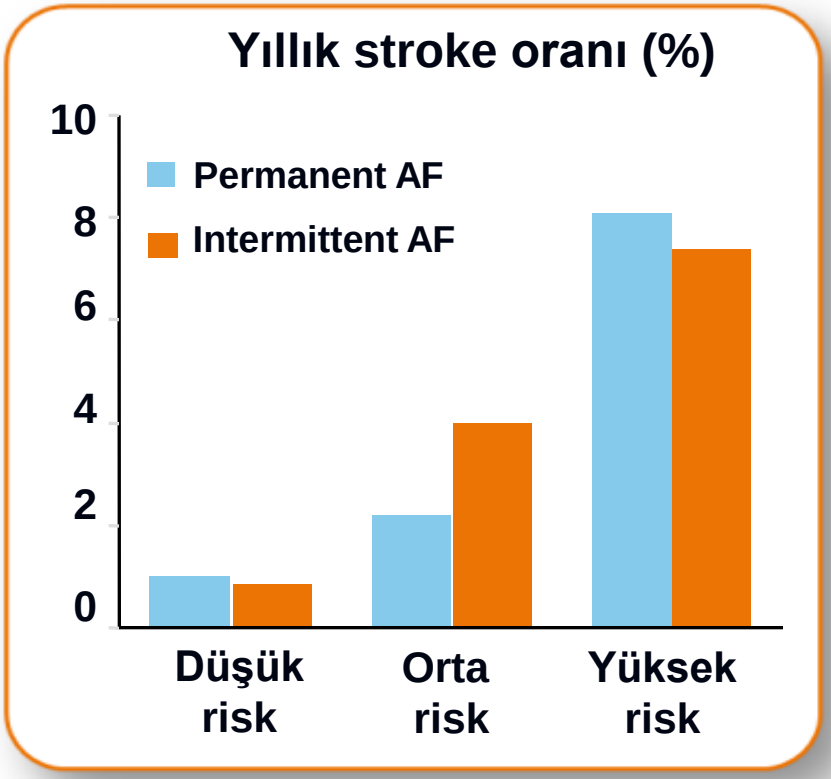
3. Atriyal Fibrilasyon Zirvesi 2014, Antalya

Yeni Oral Antikoagülanlar ile Gerçek Dünya Verileri

Dr. Ahmet Kaya Bilge

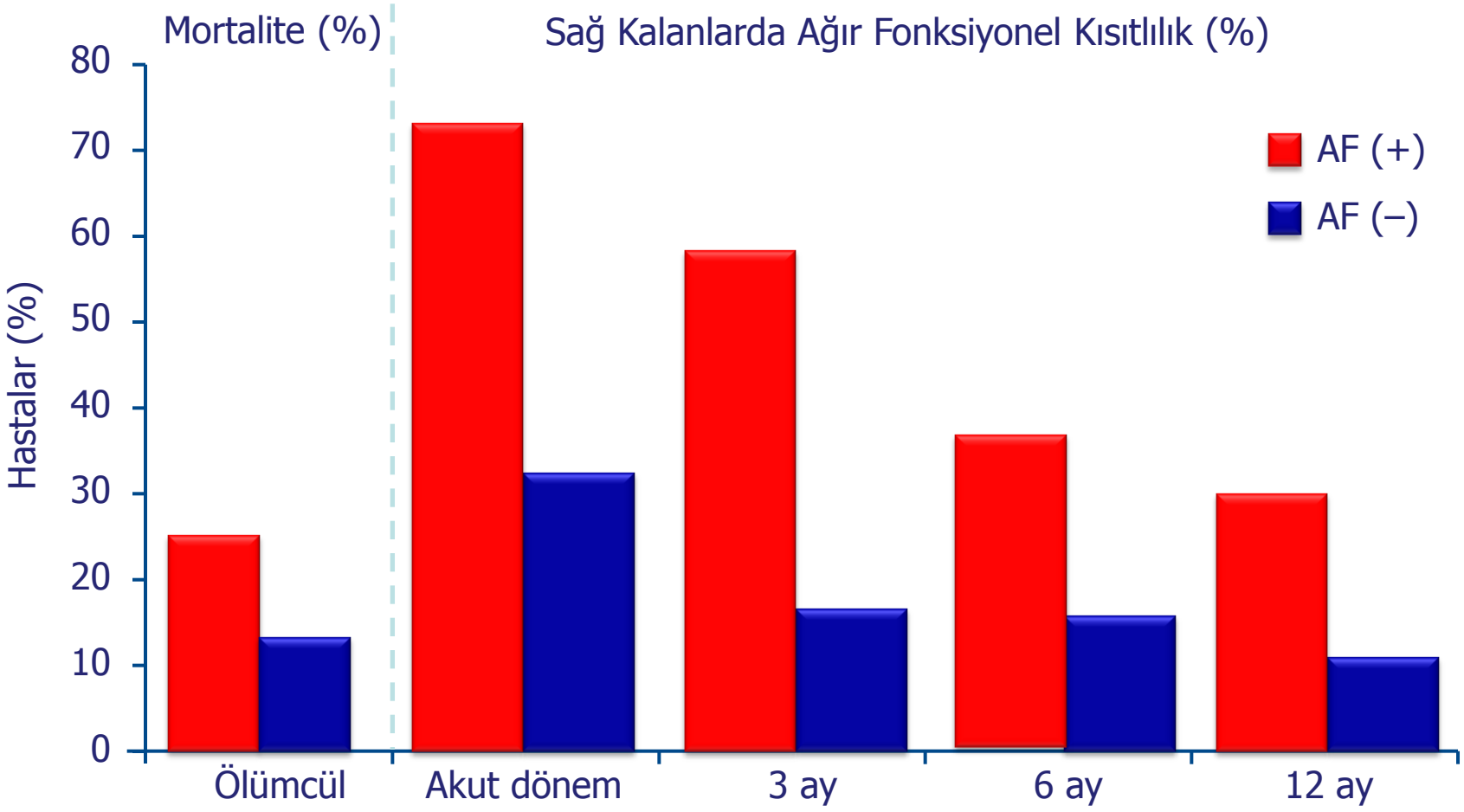
Stroke AF'nin en sık görülen ve sakat bırakıcı komplikasyonudur.

- AF'li hastalarda tüm-nedenlere bağlı stroke'un yıllık insidensi %5'dir[1]
- Stroke için bağımsız bir risk faktörüdür[2]
  - AF stroke riskini ~5-kat arttırır[2]
  - ABD'deki tüm stroke'ların ~1/3'nün nedeni AF'dir. [1]
  - Stroke riski yaşla artar[1]
- Stroke riski asemptomatik AF'de bile devam eder[3]



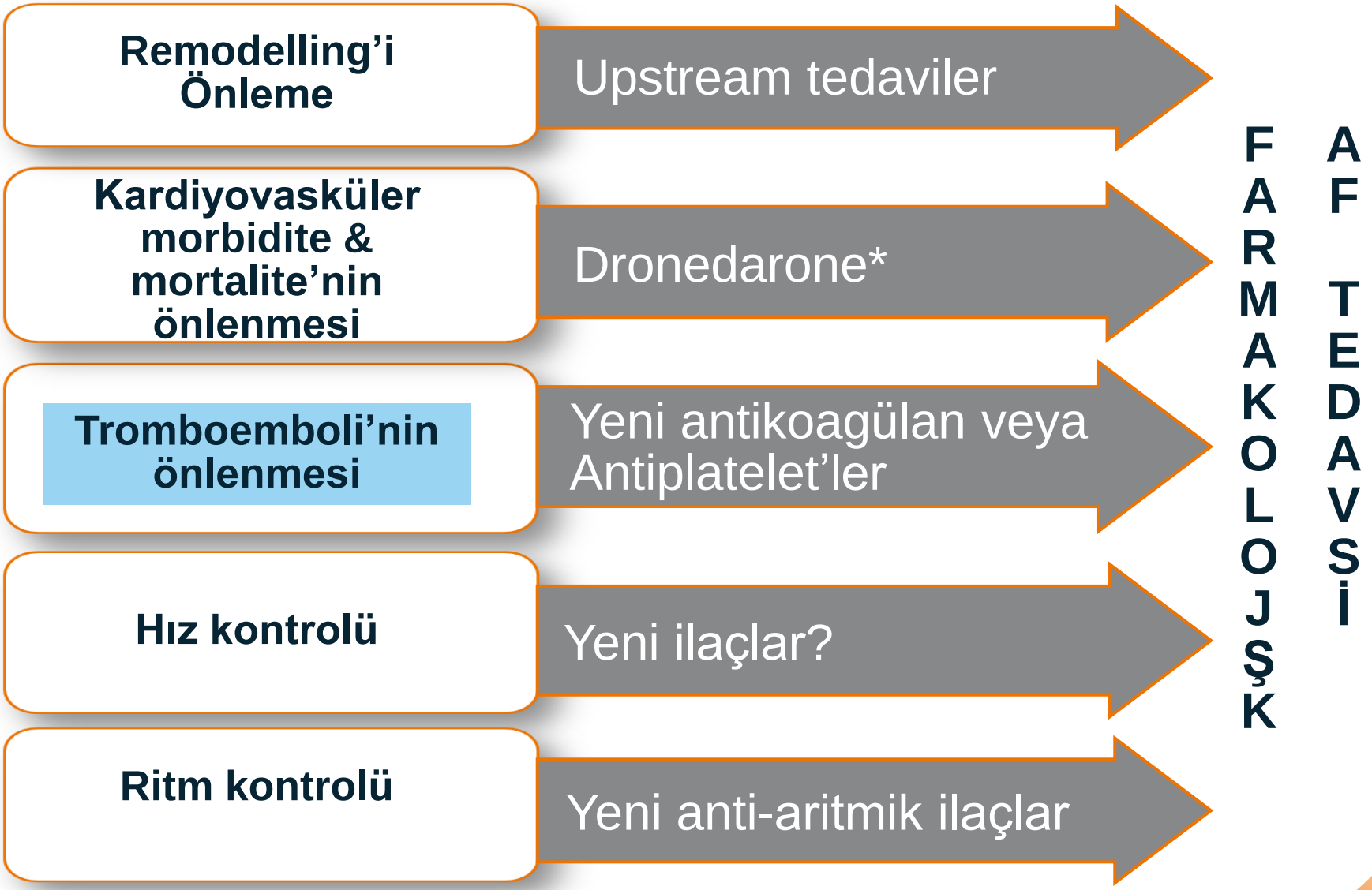
1. Fuster V, et al. *Circulation* 2006;114:e257-e354.
2. Wolf PA, et al. *Stroke* 1991;22:983-8.
3. Page RL, et al. *Circulation* 2003;107:1141-5.
4. Hart RG, et al. *J Am Coll Cardiol* 2000;35:183-7.

