual thromboembolic risk was 1.1% for patients with no AF, 1.1% for patients with AF episodes lasting <5.5 h (low burden), and 2.1% for patients with AF episodes lasting ≥5.5 h (high burden) No statistically significant difference in thromboembolic events between no AF, low burden, and high burden groups, although P value of borderline significance in comparison between high burden and zero burden (HR 2.20, P=0.06) 30-day cumulative AF burden ≥10.8 h showed a trend toward association with an increased risk of thromboembolism (HR 2.22, P=0.06)
Healey et al (2012)[4]	2580	Primary analysis of RCT (ASSERT)	Dual-chamber PPM or ICD	Mean 2.5 y	Annual rate of thromboembolism 1.69% in patients with atrial tachyarrhythmia episodes lasting >6 min compared with 0.69% in patients with episodes <6 min (HR 1.76, P=0.05) Longest atrial tachyarrhythmia <17.7 h—annual rate of stroke or systemic embolism was 1.2% Longest atrial tachyarrhythmia >17.7 h—annual rate of stroke or systemic embolism was 4.9%
Shanmugan et al (2012)[8]	560	Secondary analysis of 2 prospective, multicenter, observational studies (Home CARE & everesT)	Biventricular PPM or ICD	Median 370 days	11 patients (2%) had a thromboembolic event AHRE ≥3.8 h/d were associated with HR 9.4, P=0.006 for stroke or systemic embolism compared with patients without arrhythmia
Boriani et al (2014)[6]	10 016	Pooled analysis of 3 prospective studies (TRENDS, PANORAMA & Italian ClinicalService® Registry	PPM or ICD with atrial lead	Median of 24 mo	95 patients (0.39%/y) experienced stroke or systemic embolism AF burden was independently associated with thromboembolism at multiple cutoff points AF episodes >1 h were associated with HR of 2.11, P=0.008 for ischemic stroke AF episodes >5 min were associated with HR 1.76, P=0.041 for ischemic stroke For every hour of AF in a 24 h period, the relative risk for stroke increased by 3%

AHRE indicates atrial high rate episodes; AF, atrial fibrillation; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; PPM, permanent pacemaker; and RCT, randomized control trial.

Advances in Arrhythmia and Electrophysiology

Role of Atrial Fibrillation Burden in Assessing Thromboembolic Risk

Peter Zimetbaum, MD; Jonathan W. Waks, MD; Ethan R. Ellis, MD; Taya V. Glotzer, MD; Rod S. Passman, MD, MSCE

Circ Arrhythm Electrophysiol December 2014

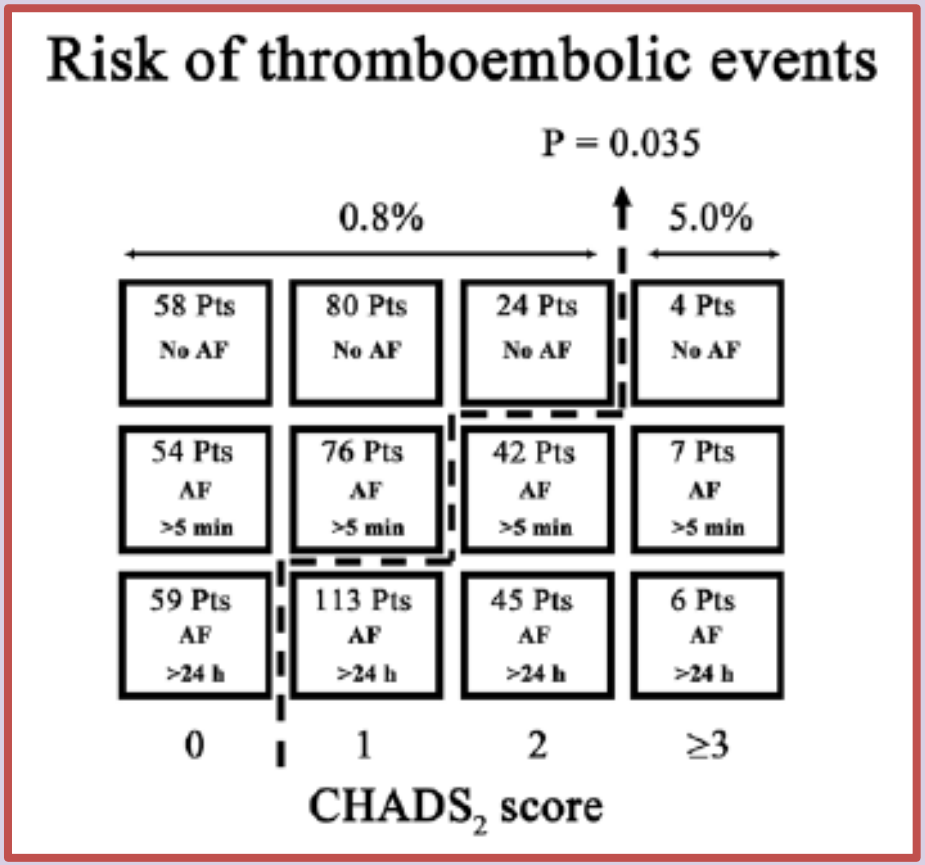

Figure 3. Thromboembolic risk stratified by atrial fibrillation (AF) duration and $CHADS_2$ score. Combination of AF burden and $CHADS_2$ score separated the study population into 2 groups with significantly different thromboembolic risk (0.8% vs 5.0%). Columns correspond to $CHADS_2$ scores and rows correspond to AF duration over the course of 1 day (none, >5 min, and 24 h continuous). Reprinted from Botto et al[33] with permission of the publisher. Copyright ©2009, Wiley Periodicals, Inc.

33. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F, Favale S, Molon G, Ricci R, Biffi M, Russo G, Vimercati M, Corbucci G, Boriani G. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. *J Cardiovasc Electrophysiol*. 2009;20:241–248.

European Heart Journal
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CLINICAL RESEARCH

Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial

Sana M. Al-Khatib[1]*, Laine Thomas[1], Lars Wallentin[2], Renato D. Lopes[1], Bernard Gersh[3], David Garcia[4], Justin Ezekowitz[5], Marco Alings[6], Hongqui Yang[1], John H. Alexander[1], Gregory Flaker[7], Michael Hanna[8], and Christopher B. Granger[1]

[1]Duke Clinical Research Institute, Duke University Medical Center, PO Box 17969, Durham, NC 27715 USA; [2]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; [3]Mayo Clinic College of Medicine, Rochester, MN, USA; [4]University of New Mexico, Albuquerque, NM, USA; [5]University of Alberta, Edmonton, Canada; [6]Amphia Ziekenhuis, Breda and WCN, Utrecht, Netherlands; [7]University of Missouri School of Medicine, Columbia, MO, USA; and [8]Bristol-Myers Squibb, Princeton, NJ, USA

Received 7 November 2012; revised 14 March 2013; accepted 28 March 2013

Table 2 Outcomes by type of atrial fibrillation

Outcome	No. of patients	Paroxysmal AF No. of events (%/100 patient-years)	Persistent or permanent AF No. of events (%/100 patient-years)	Unadjusted HR (95% CI)	Unadjusted *P*-value
Stroke or systemic embolism	18 198	51 (0.98)	426 (1.52)	0.65 (0.48, 0.87)	0.003
All-cause mortality	18 198	149 (2.81)	1123 (3.90)	0.72 (0.61, 0.853)	0.0002
Major bleeding	18 137	104 (2.22)	685 (2.68)	0.83 (0.68, 1.02)	0.078
Composite of stroke or systemic embolism, all-cause mortality, major bleeding	18 198	272 (5.31)	1905 (6.91)	0.77 (0.68, 0.87)	<0.0001

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

AF Type	No. of Patients	Apixaban No. of Events (%/year)	Warfarin No. of Events (%/year)	HR (95% CI)	P-value for Interaction
Stroke or Systemic Embolism					
Paroxysmal	2786	21(0.82)	30(1.14)	0.72(0.41, 1.25)	0.71
Persistent or permanent	15412	191(1.35)	235(1.69)	0.80(0.66, 0.97)	
Major Bleeding					
Paroxysmal	2776	44(1.88)	60(2.56)	0.73(0.49, 1.08)	0.75
Persistent or permanent	15361	283(2.18)	402(3.19)	0.68(0.59, 0.80)	
All-cause Mortality					
Paroxysmal	2786	73(2.79)	76(2.82)	0.99(0.72, 1.37)	0.50
Persistent or permanent	15412	530(3.65)	593(4.15)	0.88(0.78, 0.99)	
Net Benefit					
Paroxysmal	2776	127(5.02)	145(5.58)	0.92(0.72, 1.16)	0.62
Persistent or permanent	15361	882(6.33)	1023(7.51)	0.83(0.76, 0.91)	

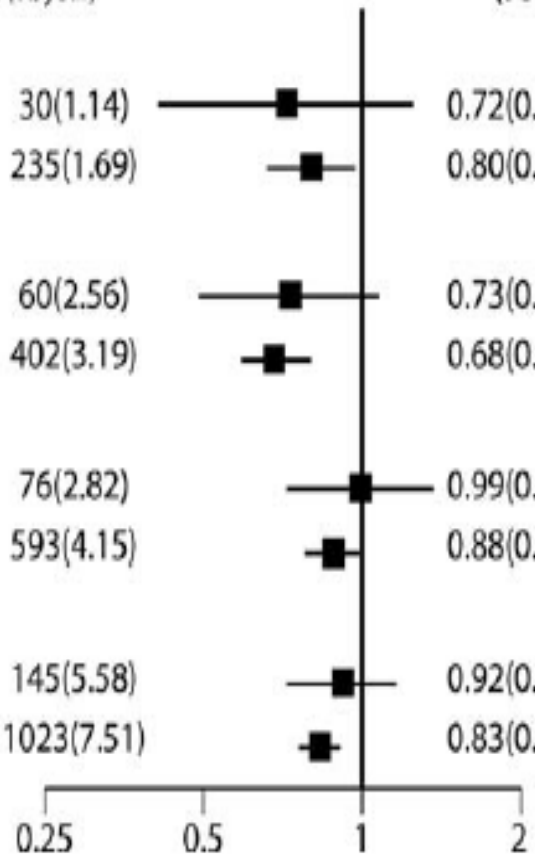


Figure 1 Outcomes by type of atrial fibrillation and study treatment.

Kadın hasta	Böbrek fonksiyonları korunmuş
Ağırlık: 71 kg	Sol atriyum dilate
Kan basıncı: 118/78 mmHg	'Orta-ciddi MD ve Mekanik Kapak OLMAYAN' AF
Kalp hızı yüksek / gözde kanama / INR izlemi ?	74 yaşında

Condition	Points
H - Hypertension	1
A - Abnormal renal or liver function (1 point each)	1 or 2
S - Stroke	1
B - Bleeding	1
L - Labile INRs	1
E - Elderly (> 65 years)	1
D - Drugs or alcohol (1 point each)	1 or 2

HAS-BLED score	Bleeds per 100 patient-years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5

Note: HAS-BLED has been validated for warfarin, but not for the new anticoagulants.

Pisters R et al. Chest 2010;138(5):1093-1100.

Kadın hasta	Böbrek fonksiyonları korunmuş
Ağırlık: 71 kg	Sol atriyum dilate
Kan basıncı: 118/78 mmHg	‘Orta-ciddi MD ve Mekanik Kapak OLMAYAN’ KRONİK AF
Kalp hızı yüksek / gözde kanama / INR izlemi ?	74 yaşında

- Digoksin kesildi

- Metoprolol 50 mg 2x1
- Aralıklı Furosemid
- Apiksaban 5 mg 2x1

Olgu 2

Hasta: Hasan Bey

Kişisel Bilgiler	
Cinsiyet	Erkek
Yaş	66 y
Ağırlık	100 kg
Kan Basıncı	150/100 mmHg
Kalp Hızı	80 bpm, düzenli
Böbrek fonksiyonu	Bozulmamış
Kişisel	• Emekli • Kendi işlerini kendisi görüyor

Hastanın öyküsü	
Tıbbi hikaye	• HT • 2 yıl önce 1 kez belgelenmiş AF atağı • 7 ay önce geçici iskemik atak. Atak sırasında AF saptanmamış • Nöroloji 6 ay antiagregan tedaviyi yeterli bulmuş.
İlaçlar	• ARB • Kalsiyum antagonisti • ASA

Olgu 2

Hasta: Hasan Bey

Başvuru ve Bulgular

- Genel kontrol için baş vuruyor
- EKG: Sinüs ritmi ve sol ventrikül hipertrofisi
- EKO: Sol atriyum 4.0cm, EF %60, Hafif MY, Sol ventrikül hipertrofisi, Evre 1 Diyastolik disfonksiyon

→ **Kriptojenik inme ?**

→ **PAF ?**

Erkek hasta	Sol ventrikül hipertrofisi, Sol atriyum dilate, Normal EF
Ağırlık: 100 kg	GİA öyküsü, Geçmiş AF öyküsü
Kan basıncı: 150/100 mmHg	‘PAROKSİSMAL AF’ ???
Kalp hızı normal /Ritim sinüs	66 yaşında

- GİA ile PAF öyküsü ilişkili olabilir mi ?