AF'ye bağlı inmenin mortalitesi ve morbiditesi daha yüksektir



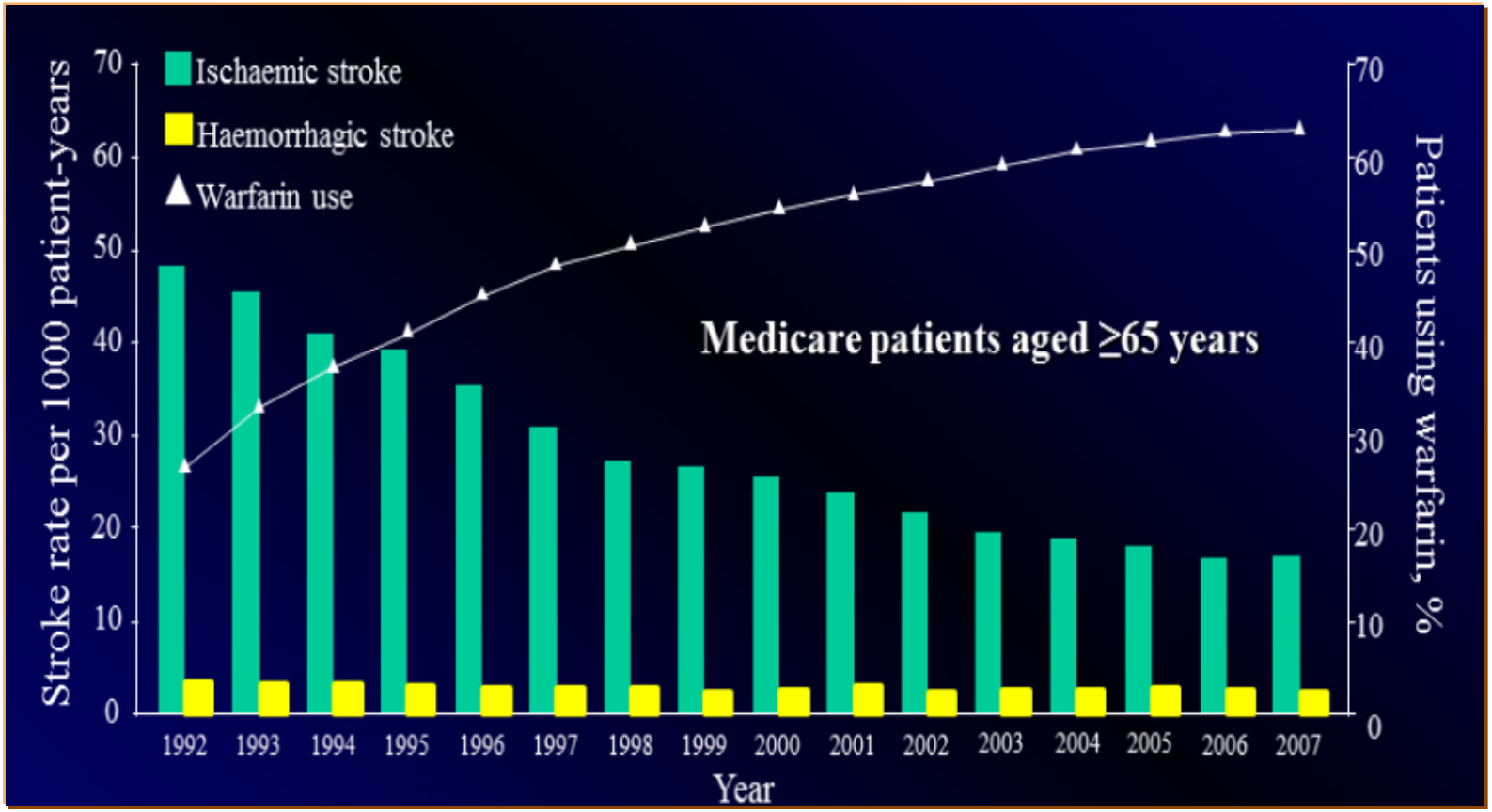
Lin HJ, et al. Stroke 1996;27:1760–4

AF'de yeni tedavi amaçları



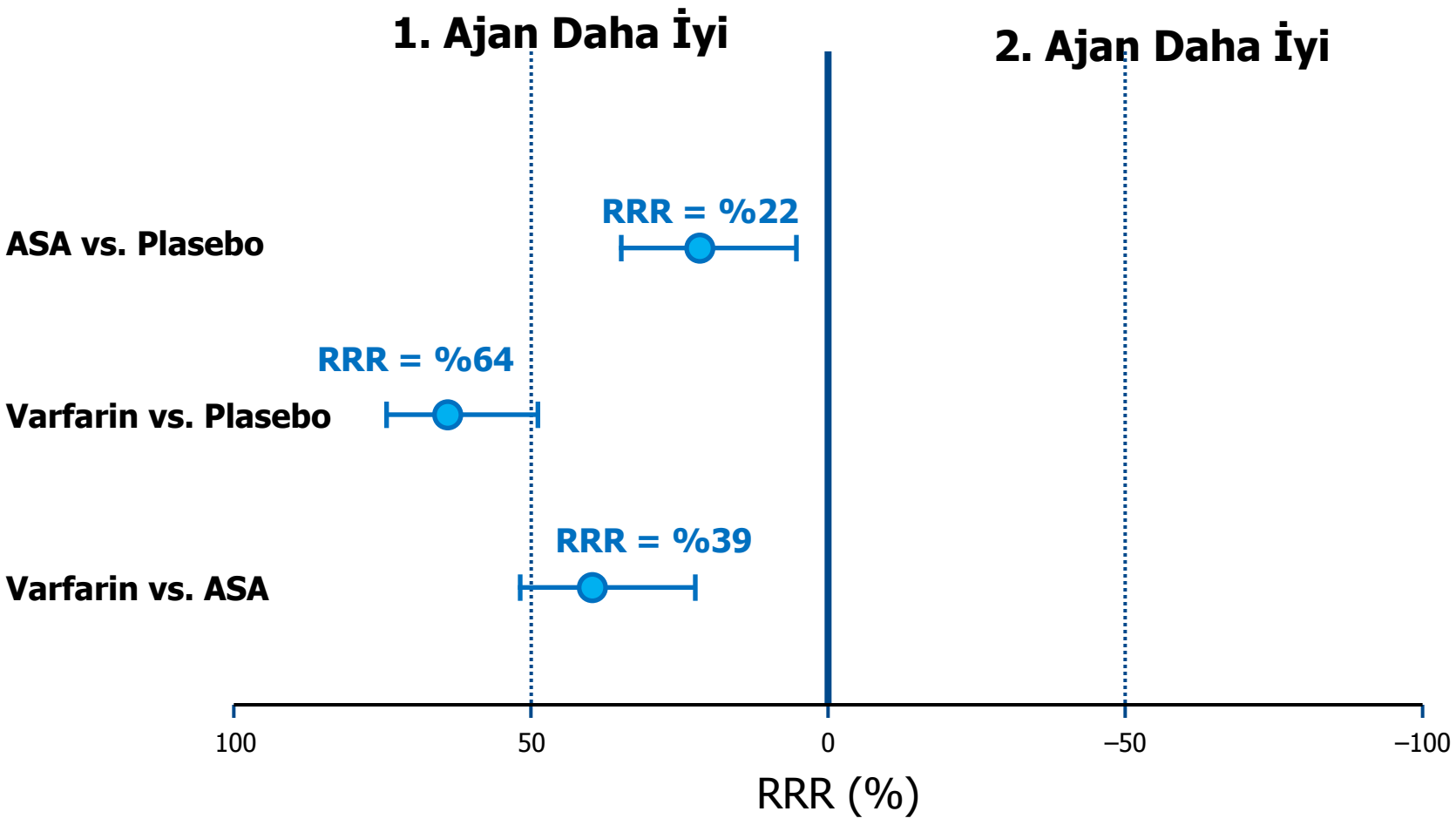
*on top of standard therapies (antihypertensives, antithrombotics, etc)

AF olan Medicare hastalarında iskemik inme ve antikoagülan tedavi eğilimleri: 15 yıllık perspektif (1992-2007)



Shroff et al. Arch Intern Med 2013;173:159-160

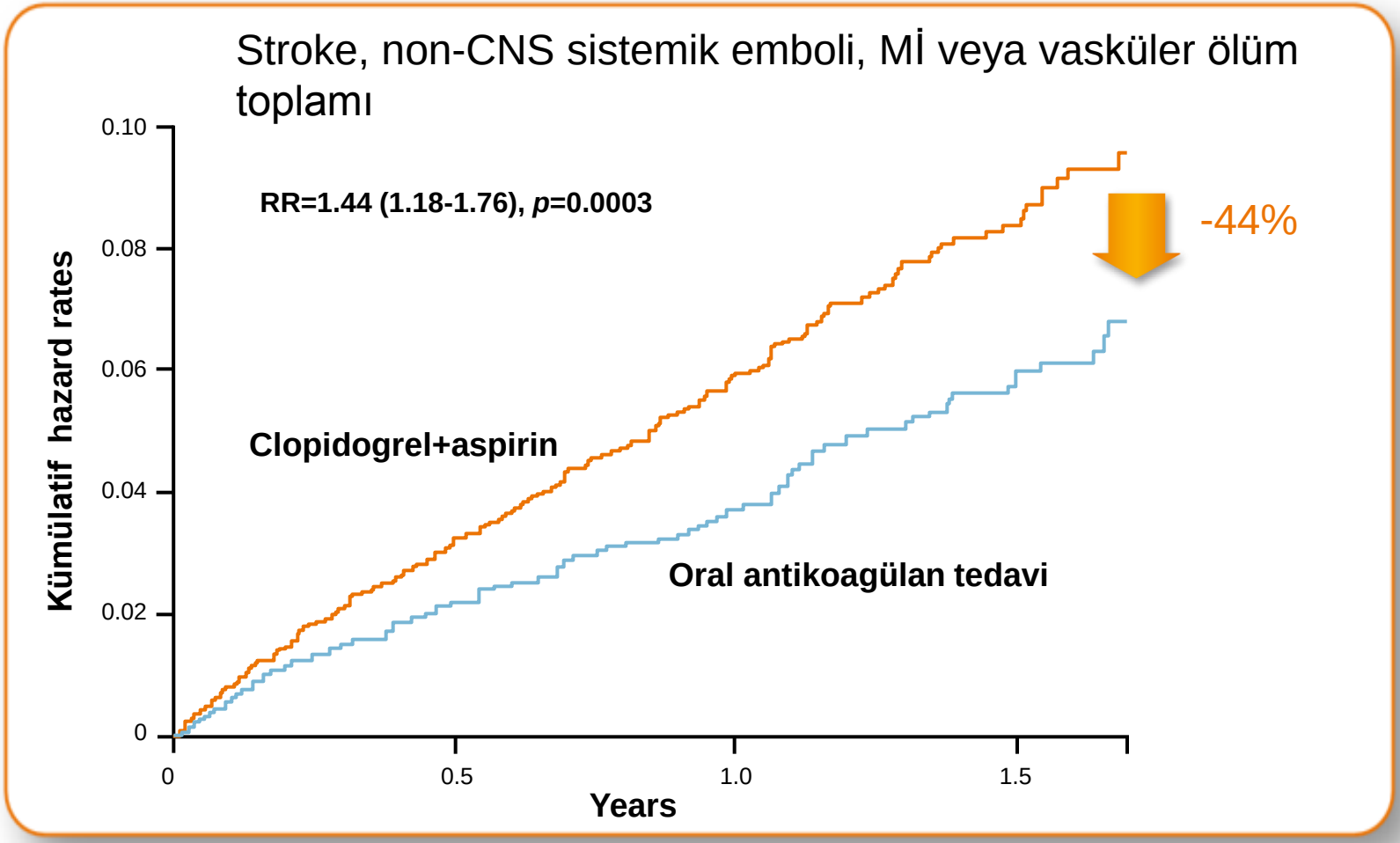
AF inmenin önlenmesinde antitrombotik tedavi



Hart RG, et al. Ann Intern Med 2007;146:857-67.

ACTIVE W
OAK'nin Önleyici Üstünlüğü (primer sonlanma)

Median 1.28 yıl takip sonunda erken sonlandırıldı.