CONTEMPORARY REVIEW

Cryptogenic stroke: Is silent atrial fibrillation the culprit?

Taya V. Glotzer, MD, FACC, FHRS,* Paul D. Ziegler, MS†

*From the *Hackensack University Medical Center, Hackensack, New Jersey, and †Cardiac Rhythm Disease Management Division, Medtronic Inc, Mounds View, Minnesota.*

BACKGROUND Stroke without an identifiable cause is frightening to patients and their families and is frustrating for the caring physician. Approximately 30% of patients with cardiac implanted electronic devices have some evidence of atrial fibrillation (AF), and much of it is silent: asymptomatic, and previously unrecognized.

OBJECTIVE The purpose of this review is to examine "silent AF" as a potential cause of cryptogenic stroke.

METHODS/RESULTS We begin by reviewing most of the published literature on screening for AF with different monitoring technologies in the setting of cryptogenic stroke. We present the results of 2 recent large randomized trials, CRYSTAL AF and EMBRACE, which compare standard of care monitoring in cryptogenic stroke patients to invasive and noninvasive monitoring strategies, respectively. Finally, we review the relationship of silent AF to stroke in the cardiac implanted electronic device population. Patient selection, duration of monitoring, sensitivity and specificity of monitoring technology, patient compliance, and several other factors affect the yield of AF detection during monitoring.

CONCLUSION Data suggest that silent AF is identified in approximately 30% of cryptogenic stroke patients and has important therapeutic implications. Oral anticoagulation likely should be prescribed when silent AF is detected.

KEYWORDS Atrial fibrillation; Stroke; Implantable device; Continuous monitoring

ABBREVIATIONS **AF** = atrial fibrillation; **AHRE** = atrial high rate episode; **CIED** = cardiac implantable electronic device; **ECG** = electrocardiogram; **HR** = hazard ratio; **ICD** = implantable cardioverter-defibrillator; **ICM** = insertable cardiac monitor; **MCOT** = mobile cardiac outpatient telemetry; **OAC** = oral anticoagulation; **TEE** = transesophageal echocardiography; **TIA** = transient ischemic attack

(Heart Rhythm 2015;12:234–241)

Cryptogenic stroke: Is silent atrial fibrillation the culprit?

Taya V. Glotzer, MD, FACC, FHRS,* Paul D. Ziegler, MS†

Table 1 AF detected by outpatient cardiac monitoring in patients with cryptogenic stroke

Study (year)	No. of patients	AF definition	Monitoring type and duration	AF detection yield	Notes
Tayal et al[18] (2008)	56	Any duration	MCOT: 21 days	Overall: 23% AF <30 seconds: 18% AF >30 seconds: 5%	Median time to AF detection: 7 days (2-19)
Elijovich et al[19] (2009)	20	Not defined	Event monitor: 30 days	20%	
Gaillard et al[20] (2010)	98	32 seconds	Transtelephonic monitoring: 30 days	9%	
Bhatt et al[21] (2011)	62	30 seconds	MCOT: 28 days	Overall: 24% AF ≥ 5 minutes: 9%	93% of AF was detected within first 21 days Median duration of monitoring: 21 days (range 2–28 days)
Flint et al[22] (2012)	236	5 seconds	MCOT: 30 days	Overall: 11% AF ≤30 seconds: 4% AF >30 seconds: 7%	
Kamel et al[23] (2013)	20	30 seconds	MCOT: 21 days	0%	Only 64% completed 21 days
Miller et al[24] (2013)	156	30 seconds	MCOT: 30 days	Overall: 17% AF <30 seconds: 12% AF ≥30 seconds: 5%	Only 62% completed 21 days
EMBRACE; Gladstone et al[12] (2014)	572	30 seconds	Event monitor: 30 days vs 24-hour Holter	16.1% (45/280) event monitor 3.2% (9/277) 24-hour Holter	
		2.5 minutes		9.9% (28/284) event monitor 2.5% (7/277) 24-hour Holter	

Cryptogenic stroke: Is silent atrial fibrillation the culprit?

Taya V. Glotzer, MD, FACC, FHRS,* Paul D. Ziegler, MS†

Table 2 AF detected by insertable cardiac monitors in patients with cryptogenic stroke

Study (year)	No. of patients	AF definition	Monitoring duration	AF detection yield	Notes
Cotter et al[25] (2013)	51	2 minutes	Mean 229 (116) days	25.5%	Median time from ICM implant to first new AF episode: 48 days (range 0–154 days) Median duration of first new AF episode: 6 minutes (range 1– 4320 minutes)
Ritter et al[26] (2013)	60	2 minutes	1 year	16.7%	Mean time from ICM implant to first new AF episode: 64 days (1-556). 7-day Holter detected AF in only 1.7%
Etgen et al[27] (2013)	22	6 minutes	1 year	27.3%	Mean time from stroke to first new AF episode: 5 months
Rojo-Martinez et al[28] (2013)	101	2 minutes	281 ± 212 days	33.7%	
SURPRISE[29] (2014)	85	2 minutes	569 ± 310 days	16.1 %	Mean time from stroke to first new AF episode 109 ± 48 days
CRYSTAL AF[11] (2014)	221	>30 seconds*	Minimum 6 months	8.9% at 6 months 12.4% at 12 months 30.0% at 36 months	

İnme ile AF ataklarının zamansal ilişkisi

- Olguların çoğunda (%73-94) tromboembolik olaydan önceki 30 gün içinde AF yok !
- İnmenin mekanizması doğrudan AF'nin kendisiyle ile ilişkili olmayabilir !
- AHRE artışı olay sıklığını artırıyor !

CONTEMPORARY REVIEW

Cryptogenic stroke: Is silent atrial fibrillation the culprit?

Taya V. Glotzer, MD, FACC, FHRS,* Paul D. Ziegler, MS†

Table 5 Temporal relationship of device-detected AF to thromboembolic events

Year	Trial	No. of patients with TE event	Definition of AF episode	Any AF detected before TE event	AF detected only after TE event	No AF in 30 days before TE event	Any AF in 30 days before TE event
2011	TRENDS[53]	40	5 minutes	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2014	ASSERT[54]	51	6 minutes	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT[55]	69	36/48 atrial beats ≥200 bpm	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)

AF = atrial fibrillation; TE = thromboembolic event.

Erkek hasta	Sol ventrikül hipertrofisi, Sol atriyum dilate, Normal EF
Ağırlık: 100 kg	TİA öyküsü, Geçmiş AF öyküsü
Kan basıncı: 150/100 mmHg	‘PAROKSİSMAL AF’ ???
Kalp hızı normal /Ritim sinüs	66 yaşında

- Olguda PAF olasılığını artıran zemin var mı ?

REVIEW TOPIC OF THE WEEK

Obesity, Exercise, Obstructive Sleep Apnea, and Modifiable Atherosclerotic Cardiovascular Disease Risk Factors in Atrial Fibrillation

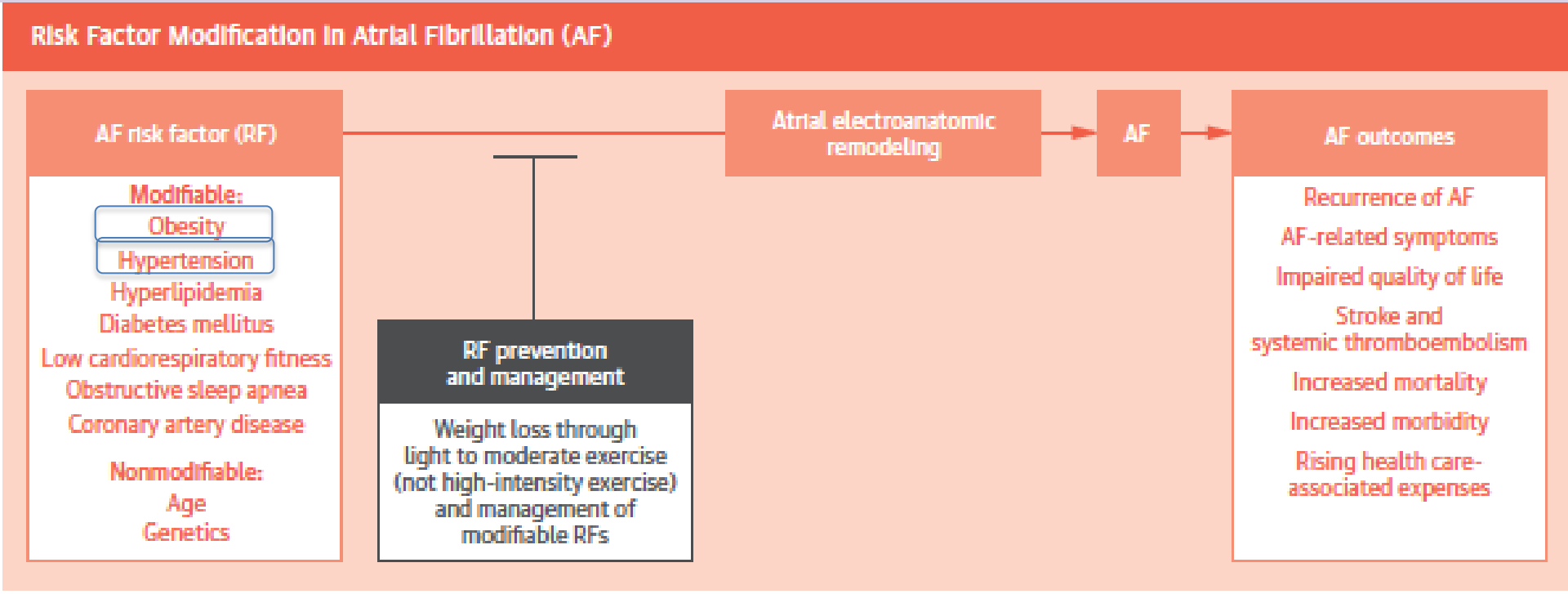
Jared D. Miller, MD, Konstantinos N. Aronis, MD, Jonathan Chrispin, MD, Kaustubha D. Patil, MD, Joseph E. Marine, MD, Seth S. Martin, MD, MHS, Michael J. Blaha, MD, MPH, Roger S. Blumenthal, MD, Hugh Calkins, MD

ABSTRACT

Classically, the 3 pillars of atrial fibrillation (AF) management have included anticoagulation for prevention of thromboembolism, rhythm control, and rate control. In both prevention and management of AF, a growing body of evidence supports an increased role for comprehensive cardiac risk factor modification (RFM), herein defined as management of traditional modifiable cardiac risk factors, weight loss, and exercise. In this narrative review, we summarize the evidence demonstrating the importance of each facet of RFM in AF prevention and therapy. Additionally, we review emerging data on the importance of weight loss and cardiovascular exercise in prevention and management of AF. (J Am Coll Cardiol 2015;66:2899–906) © 2015 by the American College of Cardiology Foundation.