ACTIVE Writing Group of the ACTIVE Investigators. Lancet 2006;367:1903-12

VKA tedavisinin dezavantajları

- Doz-yanıt bakımından hastalar arası ve bireysel önemli değişkenlik
  - Komorbid durumlar
  - Genetik polimorfizmler
  - Gıda ve eşzamanlı ilaçlarla çok sayıda etkileşim
  - Öngörülemeyen farmakoloji
- Dar terapötik aralık
- Yetersiz kullanım
  - Özellikle olası faydalar karşısında yüksek kanama riski öngörülen yaşlı hastalarda

1. Ansell J *et al*. *Chest* 2008;133:160S–198S; 2. Nieuwlaat R *et al*. *Am Heart J* 2007;153:1006–1012;
3. Ogilvie IM *et al*. *Am J Med* 2010;123:638–645; 4. Nieuwlaat R *et al*. *Eur Heart J* 2005;26:2422–2434;
5. Waldo A *et al*. *J Am Coll Cardiol* 2005;46:1729–1736

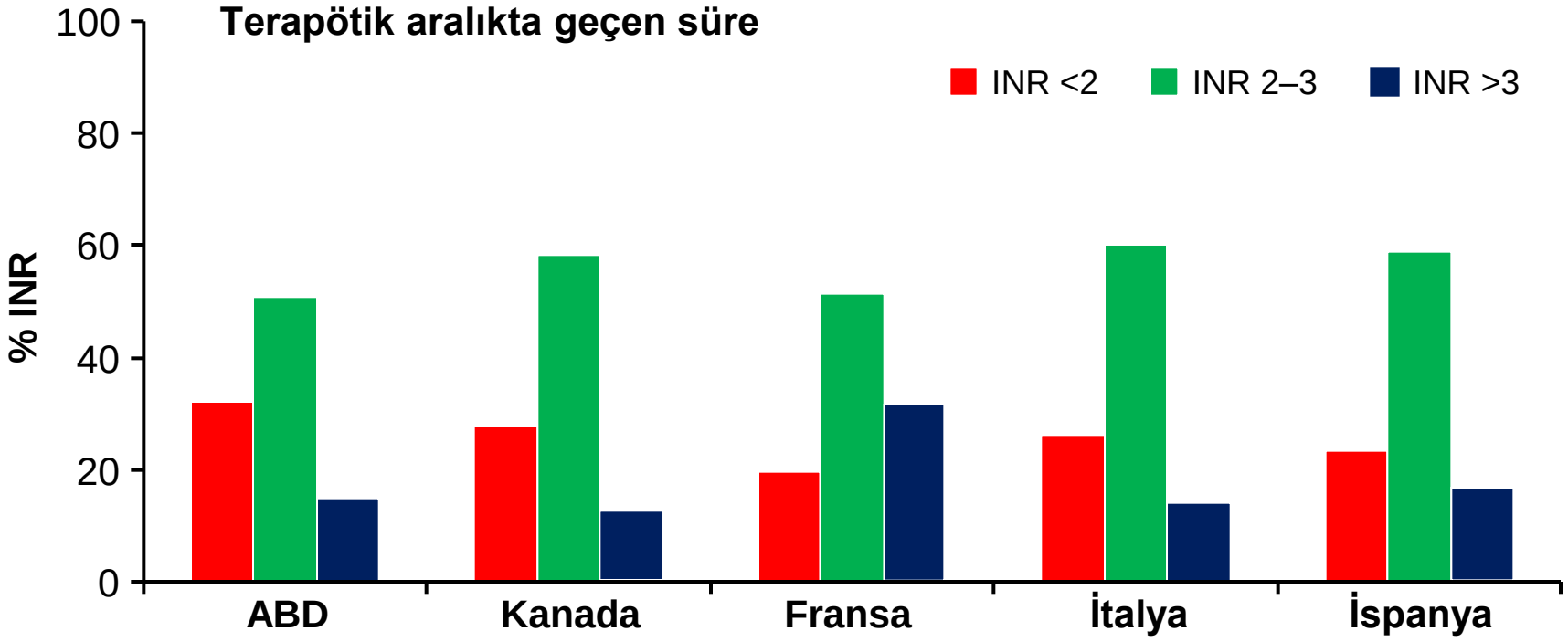
Kanada İnme Ağı Kaydı verileri

- İnme nedeniyle hastaneye yatan ve yüksek inme riski olan AF hastaları (n=537) belirlenmiştir
- Hastaların %70'inden fazlasına antitrombotik tedavi reçete edilmiştir:
  - Yalnızca %40'ı varfarin almıştır
  - Yalnızca %10'u Warfarin terapötik aralığında olmuştur

Gladstone D *et al*. *Stroke* 2009;40:235–240

Rutin uygulamada INR kontrolü

Retrospektif, çok merkezli kohort çalışması



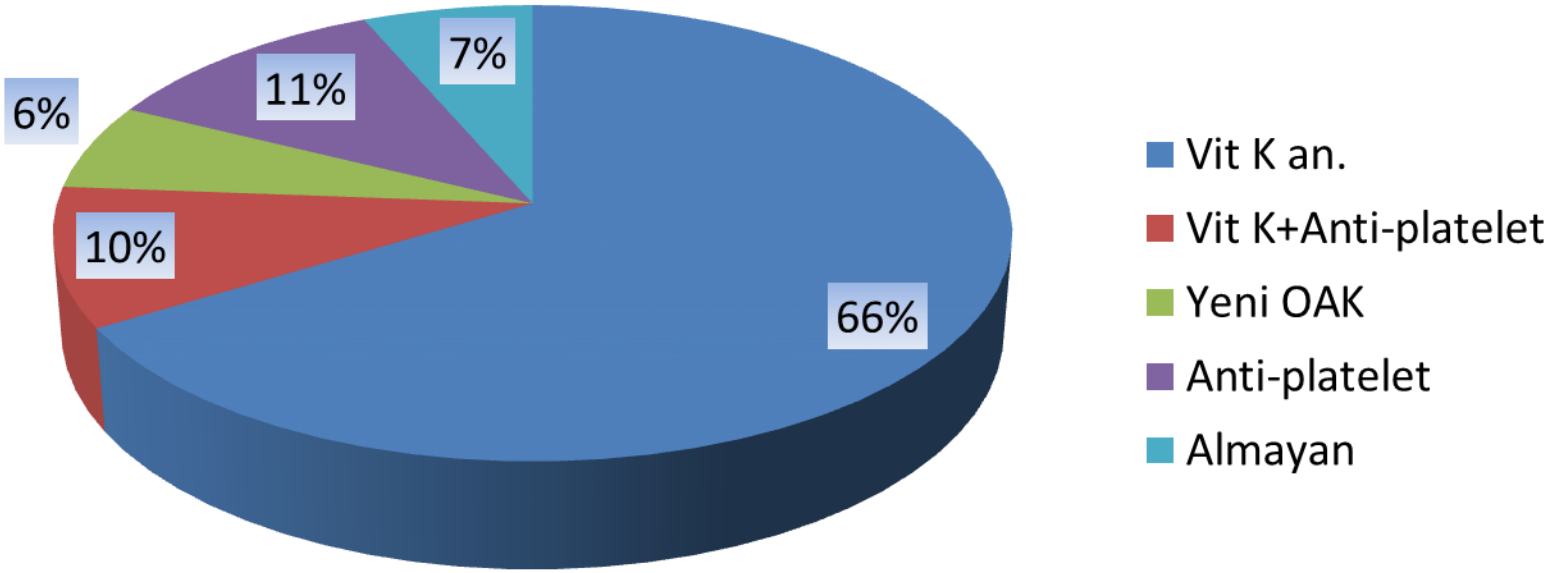
Ansell J *et al*. *J Thromb Thrombolysis* 2007;23:83–91

Atriyal Fibrilasyon

ESC 2010 kılavuz sonrası; PREFER in AF

7 Avrupa ülkesi, 461 merkez, N: 7232 hasta

Yaş: 71.5±11,% 60 erkek; CH_2DS_2VASc skor: 3.4±1.8

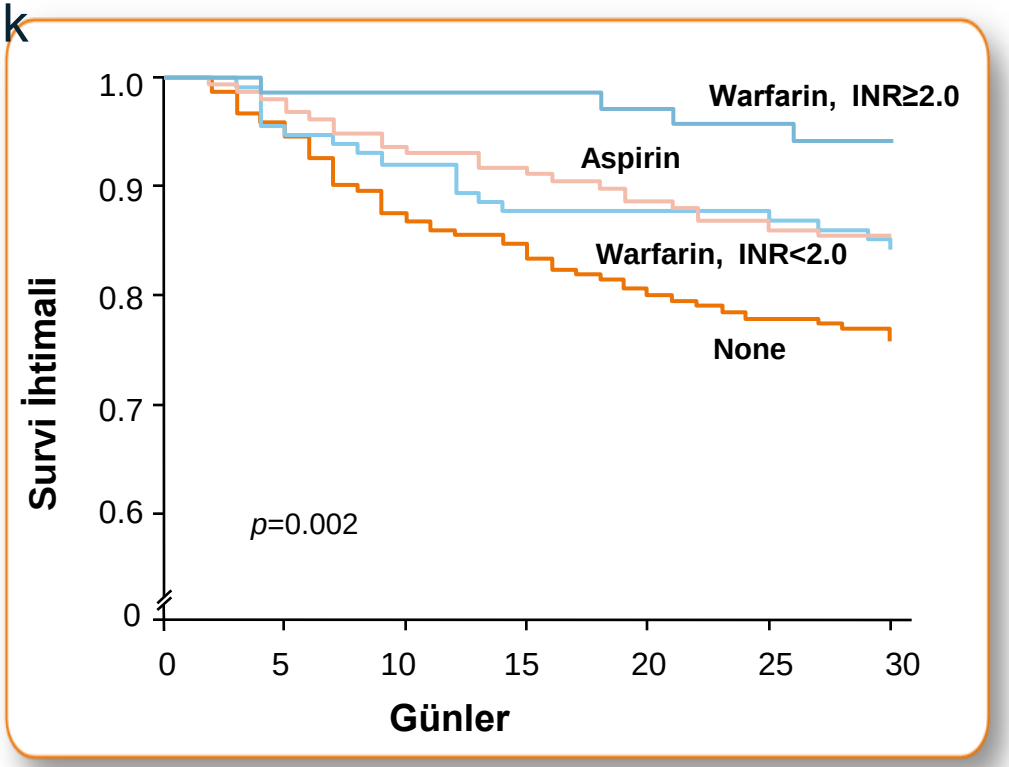


Yaş: 71.5±11,% 60 erkek; CH2DS2VASc skor: 3.4±1.8

2013

Uygun Oral Antikoagülan Tedavisi Stroke Nedeniyle Ölüm Riskini Azaltır

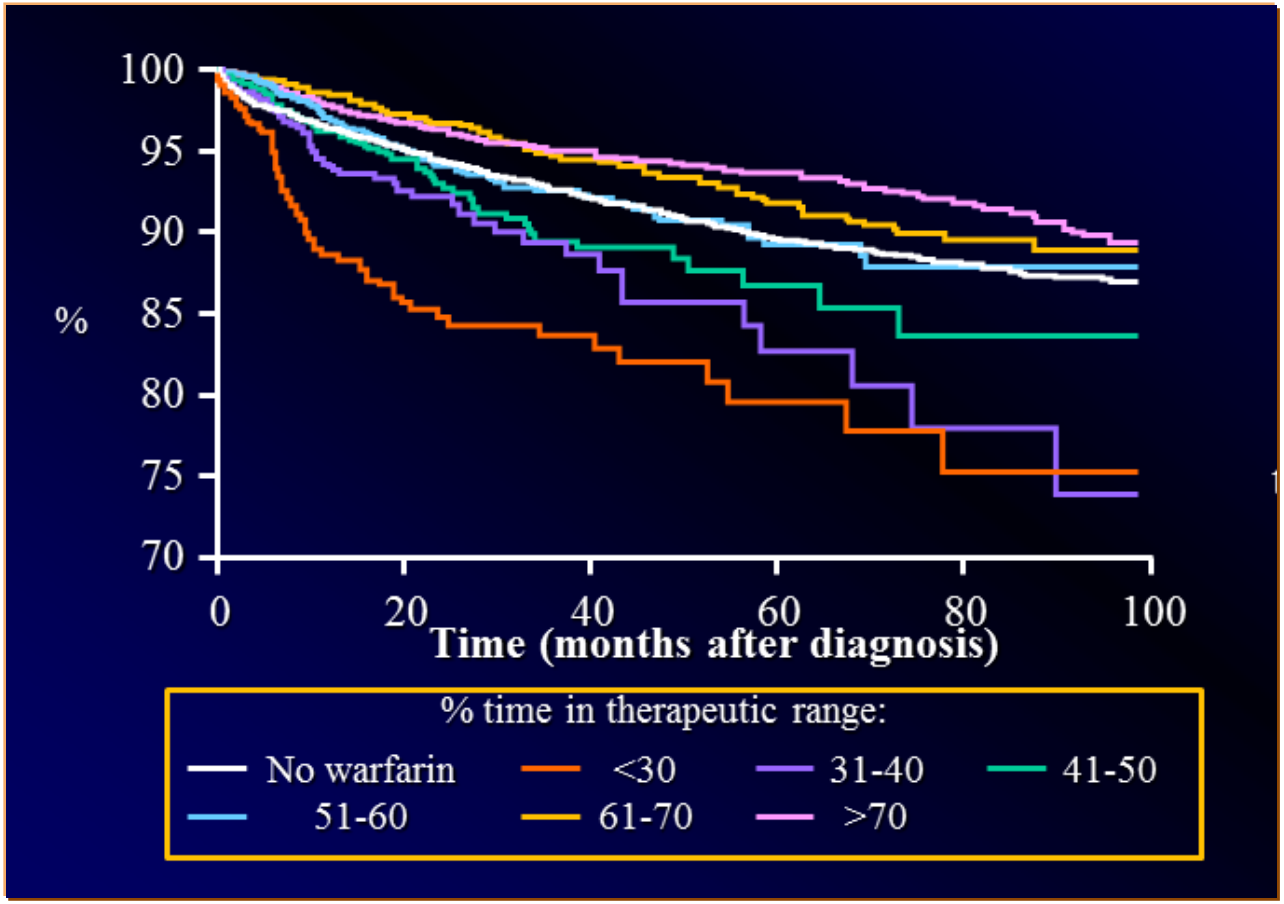
- Cohort çalışma: Non-valvular AF'li 13.559 hasta (596'si iskemik stroke'lu)
- Warfarin alanlar karşılaştırıldığında, iskemik stroke'dan sonraki 30-günlük mortalite riski INR <2.0 olanlarda, INR ≥2.0 olanlara nispeten aşikar yüksek