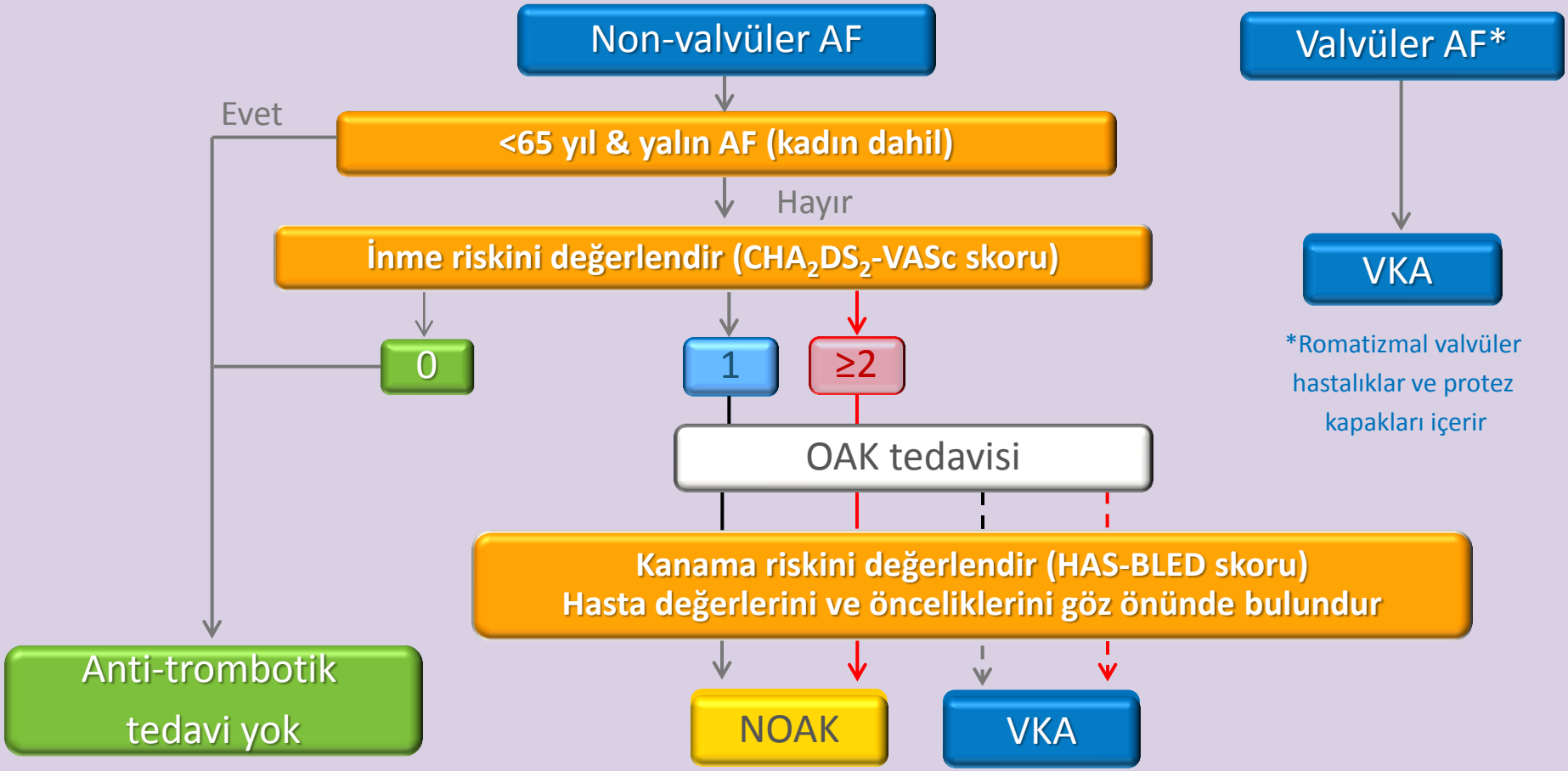
Erkek hasta	Sol ventrikül hipertrofisi, Sol atriyum dilate, Normal EF
Ağırlık: 100 kg	TİA öyküsü, Geçmiş AF öyküsü
Kan basıncı: 150/100 mmHg	'PAROKSİSMAL AF' ???
Kalp hızı normal /Ritim sinüs	66 yaşında

Olguda PAF olasılığını artıran zemin var mı ?



Miller, J.D. et al. J Am Coll Cardiol. 2015; 66(25):2899-906.

Antikoagülan seçimi



AF: atriyal fibrilasyon; OAC: oral antikoagülant; VKA: vitamin K antagonisti; YOAK: yeni oral antikoagülan

Renk: CHA_2DS_2-VASc; yeşil = 0; mavi = 1; kırmızı ≥ 2

çizgi; devamlı = en iyi seçenek; kesik = alternatif seçenek

Camm et al. *Europace* 2012;14:1385–1413.

Erkek hasta	Sol ventrikül hipertrofisi, Sol atriyum dilate, Normal EF
Ağırlık: 100 kg	TİA öyküsü, Geçmiş AF öyküsü
Kan basıncı: 150/100 mmHg	‘PAROKSİSMAL AF’ ???
Kalp hızı normal /Ritim sinüs	66 yaşında

Risk factors		
C	Congestive Heart Failure	+1 point
H	Hypertension	+1 point
A_2	Age ≥75	+2 point
D	Diabetes	+1 point
S_2	Stroke/TIA History	+2 point
V	Vascular Disease	+1 point
A	Age 65-74	+1 point
S	Sex (Female)	+1 point

Stroke risk per year	
SCORE	% RATE PER YEAR
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Reference: European Heart Rhythm Association. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31(19):2369-2429.

Erkek hasta	Sol ventrikül hipertrofisi, Sol atriyum dilate, Normal EF
Ağırlık: 100 kg	TİA öyküsü, Geçmiş AF öyküsü
Kan basıncı: 150/100 mmHg	'PAROKSİSMAL AF' ???
Kalp hızı normal /Ritim sinüs	66 yaşında

Condition	Points
H - Hypertension	1
A - Abnormal renal or liver function (1 point each)	1 or 2
S - Stroke	1
B - Bleeding	1
L - Labile INRs	1
E - Elderly (> 65 years)	1
D - Drugs or alcohol (1 point each)	1 or 2

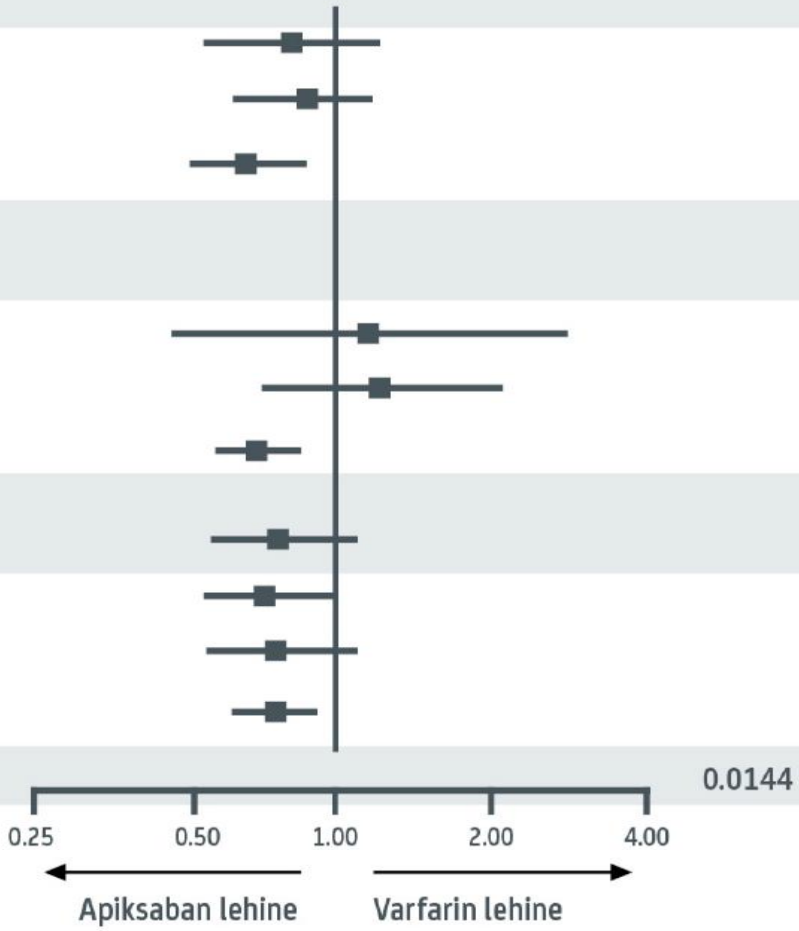
HAS-BLED score	Bleeds per 100 patient-years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5

Note: HAS-BLED has been validated for warfarin, but not for the new anticoagulants.

Pisters R et al. Chest 2010;138(5):1093-1100.

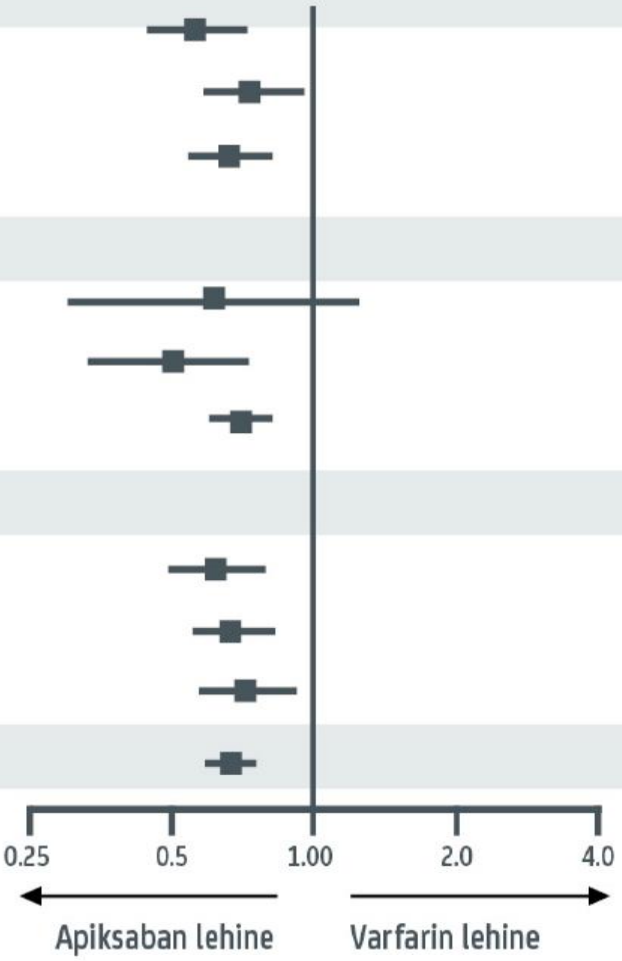
Apiksaban – etkililik - *risk skoruna göre*

		Apiksaban	varvarin	Tehlike oranı (%95 Cl)	P değeri
	Hasta sayısı	%/yıl (olay sayısı)			
$CHADS_2$ etkileşim: 0.4457					
1	6,183	%0.74 (44)	%0.87 (51)		
2	6,516	%1.24 (74)	%1.37 (82)		
≥3	5,502	%1.95 (94)	%2.80 (132)		
CHA_2DS_2VASc etkileşim: 0.1210					
1	1,604	%0.62 (10)	%0.53 (8)		
2	3,771	%0.85 (30)	%67 (24)		
≥3	12,826	%1.48 (172)	%2.03 (233)		
HAS-BLED etkileşim: 0.9422					
0-1	7,461	%0.92 (65)	%1.14 (79)		
2	6,568	%1.39 (83)	%1.81 (109)		
≥3	4,172	%1.73 (64)	%2.14 (77)		
Genel	18,201	%1.27 (212)	%1.60 (265)		0.0144



Apiksaban – güvenlik – *risk skoruna göre*

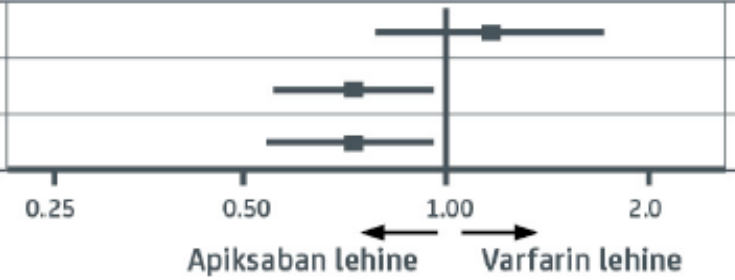
		Apiksaban	varvarin	Tehlike oranı (%95 GA)	P değeri
	Hasta sayısı	%/yıl (olay sayısı)			
$CHADS_2$					Etkileşim: 0.4018
1	6,169	%1.38 (76)	%2.34 (126)		
2	6,492	%2.30 (125)	%3.03 (163)		
≥3	5,479	%2.88 (126)	%4.15 (173)		
CHA_2DS_2VASc					Etkileşim: 0.2059
1	1,602	%0.80 (12)	%1.21 (17)		
2	3,759	%1.26 (42)	%2.48 (82)		
≥3	12,779	%2.60 (273)	%3.55 (363)		
HAS-BLED					Etkileşim: 0.7127
0-1	7,433	%1.36 (89)	%2.16 (137)		
2	6,544	%2.25 (123)	%3.23 (175)		
≥3	4,163	%3.46 (115)	%4.70 (150)		
Genel	18,140	%2.13 (327)	%3.09 (462)		<0.001