INR: international normalised ratio;
OAC: oral antikoagülan

Hylek EM, et al. N Engl J Med 2003;349:1019-26

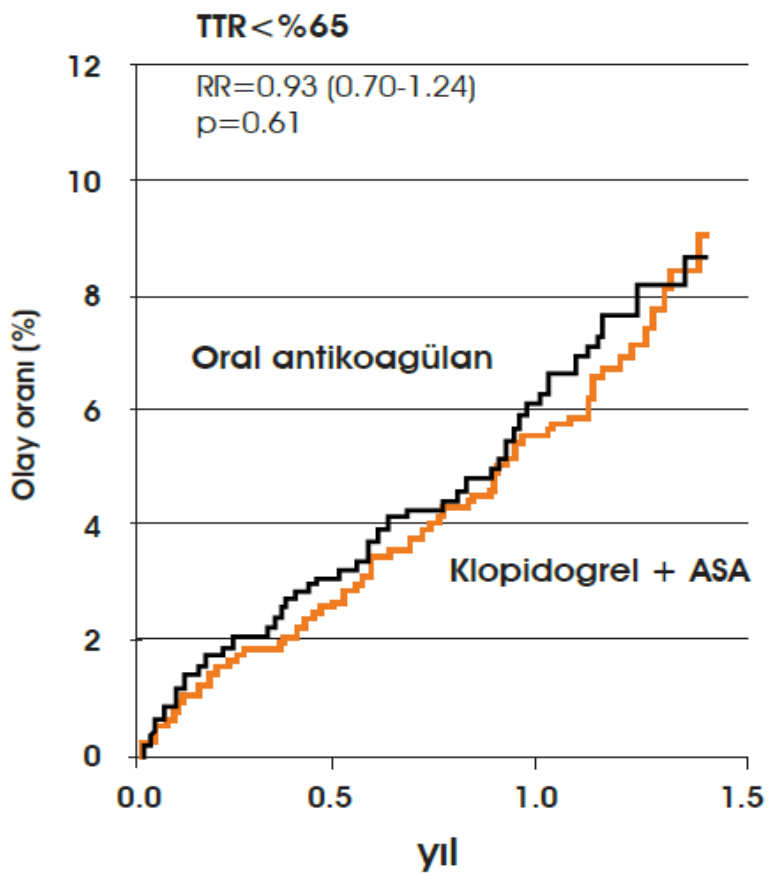
Suboptimal antikoagulasyon inme ve mortalite ile ilişkilidir

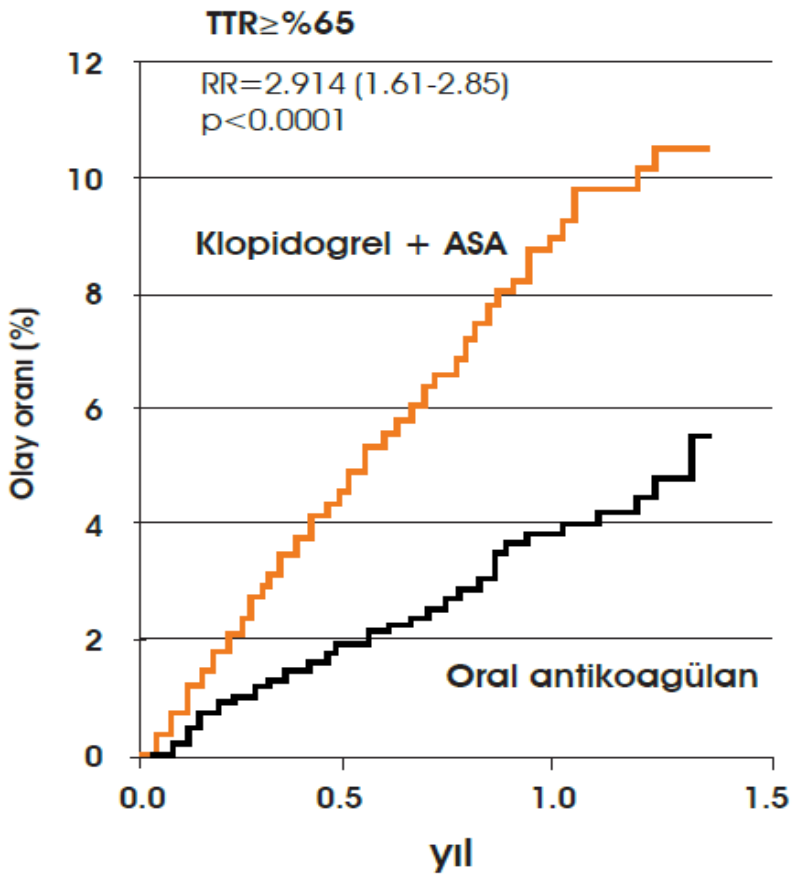


TTR >%70 olan hastalarda inme riski TTR<%30 olanlara göre %79 daha azdır

Gallagher et al. Thromb Haemost 2011

Terapötik aralıkta geçen süre neden önemli? ACTIVE-W çalışması





Klopidogrel + ASA	1598	1527	1156	439
Oral Antikoagülan	1600	1525	1152	417

1737	1625	1233	488
1771	1697	1306	507

Şekil 1: TTR oranı medyan (%65) değerin altında ve üstünde olan merkezlerde tedavi edilen hastaların İnme, miyokard enfarktüsü, sistemik embolizim ve vasküler ölüm açısından kümülatif risk oranları. RR: Rölatif Risk, C+A: Klopidogrel ve Aspirin

Circulation. 2008;118:2029-2037; originally published online October 27, 2008.

Türkiye AF epidemiyolojisi; çok merkezli AFTER çalışması ön sonuçları

Warfarin	1115	49.7
Acetylsalicylic acid	1183	52.7
Clopidogrel	134	6
Ticlopidine	12	0.5
ACE-I	723	32.2
ARB	427	19.0
Beta-blockers	1316	58.7
Non-dihydropyridine CCB	355	15.8
Dihydropyridine CCB	171	7.6
Digoxin	622	27.7
Diuretics	1047	46.7
Statins	318	14.2
Alfa-blockers	40	1.8
Nitrates	65	2.9
Amiodarone	97	4.3
Propafenone	33	1.5

Türkiye AF epidemiyolojisi

	n	%	Mean±SD
Gender (Male / Female)	900 / 1342	40.1 / 59.9	
Age	2242		66.8±12.3
Age ≥75	669	29.8	
Body mass index	2227		27.8±5.3
Atrial fibrillation type			
Non-valvular	1745	77.8	
Valvular	497	22.2	
Prosthetic valve	280	12.5	
First attack	91	4.1	
Paroxysmal	328	14.6	
Persistent-permanent	1823	81.3	
Hypertension	1501	66.9	
Heart failure / LV dysfunction	641	28.6	
Type II diabetes mellitus	494	22	
Vascular disease	566	25.2	
Thyroid dysfunction	118	5.3	
Smoking	280	12.5	
Stroke / TIA / Thromboembolism	342	15.3	
Bleeding history	250	11.2	
Labile INR	252	11.2	
Effective INR	460	41.3	

Türk Kardiyol Dern Arş-Arch Turk Soc Cardiol 2013;41(2): 99-104

Türkiye AF epidemiyolojisi

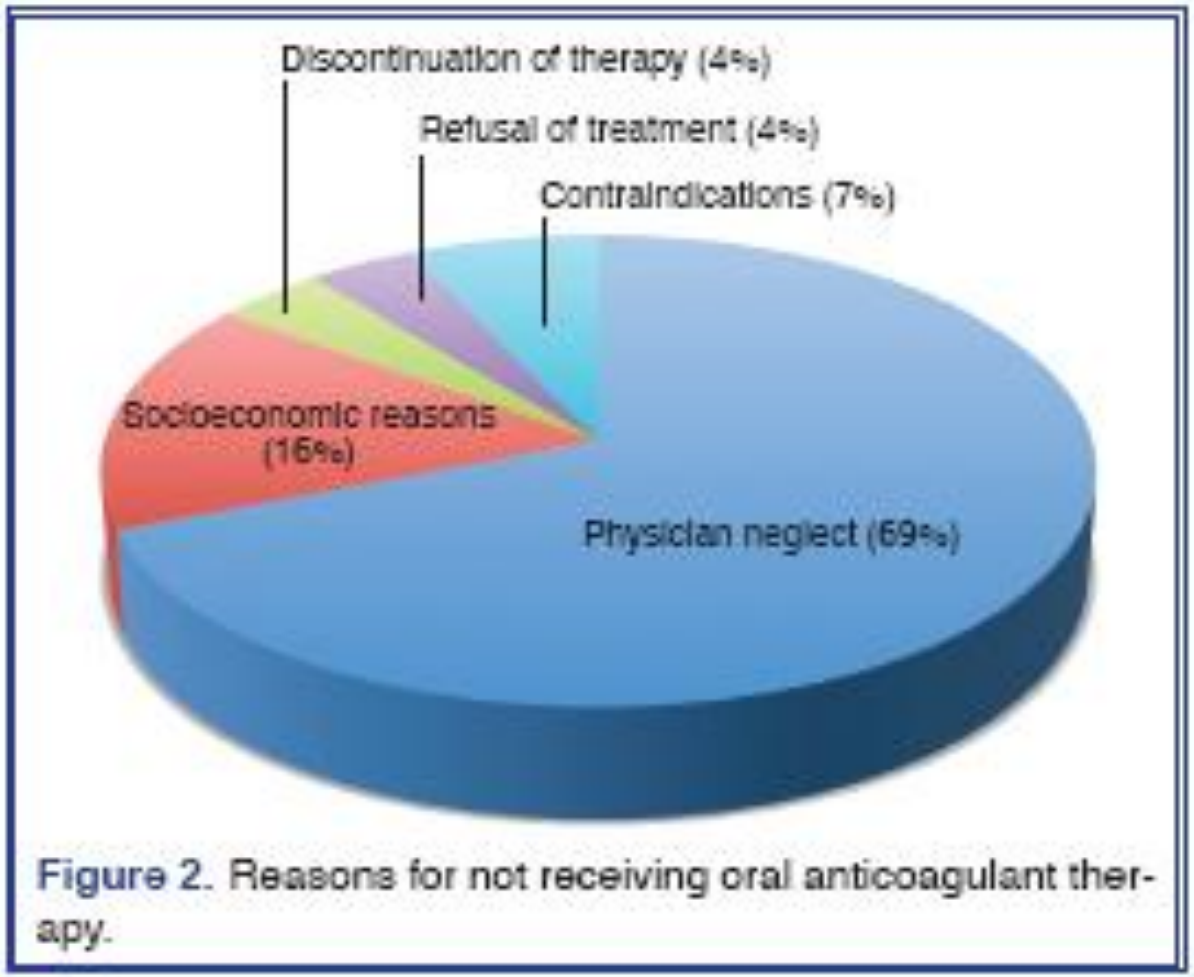


Figure 2. Reasons for not receiving oral anticoagulant therapy.

Türk Kardiyol Dern Arş-Arch Turk Soc Cardiol 2013;41(2): 99-104

Yeni oral antikoagülanlar

- Öngörülebilir farmakoloji
  - Gıda ve eşzamanlı ilaçlarla daha az sayıda etkileşim
  - Sabit dozlarda kullanım
  - Rutin koagülasyon takibi gerekliliği olmaması
- Daha iyi fayda-risk profili

Bauer KA. *Rev Neurol Dis* 2010;7:1–8; Turpie AG. *Eur Heart J* 2007;29:155–165; Weitz JI. *Thromb Haemost* 2010;103:62–70

Yeni Anti-trombotik Ajanlar

ESC 2012

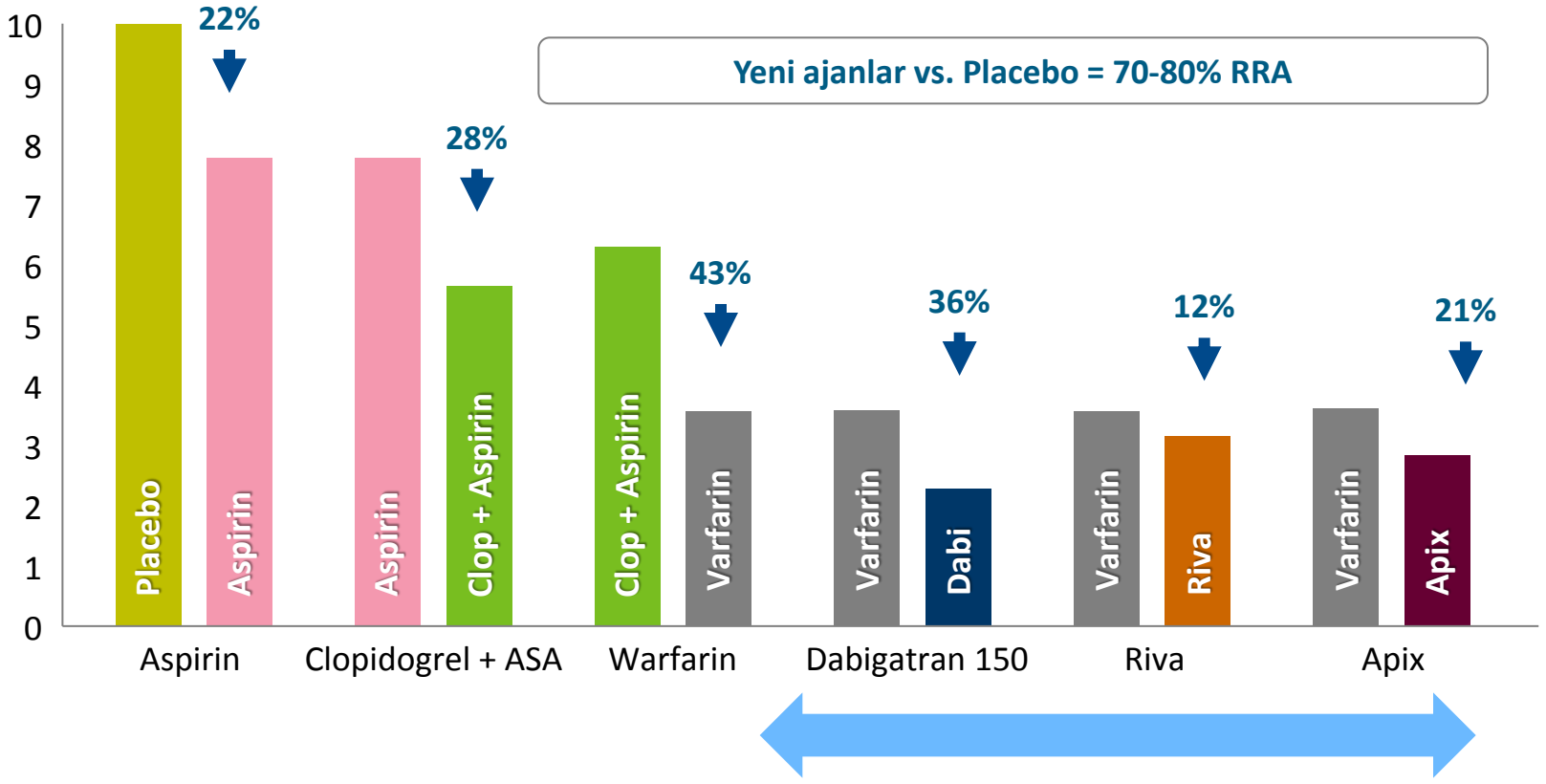
	Dabigatran	Rivaroxaban	Apixaban
Mekanizma	Oral direkt trombin inhibitörü	Oral direkt faktör Xa inhibitörü	Oral direkt faktör Xa inhibitörü
Biyoyararlılık	% 6	% 60-80	% 50
Pik düzeye ulaşma	3 saat	3 saat	3 saat
Yarılanma Ömrü	12-17 saat	5-13 saat	9-14 saat
Atılım	% 80 renal	2/3 karaciğer, 1/3 renal	% 25 renal, % 75 dışkı
Doz	2x150 mg/gün	1x20 mg/gün	2x5 mg/gün
Böbrek disfonksiyonunda doz	2x110 mg/gün	1x15 mg/gün	2x2.5 mg/gün

Yeni Anti-trombotik Ajanlar

ESC 2012

	Dabigatran RE-LY	Rivaroxaban ROCKET-AF	Apixaban (ARISTOTLE)
Çalışma düzeni	Randomize, açık	Randomize,çift kör	Randomize, çift kör
Hasta sayısı	18.111	14.264	18.201
Yaş ort.	71.5±8.7 yıl	73 (65-78 yaş)	70 (63-76 yaş)
Takip süresi	2 yıl	1.9 yıl	1.8 yıl
Erkek oranı	% 63.6	% 61.3	% 64.5
Ortalama $CHADS_2$	2.1	3.5	2.1
Gruplar	Doz ayarlı warfarin ile 2x150 ve 2x110 mg/gün dabigatran	Doz ayarlı warfarin ile 1x20 mg/gün rivaroxaban	Doz ayarlı warfarin ile 2x5 mg/gün

İnmeyi önleme gücü



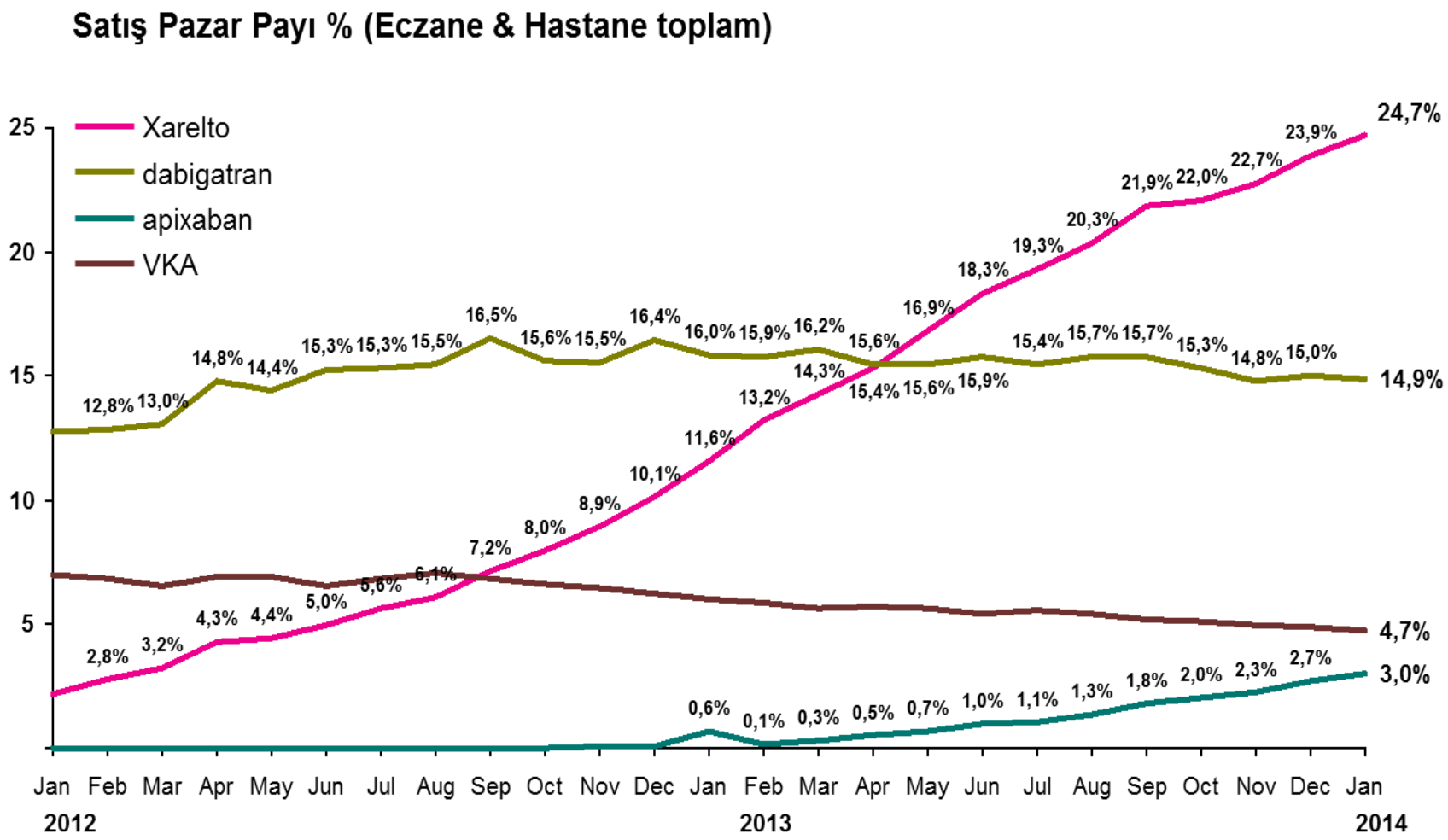
Reference: Granger et al. 2012; CIRCULATION; 125: 159-164

Yeni OAK'ların warfarin ile kıyaslanması: *RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF*

Effect on outcome event, *vs warfarin*	D150	D110	Riva	Apix	Edo60	Edo30
Noninferiority stroke/SE	√	√	√	√	√	√
Superiority for 1º endpoint of stroke/SE	√			√		
Reduction hemorrhagic stroke/ICH	√	√	√	√	√	√
Reduction ischemic stroke	√					(⇧)
Reduction all-cause mortality	(√)			√		√
Reduction in CV mortality	√				√	√
Reduction major bleeding		√		√	√	√
Reduced major & minor bleeds	√	√		√	√	√
Increased gastrointestinal bleeds	√		√		√	
Increased myocardial infarction	?	?				?

Connolly et al NEJM 2009; Patel et al NEJM 2011;Granger et al NEJM 2011; Giugliano et al NEJM 2013

2012-2014 OAK'ların pazar payları



Source: IMS MIDAS, Database: MonthlySales January 2014
AC market (B1A0 Vitamin K Antagonists, B1B1 Unfractionated Heparins, B1B2 LMWH, B1E Direct Thrombin Inhibitors without Bivalirudin, B1F Direct Factor Xa Inhibitors, B1X Other Antithrombotics without Dotrecogin alpha, Chuan Qing and all ligustrazine products)

Neden «Gerçek Dünya» verileri ?

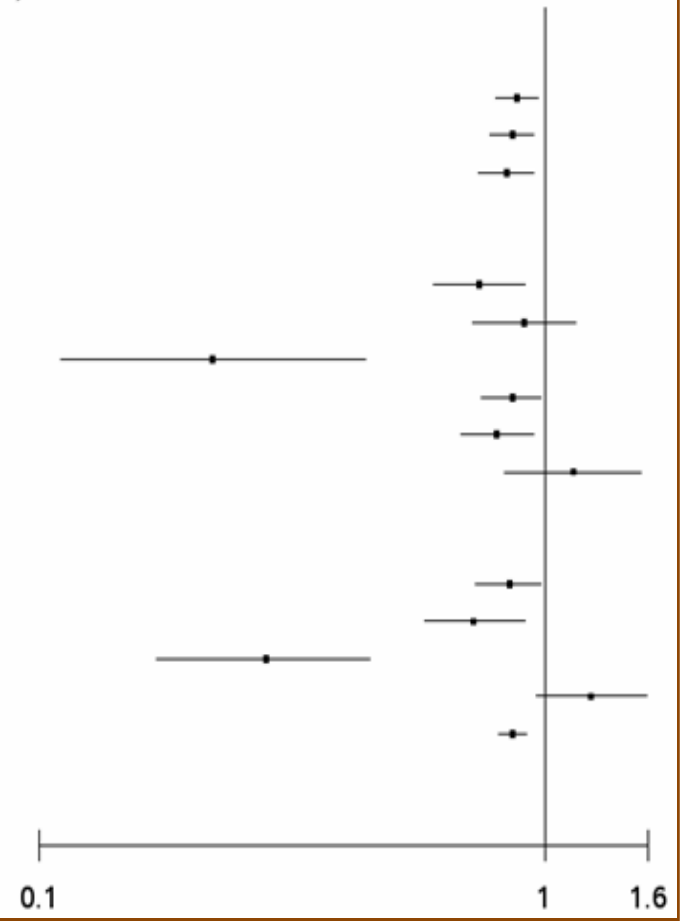
Faz III çalışmalar;

- Hastaların homejen gruplardan seçilmesi
- Dışlanma kriterlerinin fazla olması
- Çift kör uygulamada yan etki ihtimali yüksek olanlarda yüksek doz riski
- Kontrollü çalışmaların dizaynları her zaman hayat gerçekleri ile örtüşmeyebilir
- Cinsiyete özgü analizlerin eksikliği
- Yaş ve farklı ırklar ile ilgili bilgilerin yetersiz olması
- İlaça maruziyet süresinin kısıtlılığı
- Weber etkisi..

⟹ özellikle ilaç güvenlik profilinin ortaya konmasında Faz IV çalışmalar değerlidir

Dabigatran EU açık etiket sonuçları: RE-LY post-hoc analizi

Source	HR vs Warfarin (95% CI)
Efficacy & Safety combined endpoints (ITT)	
- NCB	0.88 (0.80,0.97)
- Stroke/Se, MBE, death	0.86 (0.78,0.95)
- Stroke/Se, MBE	0.84 (0.74,0.95)
Efficacy endpoints (ITT)	
- Primary: Stroke/SE	0.74 (0.60,0.91)
- Ischemic stroke	0.91 (0.72,1.15)
- Hemorrhagic stroke	0.22 (0.11,0.44)
- Death	0.86 (0.75,0.98)
- Vascular death	0.80 (0.68,0.95)
- MI	1.14 (0.83,1.55)
Safety endpoints (safety)	
- MBE	0.85 (0.73,0.98)
- Life-threatening MBE	0.72 (0.58,0.91)
- ICH	0.28 (0.17,0.45)
- GI MBE	1.23 (0.96,1.59)
- Any bleeds	0.86 (0.81,0.92)



Summary of results for dabigatran EU label simulated dabigatran treatment group compared to warfarin.

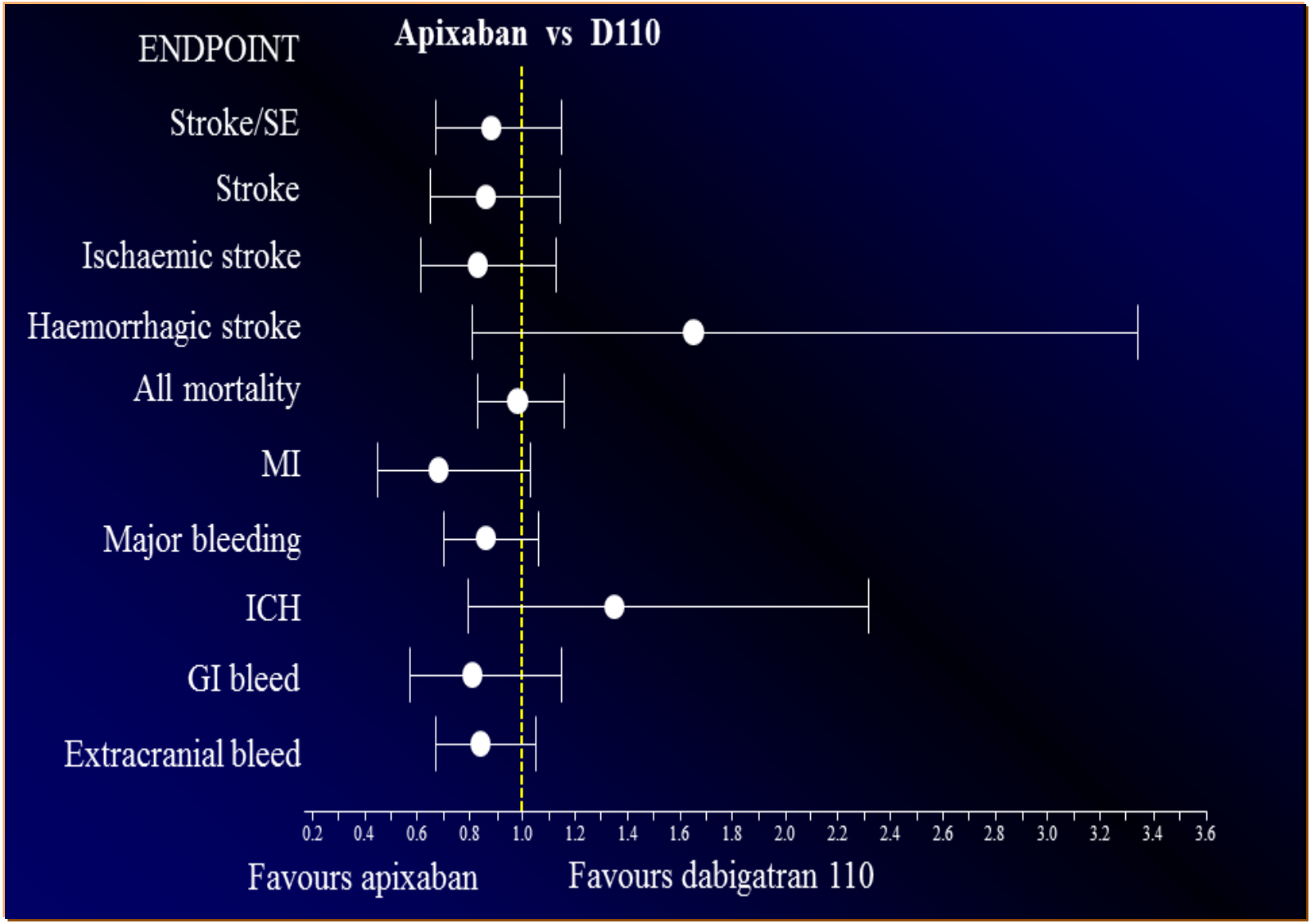
Dabigatran (n=6004); <80 y, HAS-BLED <3, verapamil(-) → *D150 mg değilse D110 mg*
Warfarin (n=6022)

Lip et al Thromb Haemostat 2014

Dabigatran vs Rivaroxaban indirekt kıyaslanması

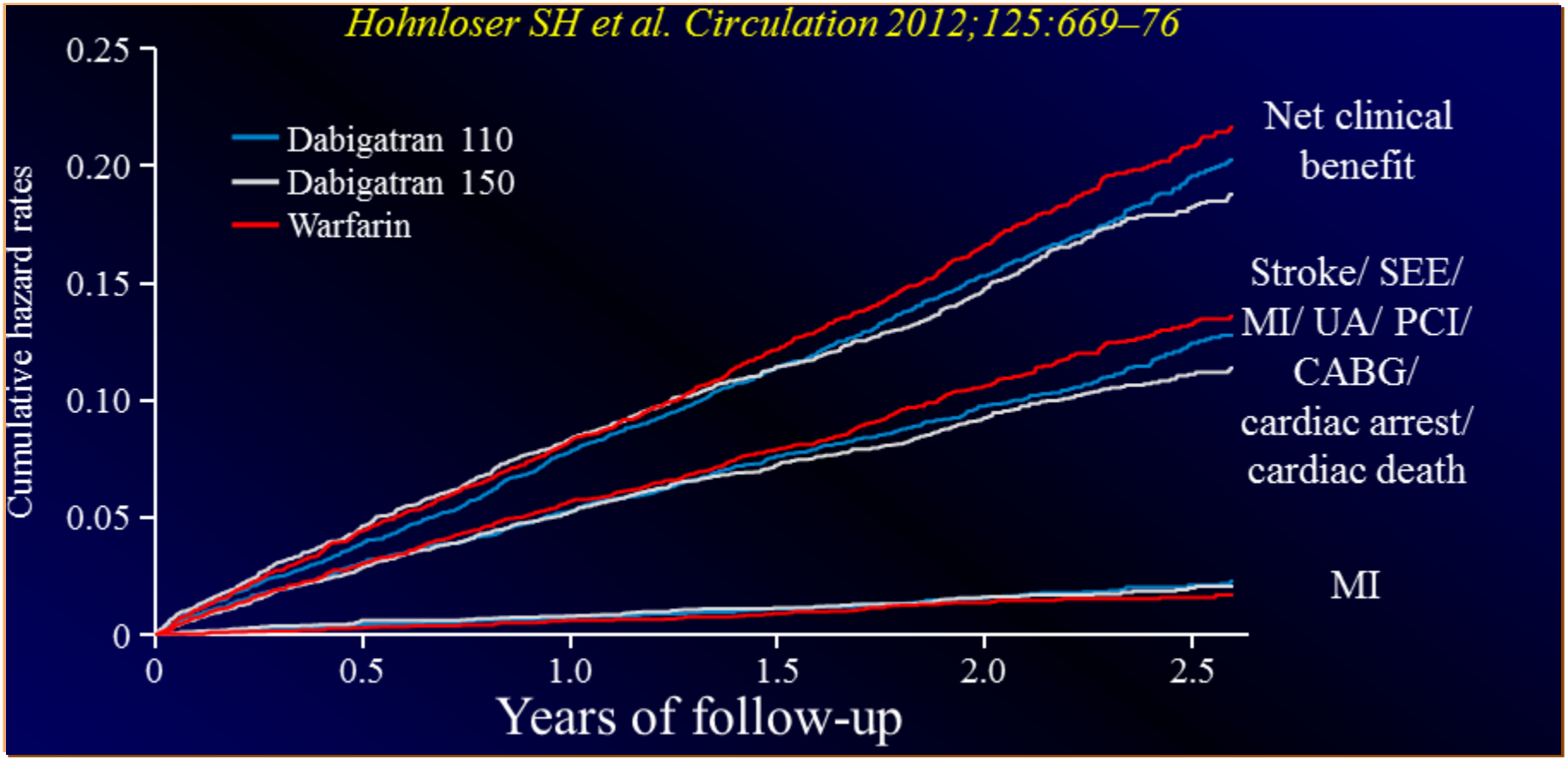
	Stroke/systemic embolism (primary endpoint)	All-cause mortality	AMI	Major bleeding	ICH	Reported type of estimate	Type of comparison
Dabigatran 150 mg bid vs. Rivaroxaban							
Kansal et al.	0.74 (0.56, 0.97)[1]	0.96 (0.80, 1.14)[1]	1.40 (0.95, 2.05)[1]	0.92 (0.75, 1.13)[2]	0.48 (0.27, 0.84)[2]	Hazard ratio	Indirect comparison
CADTH	0.74 (0.56–0.97)[1]	0.95 (0.79–1.14)[1]	1.59 (1.08–2.38)[4]	0.91 (0.74–1.11)[4]	0.63 (0.38–1.05)[4]	Odds ratio	Bayesian MTC (fixed effects)
Lip et al.	0.74 (0.56–0.97)[1]	1.04 (0.82–1.30)[4]	1.57 (1.05–2.33)[4]	0.89 (0.73–1.09)[4]	0.60 (0.35–1.01)[4,5]	Hazard ratio	Indirect comparison
Mantha and Ansell	0.74 (0.56–0.98)[1]	0.96 (0.81–1.15)[1]	1.61 (1.08–2.38)[4]	0.91 (0.75–1.11)[4]	0.63 (0.38–1.06)[4]	Odds ratio	Indirect comparison
Testa et al.[5]	0.85 (0.65–1.11)[6]	1.06 (0.80–1.30)[4]	1.76 (1.10–2.60)[4]	0.90 (0.76–1.19)[4,7]	NA	Odds ratio	Indirect comparison
Dabigatran 110 mg bid vs. Rivaroxaban							
Kansal et al.	1.02 (0.79, 1.32)[1]	0.99 (0.83, 1.17)[1]	1.42 (0.97, 2.08)[1]	0.78 (0.63, 0.96)[2]	0.36 (0.20, 0.65)[2]	Hazard ratio	Indirect comparison
CADTH	1.03 (0.79–1.33)[1]	0.98 (0.83–1.16)[1]	1.64 (1.10–2.44)[4]	0.78 (0.63–0.96)[4]	0.45 (0.26–0.78)[4]	Odds ratio	Bayesian MTC (fixed effects)
Lip et al.	1.02 (0.79–1.32)[1]	1.07 (0.85–1.34)[4]	1.59 (1.07–2.37)[4]	0.77 (0.63–0.94)[4]	0.46 (0.27–0.80)[4,5]	Hazard ratio	Indirect comparison
Mantha and Ansell	1.03 (0.79–1.35)[1]	0.99 (0.83–1.19)[1]	1.64 (1.10–2.44)[4]	0.78 (0.64–0.96)[4]	0.45 (0.26–0.79)[4]	Odds ratio	Indirect comparison
Testa et al.[5]	1.18 (0.89–1.57)[6]	1.09 (0.80–1.37)[4]	1.70 (1.12–2.60)[4]	0.80 (0.67–1.05)[4,7]	NA	Odds ratio	Indirect comparison

Apixaban vs Dabigatran 110 mg indirekt kıyaslanması



Lip et al J Am Coll Cardiol 2012

RE-LY: Miyokardiyal iskemik olayların subanalizi



Dabigatran kolunda MI sayısında artışa rağmen inme ve kanama üzerindeki olumlu etkisi warfarine göre net klinik yararını öne çıkarmaktadır

İnme proflaksisinde kullanılan warfarin MI karşı koruyucu mu?

	Average TTR in warfarin patients	MI events with comparator *n/N [%] (rate, per 100 patient years)*	MI events on warfarin *n /N [%] (rate, per 100 patient years)*	HR (95%CI)
RELY Main trial	64%	D110: 98/6015 (0.82) D150: (97/6076) (0.81)	75/6022 (0.64)	1.28 (0.98-1.67)
ROCKET-AF Main trial (OT)	55%	101/7061 (0.91)	126/7082 (1.12)	0.81 (0.63-1.06)
ROCKET-AF North America* (ITT)	64%	41/1339 (1.51)	36/1342 (1.31)	1.15 (0.74, 1.80)
ACTIVE-W	63.8%	36/3335 (0·86)	23/3371 (0·55)	1·58 (0·94–2·67)
HOKUSAI VTE trial	63.5%	20 /4118 (0.5%)	13 /4122 (0.3%)	

Lip and Lane, Am J Med 2010
HOKUSAI Investigators, NEJM 2013

INR kontrolünün MI üzerine etkisi

Table 5 Effect of INR control on MI rates in warfarin-treated patients in RE-LY

	INR TTR <65%	INR TTR ≥65%
Subject number (n)	2,595	3,194
Subject years (n)	4,451	6,175
MI (n, % per year)	32 (0.72)	30 (0.49)

Abbreviations: INR, international normalized ratio; MI, myocardial infarction; TTR, time in therapeutic range; RE-LY, Randomized Evaluation of Long-term anticoagulation therapY.

RELY-ABLE: ortalama 4.3 yıl takip, *150 mg Dabigatran ile yıllık MI oranı %0.69, 110 mg Dabigatran ile %0.72*

Clemens et al, Vascular Health and Risk Management 2013;9:599-615

İntrakraniyal ve GI kanama
Dabigatran vs Warfarin

Mini-Sentinel Database, Ekim 2010-Aralık 2011

	Dabigatran			Warfarin		
Analysis	**No of patients**	**No of events**	**Incidence *no of events/ 100,000 days at risk***	**No of patients**	**No of events**	**Incidence *no of events/ 100,000 days at risk***
Gastrointestinal haemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of AF	12,195	19	1.6	119,940	338	3.1
Intracranial haemorrhage						
Analysis with required diagnosis of AF	10,587	8	1.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of AF	12,182	10	0.9	120,020	204	1.9

Southworth et al, NEJM 2013

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Atrial Fibrillation

Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

A Prospective Nationwide Cohort Study

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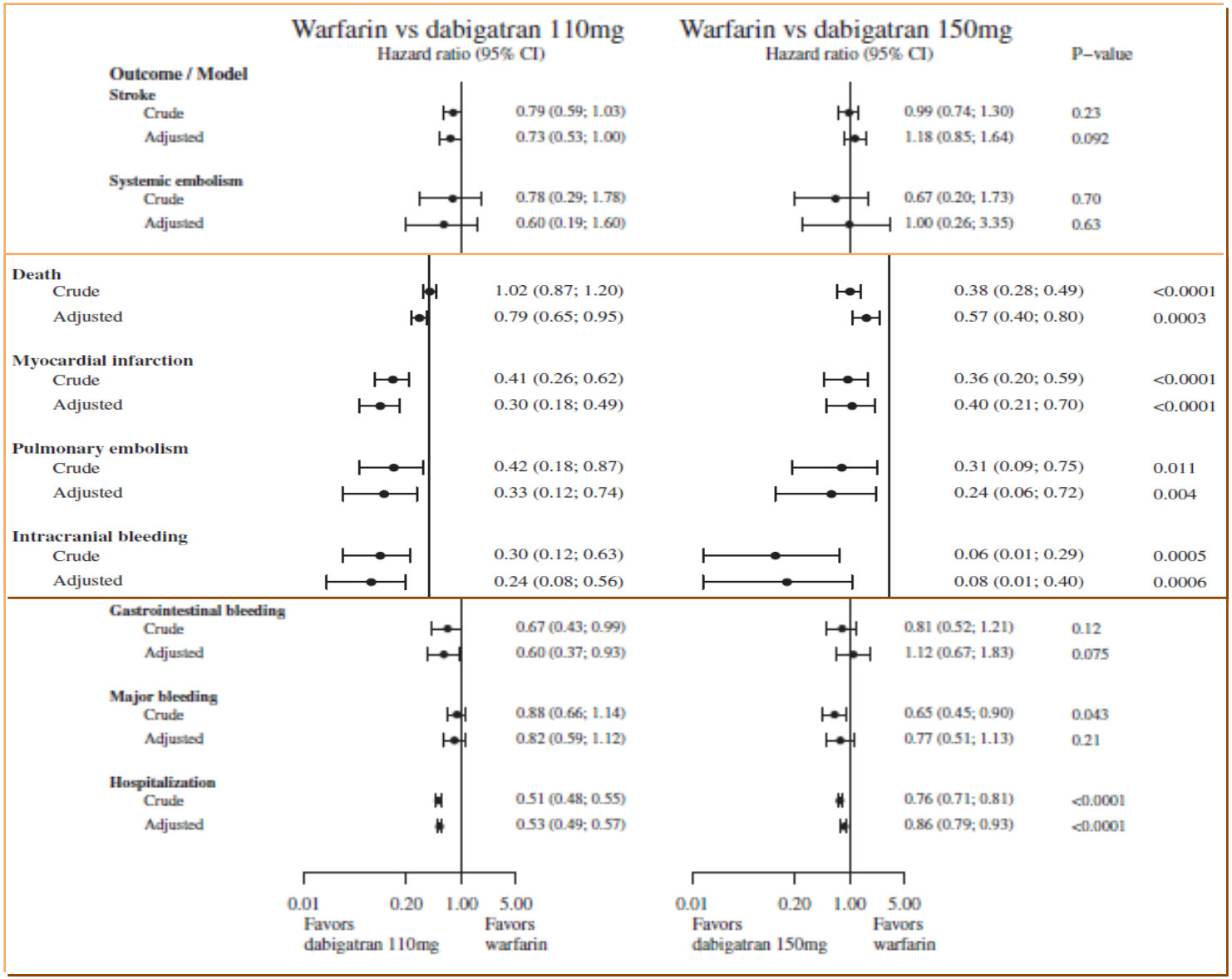
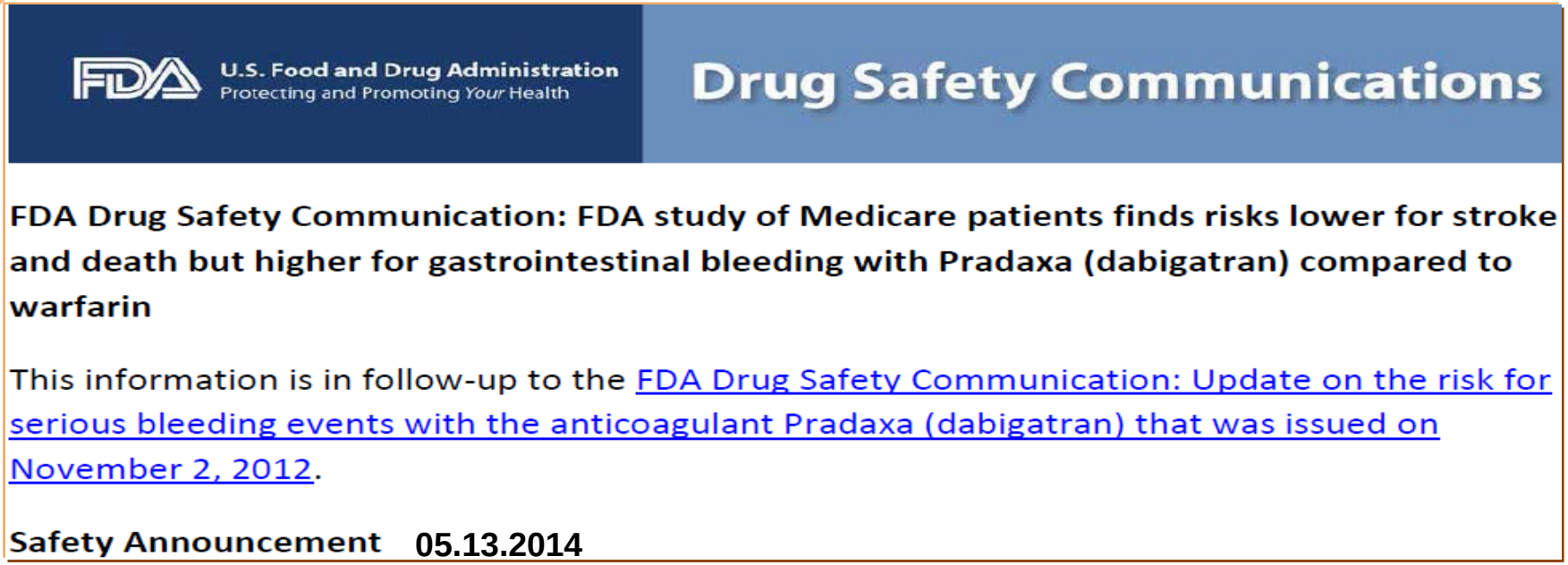
Flemming Skjøth, MSc, PhD,* Karen Margrete Due, MSc,* Torbjörn Callréus, MD, PhD,‡
Mary Rosenzweig, MSc,‡ Gregory Y. H. Lip, MD†§

Aalborg and Copenhagen, Denmark; and Birmingham, United Kingdom

- Post FDA Faz IV çalışma «Danish Registry» verileri
- 1:2 Eşleştirme
- 4978 Dabigatran vs 8936 Warfarin
- Ortalama takip 13.9 ay



Larsen TB, et al. JACC 2013



- Onay verilen ekim 2010-aralık 2013 arasında 934,000 hastaya reçete edilmiş (US)
- Medicare sisteminden Dabigatran veya VKA kullanmaya yeni başlamış 65 yaş üzeri 134, 000 hasta

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

	Dabigatran 1000 hasta/yıl	Warfarin 1000 hasta/yıl	Düzeltilmiş HR %95 CI
İskemik inme	11.3	13.9	0.80 (0.67-0.96)
İntrakraniyal kanama	3.3	9.6	0.34 (0.26-0.46)
Major GI kanama	34.2	26.5	1.28 (1.14-1.44)
Akut MI	15.7	16.9	0.92 (0.78-1.08)
Mortalite	32.6	37.8	0.86 (0.77-0.96)

Dabigatran;

- Daha düşük iskemik inme, intrakraniyal kanama ve ölüm
- GI kanama riskinde artış
- Benzer MI riski

13.05.2014

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Thromb Haemost 2014;111

A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment

Alexander G. G. Turpie[1]; Sylvia Haas[2]; Reinhold Kreutz[3]; Lorenzo G. Mantovani[4]; Cassandra W. Pattanayak[5]; Gerlind Holberg[6]; Waheed Jamal[6]; André Schmidt[6]; Martin van Eickels[6]; Michael R. Lassen[7]

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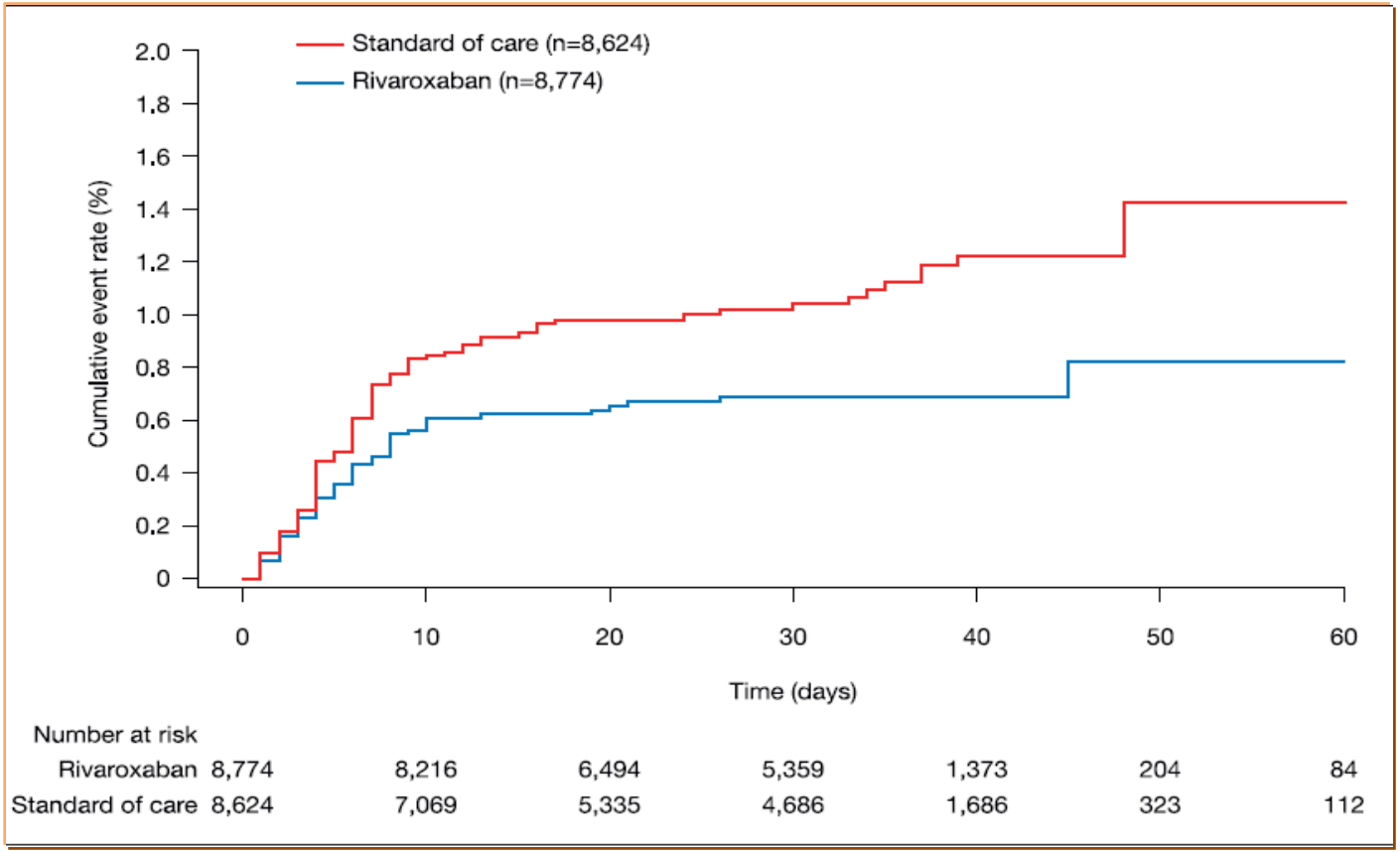
XAMOS ('Xarelto in the prophylaxis of postsurgical VTE after elective Major Orthopaedic Surgery of hip or knee')

- Open label, cohort, non-interventional, 252 merkez
- 8,844 hasta Rivaroxaban vs 8,745 hasta standart (LMWH,UFH,vb..)

Semptomatik tromboembolik olaylar



from Xamos

Yan etkiler

Outcome	Safety population					Adjusted safety population				
	Rivaroxaban (n=8,778)		Standard-of-care (n=8,635)		OR (95% CI)	Rivaroxaban (n=8,548)		Standard-of-care (n=7,968)		Weighted OR (95% CI)
	n	Incidence (%)	n	Incidence (%)		n	Weighted incidence (%)	n	Weighted incidence (%)	
Major bleedingc	35	(0.4)	29	(0.3)	1.19 (0.73–1.95)	35	(0.4)	27	(0.3)	1.35 (0.94–1.93)
EMA major bleeding	149	(1.7)	124	(1.4)	1.19 (0.93–1.51)	148	(1.9)	122	(1.5)	1.21 (1.01–1.45)
Non-major bleeding[c]	367	(4.2)	241	(2.8)	1.52 (1.29–1.79)	365	(4.4)	232	(2.9)	1.52 (1.35–1.71)
EMA non-major bleeding	258	(2.9)	150	(1.7)	1.71 (1.40–2.10)	257	(3.0)	141	(1.7)	1.76 (1.52–2.04)
Any bleeding	410	(4.7)	280	(3.2)	1.46 (1.25–1.71)	408	(4.9)	266	(3.3)	1.50 (1.34–1.68)
All other adverse events	1,952	(22.2)	1,841	(21.3)	1.06 (0.98–1.13)	1,925	(22.4)	1,699	(21.4)	1.06 (1.01–1.11)
All other serious adverse events	271	(3.1)	259	(3.0)	1.03 (0.87–1.22)	267	(3.2)	233	(2.9)	1.10 (0.97–1.25)

from Xamos

FAERS («FDA's Adverse Event Reporting System»)

AdverseEvents
REDEFINING DRUG SAFETY

SPECIAL REPORT

Examining the Comparative Safety of Blood Thinners:

An Analysis Utilizing AdverseEvents Explorer

February 2014

www.adverseevents.com

Drug Name	Date Range	Primary Suspect Cases	Stroke* Cases (%)	Heart Attack* Cases (%)	Hospitalization Cases (%)	Death Cases (%)	Top 3 Adverse Events
apixaban (Eliquis)	Dec 2012-Dec 2013	1,031	54 (5.24%)	10 (0.97%)	212 (20.56%)	51 (4.95%)	Haemoglobin decreased, Ischaemic stroke, Haematoma
dabigatran (Pradaxa)	Oct 2010-Dec 2012	20,965	1,467 (6.99%)	324 (1.55%)	8,095 (38.64%)	2,529 (12.05%)	Gastrointestinal haemorrhage, Haemorrhage, Dyspepsia
rivaroxaban (Xarelto)	July 2011-Dec 2012	10,075	747 (7.41%)	107 (1.06%)	4,357 (43.25%)	1,115 (11.07%)	Pulmonary embolism, Deep vein thrombosis, Gastrointestinal haemorrhage
warfarin (Coumadin)	Nov 1997#-Dec 2012	22,338	687 (3.08%)	228 (1.02%)	11,152 (49.92%)	1,841 (8.24%)	International normalised ratio increased, Gastrointestinal haemorrhage, Haemorrhage

**See Appendix B*

#Although warfarin was FDA-approved in 1954, our database begins 11/01/1997.

FAERS, 2014

«RxScore»;

- *Yan etkinin ciddiyeti, genişliği, orantısızlık, rapor ve raporcunun tipi gibi özelliklere göre 100 üzerinden puanlama*

Drug	RxScore	Outcome	Event Seriousness	Disproportionality	Literature	Reporter Type	Report Priority
warfarin (Coumadin)	67.56	41.08%	51.70%	28.76%	66.33%	51.32%	69.96%
dabigatran (Pradaxa)	67.15	37.85%	58.86%	17.76%	56.37%	73.43%	67.19%
rivaroxaban (Xarelto)	67.08	41.65%	55.67%	20.18%	56.37%	60.76%	91.95%
apixaban (Eliquis)	39.45	33.67%	25.23%	5.51%	56.37%	40.62%	66.60%

FAERS, 2014

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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

Walter N. Kernan, Bruce Ovbiagele, Henry R. Black, Dawn M. Bravata, Marc I. Chimowitz, Michael D. Ezekowitz, Margaret C. Fang, Marc Fisher, Karen L. Furie, Donald V. Heck, S. Claiborne (Clay) Johnston, Scott E. Kasner, Steven J. Kittner, Pamela H. Mitchell, Michael W. Rich, DeJuran Richardson, Lee H. Schwamm and John A. Wilson

Stroke. published online May 1, 2014;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Non-valvüler AF'de inmenin sekonder proflaksisinde;

***Class I*;** VKA (*kanıt düzeyi A*), Apixaban (*kanıt düzeyi A*), Dabigatran (*kanıt düzeyi B*). İlaç seçimi; risk faktörleri, maliyet, tölerabilite, hasta tercihi, ilaç etkileşimleri, renal fonksiyonlar, warfarin kullanlarda TTR gibi parametrelere bakarak kişiselleştirilmelidir.

Class IIa; Rivaroxaban (*kanıt düzeyi B*)