Apiksaban – etkililik ve güvenlik – *yaşa göre*

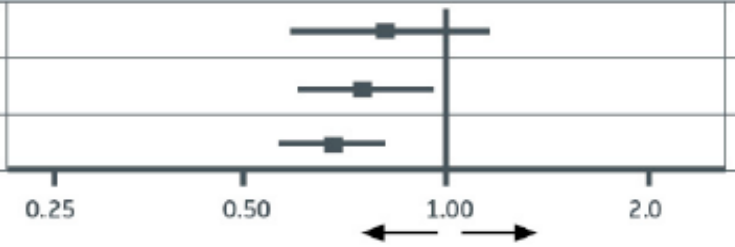
A. Birincil etkililik sonuçları: inme ve sistemi embolizm[1]

Altgrup	Hasta sayısı	Apiksaban	Varfarin	Tehlike Oranı (%95 GA)	Etkileşim için p değeri
		%/yıl (olay sayısı)			
Yaş					0.11*
<65 y	5,471	51 (1.00)	44 (0.86)		
65 to <75 y	7,052	82 (1.25)	112 (1.73)		
≥75 y	5,678	79 (1.56)	109 (2.19)		



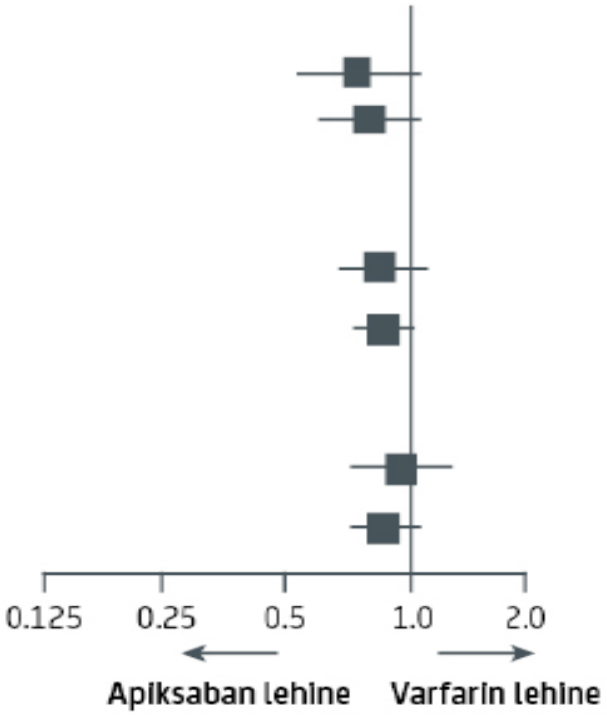
B. Majör kanama[1]

Altgrup	Hasta sayısı	Apiksaban	Varfarin	Tehlike Oranı (%95 GA)	Etkileşim için p değeri
		%/yıl (olay sayısı)			
Yaş					0.63*
<65 y	5,455	56 (1.17)	72 (1.51)		
65 to <75 y	7,030	120 (1.99)	166 (2.82)		
≥75 y	5,655	151 (3.33)	224 (5.19)		



Apiksaban – etkililik ve güvenlik – *önceden geçirilmiş inme*

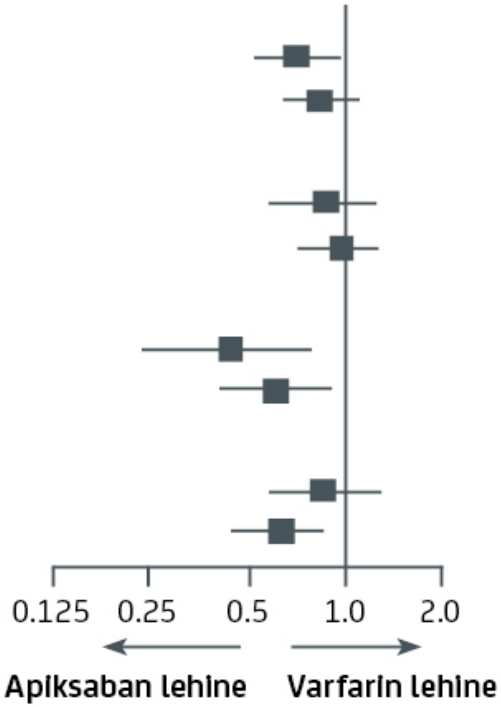
	Apiksaban (N=9120)	Varfarin (N=9081)	Etkileşim için P değeri
	%/yıl (olay sayısı)		
İnme / SE			0.71
Geçirilmiş inme veya GİA	2.46 (73)	3.24 (98)	
Geçirilmiş inme veya GİA yok	1.01 (139)	1.23 (167)	
Herhangi nedenli ölüm			0.89
Geçirilmiş inme veya GİA	4.22 (129)	4.77 (150)	
Geçirilmiş inme veya GİA yok	3.37 (474)	3.75 (519)	
Kardiyovasküler ölüm			0.53
Geçirilmiş inme veya GİA	2.35 (72)	2.41 (76)	
Geçirilmiş inme veya GİA yok	1.68 (236)	1.94 (268)	



Easton et al. Lancet Neurol 2012;11:503-11' den uyarlanmıştır.

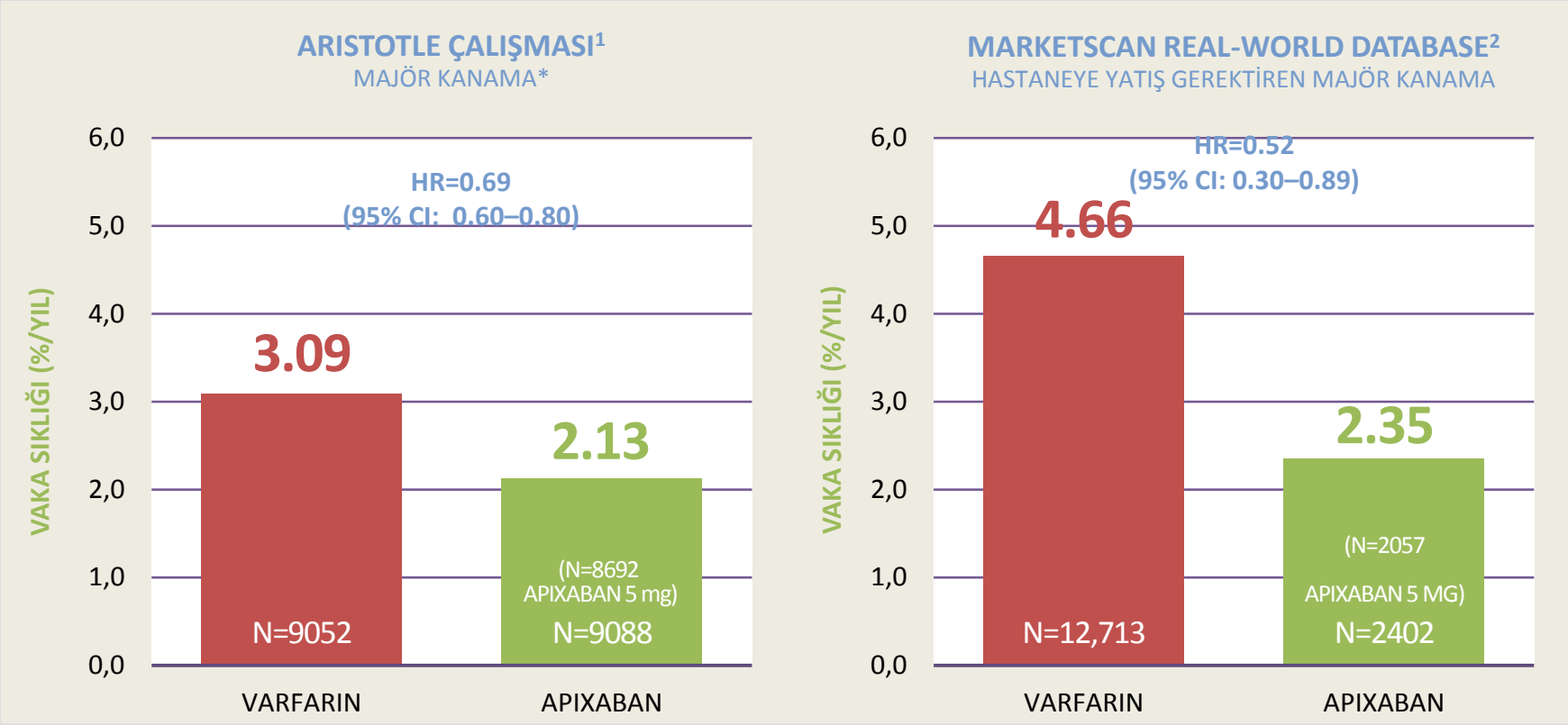
Apiksaban – etkililik ve güvenlik – *önceden geçirilmiş inme*

	Apiksaban (N=9120)	Varfarin (N=9081)	Etkileşim için P değeri
	%/yıl (olay sayısı)		
Tüm inmeler			0.40
Geçirilmiş inme veya GIA	2.26 (67)	3.17 (96)	
Geçirilmiş inme veya GIA yok	0.96 (132)	1.14 (154)	
İstemik veya bilinmeyen tip			0.61
Geçirilmiş inme veya GIA	1.92 (57)	2.23 (68)	
Geçirilmiş inme veya GIA yok	0.76 (105)	0.79 (107)	
Hemorajik			0.35
Geçirilmiş inme veya GIA	0.40 (12)	1.00 (31)	
Geçirilmiş inme veya GIA yok	0.20 (28)	0.34 (47)	
Sakat bırakan veya ölümcül			0.18
Geçirilmiş inme veya GIA	1.31 (39)	1.49 (46)	
Geçirilmiş inme veya GIA yok	0.33 (46)	0.56 (76)	



Easton et al. Lancet Neurol 2012;11:503-11' den uyarlanmıştır.

NVAF Hastalarında İlk Majör Kanama Riski:
Apixaban vs Varfarin



Adapted from ESC Poster, Lip et al, 2015

RCT ve Gerçek-yaşam analizleri referans karakteristikleri, bitiş noktaları ve metodoloji arasındaki önemli farkları göstermektedir. Sonuçlar direkt karşılaştırılamaz

The definition of major bleeding in clinical trials was different than in the real-world data initiative

*Clinically overt bleeding accompanied by a decrease in the haemoglobin level of at least 2 g/dL or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death

CI, confidence interval; HR, hazard ratio; NVAF, non-valvular atrial fibrillation; RCT, randomized clinical trial; RWD, real world data

1. Granger et al. N Engl J Med. 2011;365:981–992; 2. Lip GYH et al. ESC 2015, London, UK. Poster P6217, ESC 2015. Accessible on congress365.escardio.org

Erkek hasta	Sol ventrikül hipertrofisi, Sol atriyum dilate, Normal EF
Ağırlık: 100 kg	TİA öyküsü, Geçmiş AF öyküsü
Kan basıncı: 150/100 mmHg	'PAROKSİSMAL AF' ???
Kalp hızı normal /Ritim sinüs	66 yaşında

- Anti HT tedavi
  - ARB
  - Kalsiyum antagonisti
- Apiksaban 5 mg 2x1
- Toplam risk yönetimi
  - Etkin KB kontrolu
  - Egzersiz
  - Kilo kontrolu

Atrial Fibrillation
Oral Anticoagulation Card

for non-vitamin K antagonist anticoagulants (NOACs)

Patient name: **DOB:**

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication and start date:

? Concomitant antiplatelet(s): type, indication, start & stop dates:

Name and address of physician, coordinating NOAC treatment:

Telephone number of coordinating physician or clinic:

EUROPEAN Heart Rhythm ASSOCIATION

EUROPEAN SOCIETY OF CARDIOLOGY®

More info:
www.NOACforAF.eu
www.noacforaf.eu

Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; pharmacist; ...):	To do / findings:

Recommended follow-up

(see EHRA at **www.NOACforAF.eu** for information & practical advice)

Check each visit:
1. **Adherence (pt. should bring remaining meds)?**
2. **Thrombo-embolic events?**
3. **Bleeding events?**
4. **Other side effects?**
5. **Co-medications and over-the-counter drugs.**

Blood sampling:
- **monitoring of anticoagulation level is not required!**
- **yearly:** Hb, renal and liver function
- **if >75-80 y (especially if dabigatran or edoxaban), or frail:** 6-monthly renal function
- **if CrCl ≤ 60 ml/min:** recheck interval in months = CrCl / 10
- **if intercurrent condition that may have impact:** renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!

Never stop your medicine without consulting your physician.

Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.

Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

Name:	Dose:

Emergency information

Standard tests do not quantitatively reflect level of anticoagulation!

Name & telephone of patient relative to contact: