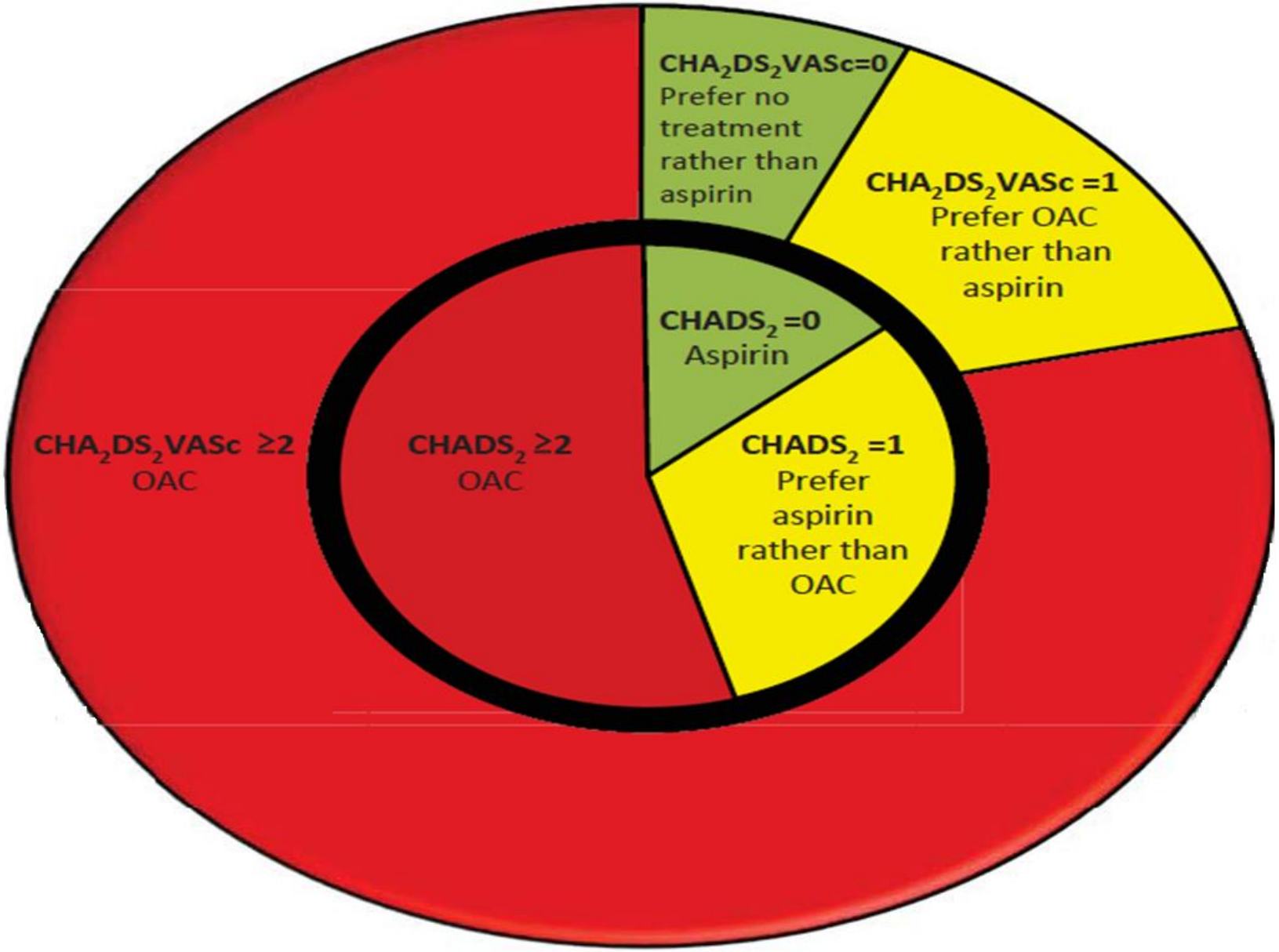
SOL ATRİYAL APENDİKS KAPATMANIN YENİ ORAL ANTİKOAGÜLANLAR ÇAĞINDA YERİ YOKTUR!

Dr. Ömer AKYÜREK

Ankara Üniversitesi

- Atriyal fibrilasyon epidemiyelojik bir sorundur:
  - AF 6 Milyon Amerikalı'yı etkilemiş durumda
  - 2050'de sayının >12 Milyon olması bekleniyor
  - Her yıl AF ve ilişkili stroke olguları için harcanan para: 16 milyar Dolar

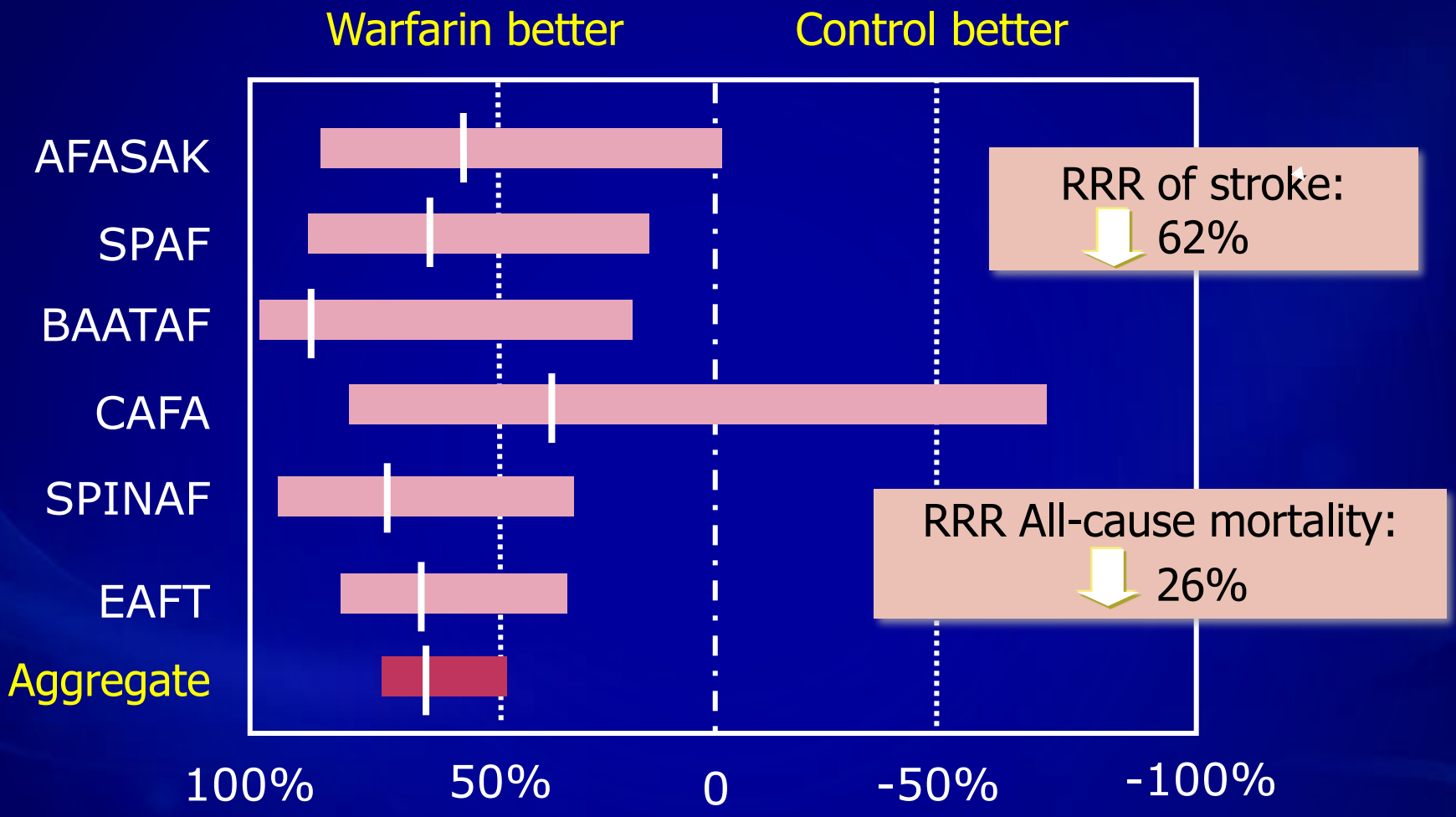
  - Hmmm… " BIG BUSINESS"


$CHA_2DS_2VASc=0$
Prefer no treatment rather than aspirin
$CHA_2DS_2VASc=1$
Prefer OAC rather than aspirin
$CHADS_2=0$
Aspirin
$CHADS_2=1$
Prefer aspirin rather than OAC
$CHADS_2 \geq 2$
OAC
$CHA_2DS_2VASc \geq 2$
OAC

Tedavi Yöntemlerini Karşılaştırma Sistematiği

- Etkinlik/Güvenlik
- Maliyet Etkinlik
- Uygulanabilirlik

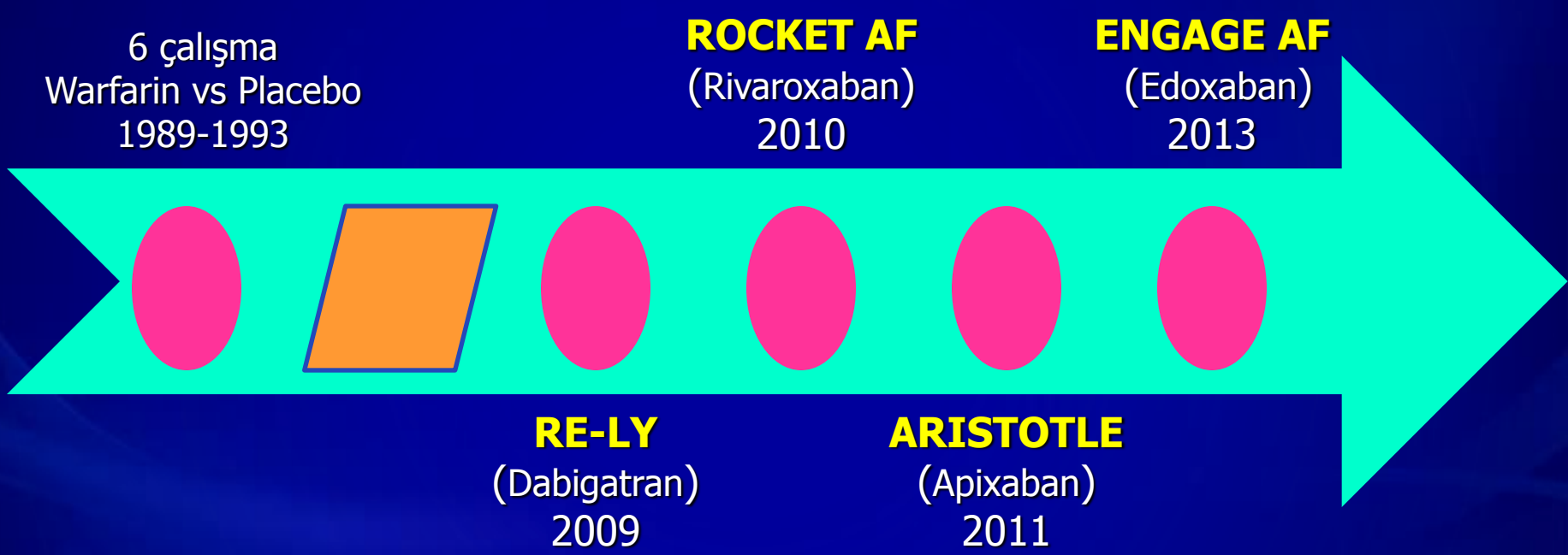
AF' de Antikoagülasyon İnme Riskinin Azaltılması



RRR, relative risk reduction.

Hart RG, et al. *Ann Intern Med.* 1999;131:492-501.

AF' de OAK Geçmişi

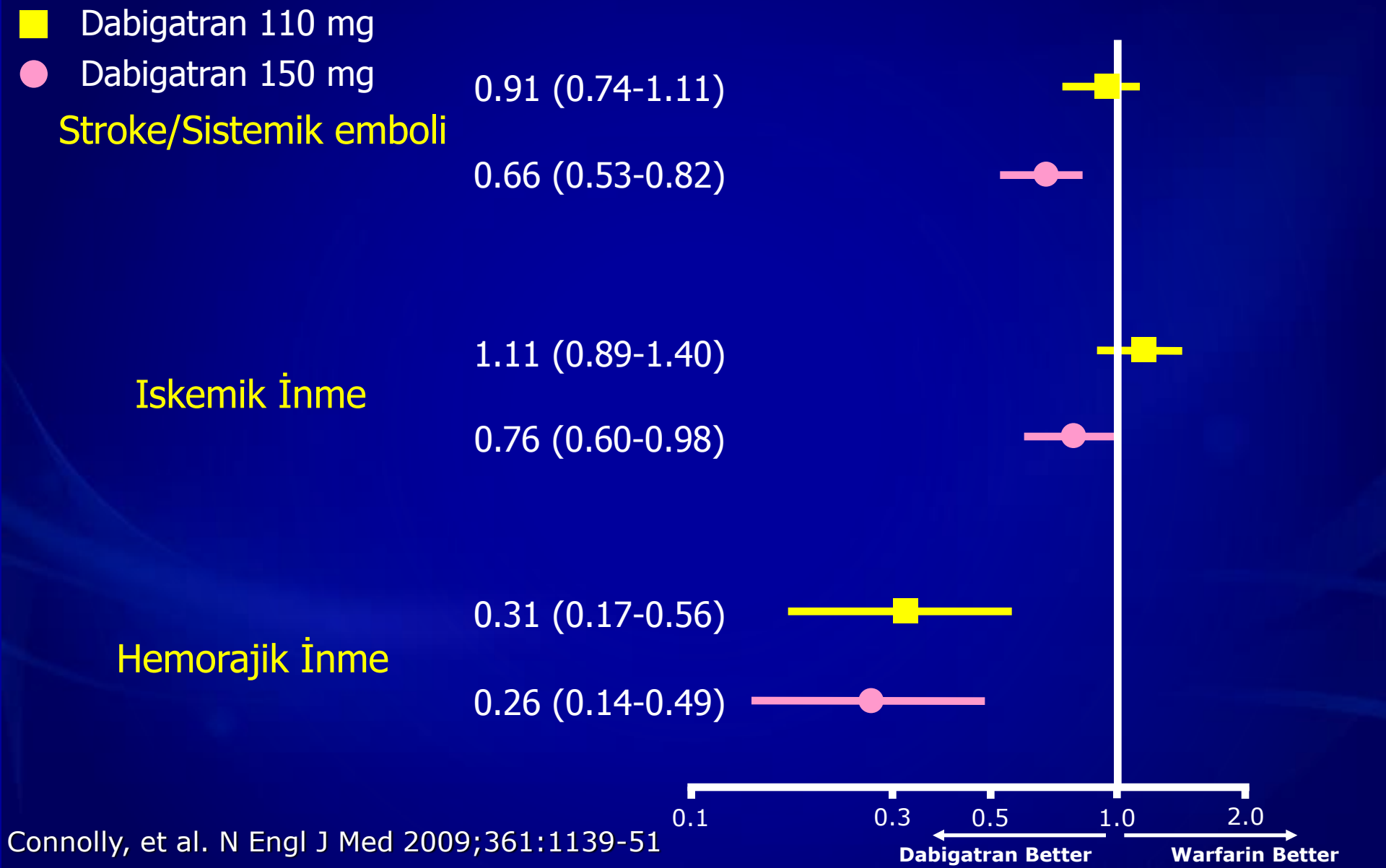


Yeni Oral Antikoagülanlar Önemli Özellikleri

Dabigatran	• Oral direk trombin inhibitörü • Günde 2 kez • Renal klirens • RE-LY
Rivaroxaban	• Direk faktör Xa inhibitörü • Günde 1 kez (İdame), günde 2 kez (Yükleme) • Renal klirens • ROCKET AF
Apixaban	• Direk faktör Xa inhibitörü • Günde 2 kez • Hepatik klirens • ARISTOTLE
Edoxaban	• Direk faktör Xa inhibitörü • Günde 1 kez • Hepatik klirens

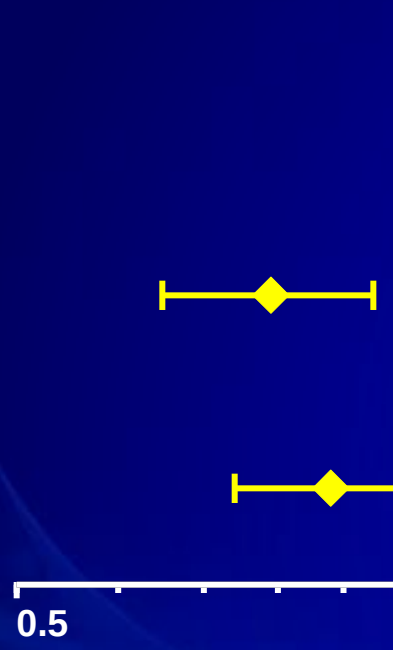
Circulation 2010;121:1523

RE-LY Etkinlik (Dabigatran)



Connolly, et al. N Engl J Med 2009;361:1139-51

ROCKET AF (Rivaroxaban) Etkinlik İnme/Sistemik Emboli



	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	*P*-value
On Treatment N = 14,143	1.70	2.15	0.79 (0.65, 0.95)	0.015
ITT N = 14,171	2.12	2.42	0.88 (0.74, 1.03)	0.117

Rivaroxaban better **Warfarin better**

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat through Site Notification populations

ROCKET AF

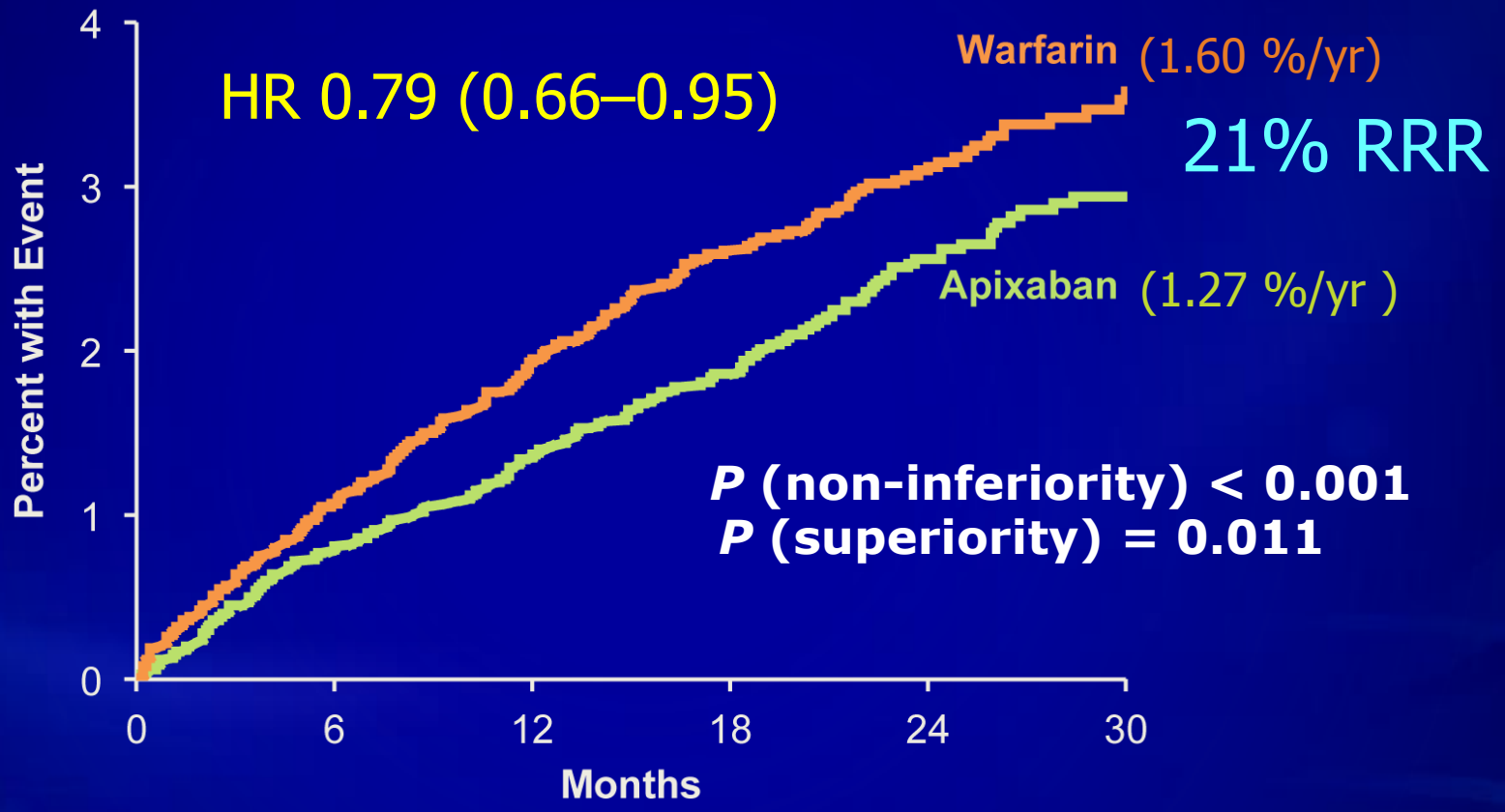
Patel, et al. N Engl J Med 2011;365(10);883-891

ROCKET AF – Sekonder Etkinlik

Olay	Rivaroxaban (%/yr)	Warfarin (%/yr)	Hazard Ratio (95% CI)	*P*-value
İskemik İnme	1.34	1.42	0.94 (0.75-1.17)	0.581
Hemorajik İnme	0.26	0.44	0.59 (0.37-0.93)	0.024
MI	0.91	1.12	0.81 (0.63-1.06)	0.121
Total Mortalite	1.87	2.21	0.85 (0.70-1.02)	0.073
Vasküler Mortalite	1.53	1.71	0.89 (0.73-1.10)	0.289

Patel, et al. N Engl J Med 2011; 365(10);883-891

ARISTOTLE Etkinlik: Apixaban



Granger CB, et al. NEJM 2011; 365:981-992

ARISTOTLE : Etkinlik

Sonuçlar	Apixaban (N = 9120) Event Rate (%/yr)	Warfarin (N = 9081) Event Rate (%/yr)	HR (95% CI)	*P* Value
İnme ya da sistemik emboli*	1.27	1.60	0.79 (0.66, 0.95)	**0.011**
İnme	1.19	1.51	0.79 (0.65, 0.95)	0.012
İskemik yada bilinmeyen	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorajik	0.24	0.47	0.51 (0.35, 0.75)	**< 0.001**
Sistemik emboli (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
Tüm nedenlere bağlı ölüm	3.52	3.94	0.89 (0.80, 0.998)	0.047
İnme, SE, yada Ölüm	4.49	5.04	0.89 (0.81, 0.98)	0.019
MI	0.53	0.61	0.88 (0.66, 1.17)	0.37

Granger CB, et al. NEJM 2011; 365:981-992

Pivotal AF Çalışmaları

Drug Dose (mg)	RE-LY		ROCKET-AF	ARISTOTLE
	Dabigatran 110 bid	150 BID	Rivaroxaban 20 mg qd	Apixaban 5 mg bid
Stroke + SEE	non-infer	Superior	ITT cohort: non-infer. On Rx cohort: Superior	Superior
ICH	Superior	Superior	Superior	Superior
Bleeding	Lower	similar	similar	Lower
Mortality	similar	*P* = 0.051	similar	Superior: *P* = 0.047
Ischemic stroke	similar	Lower	similar	similar
Mean TTR	64%		55%	62%
Stopped drug	21%		23%	23%
WD consent	2.3%		8.7%	1.1%

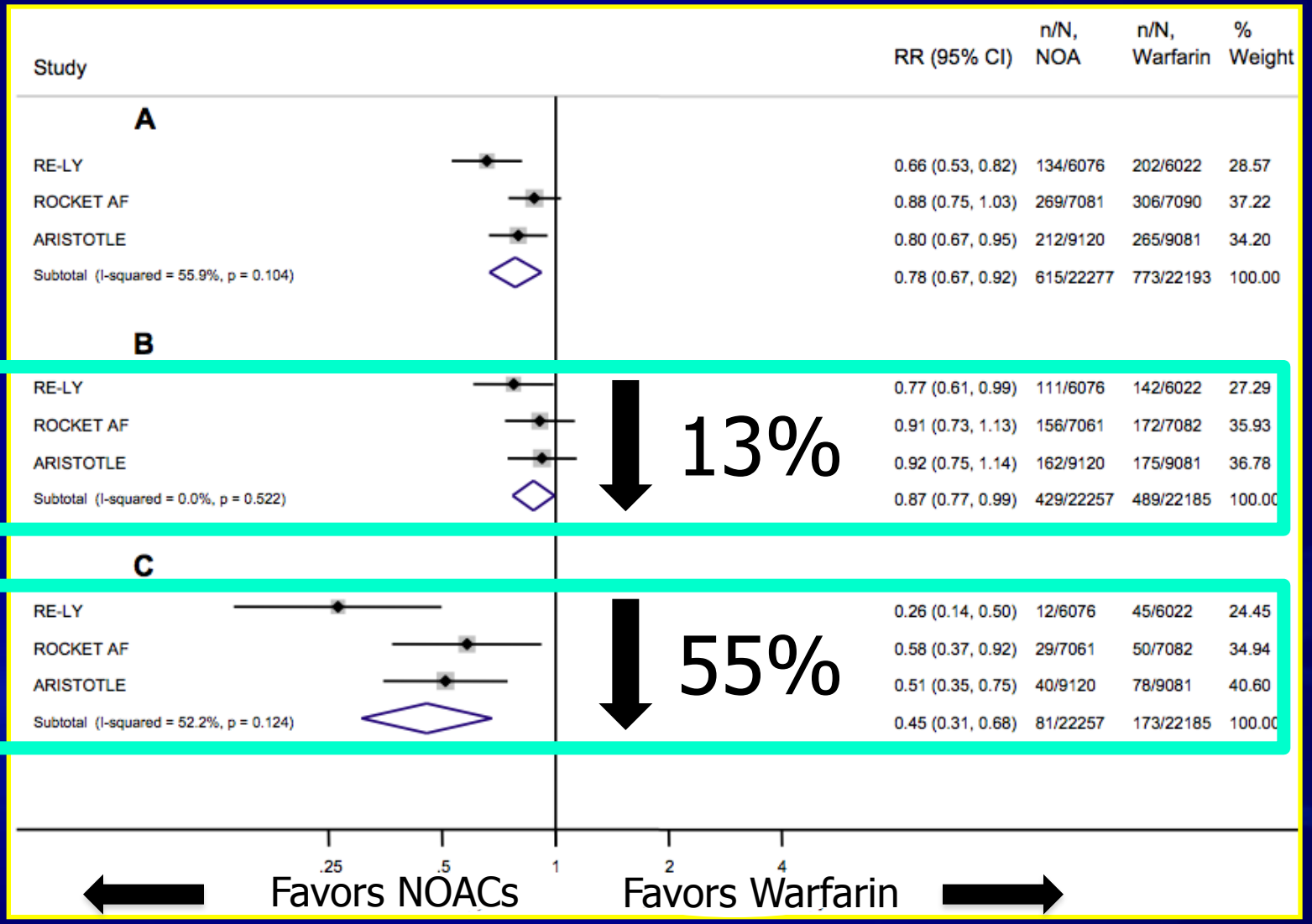
TTR = time in therapeutic range
WD consent = withdrawal of consent, no further data available

Etkinlik - YOAK

İnme & SE

İskemik İnme

Hemorajik İnme



Miller CS, et al. Am J Cardiol 2012;110(3):453-460.

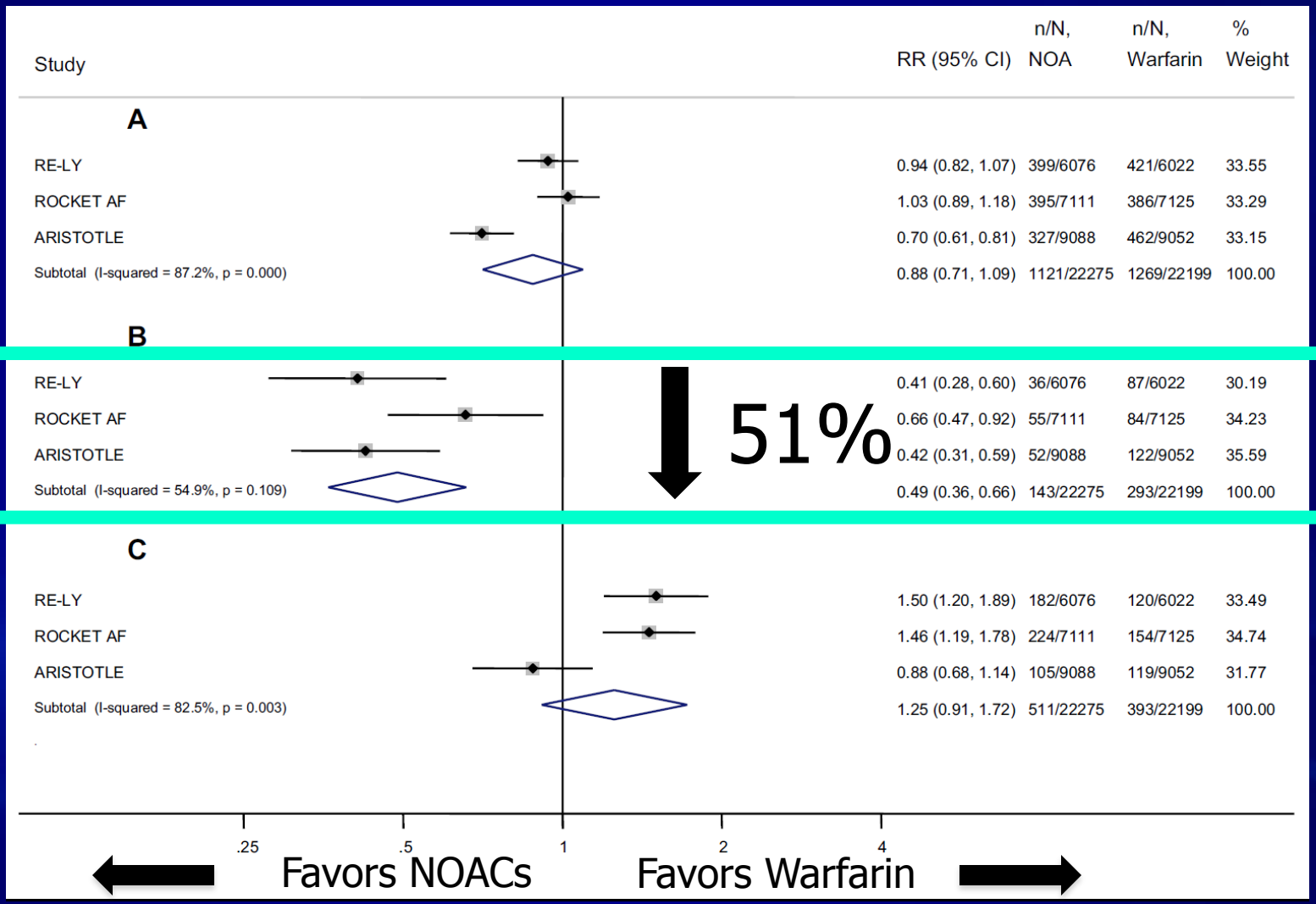
Safety of New Oral Anticoagulants

Bleeding

Major

ICH

GI



iller CS, et al. Am J Cardiol 2012;110(3):453-460.

ESC 2016 Atriyal Fibrilasyon Kılavuzu

Risk Profili	Class / Level
CHA_2DS_2-VASc = 0	No antithrombotic therapy III/B
CHA_2DS_2-VASc = 1	1-Dabigatran / Rivaroxaban / Apixaban II a/B Ya da 2-VKA (INR 2-3) IIa/B
CHA_2DS_2-VASc ≥ 2	1- Dabigatran / Rivaroxaban / Apixaban I/A Ya da 2- VKA (INR 2-3) I/A 3- *OAK kontrendike ise LAA kapatma (IIb/C)

- Tedavinin etkinliği sadece randomize çalışmalar ile değil gerçek yaşam verileri ile de kanıtlanmalı

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

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Background—The introduction of non–vitamin K antagonist oral anticoagulants has been a major advance for stroke prevention in atrial fibrillation; however, outcomes achieved in clinical trials may not translate to routine practice. We aimed to evaluate the effectiveness and safety of dabigatran, rivaroxaban, and apixaban by comparing each agent with warfarin.

Methods and Results—Using a large US insurance database, we identified privately insured and Medicare Advantage patients with nonvalvular atrial fibrillation who were users of apixaban, dabigatran, rivaroxaban, or warfarin between October 1, 2010, and June 30, 2015. We created 3 matched cohorts using 1:1 propensity score matching: apixaban versus warfarin (n=15 390), dabigatran versus warfarin (n=28 614), and rivaroxaban versus warfarin (n=32 350). Using Cox proportional hazards regression, we found that for stroke or systemic embolism, apixaban was associated with lower risk (hazard ratio [HR] 0.67, 95% CI 0.46–0.98, *P*=0.04), but dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR 0.98, 95% CI 0.76–1.26, *P*=0.98; rivaroxaban: HR 0.93, 95% CI 0.72–1.19, *P*=0.56). For major bleeding, apixaban and dabigatran were associated with lower risk (apixaban: HR 0.45, 95% CI 0.34–0.59, *P*<0.001; dabigatran: HR 0.79, 95% CI 0.67–0.94, *P*<0.01), and rivaroxaban was associated with a similar risk (HR 1.04, 95% CI 0.90–1.20], *P*=0.60). All non–vitamin K antagonist oral anticoagulants were associated with a lower risk of intracranial bleeding.

Conclusions—In patients with nonvalvular atrial fibrillation, apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin. **(*J Am Heart Assoc*. 2016;5:e003725 doi: 10.1161/JAHA.116.003725)**

Key Words: atrial fibrillation • bleeding • non–vitamin K antagonist oral anticoagulants • stroke • warfarin

	Event Rate per 100 person-years		Hazard Ratio (95% CI)	p value
	Apixaban vs.	Warfarin		
	n=7,695	n=7,695		
S/SE	1.33	1.66	0.67 (0.46–0.98)	0.04
Ischemic	1.03	1.05	0.83 (0.53–1.29)	0.40
Hemorrhagic	0.19	0.46	0.35 (0.14–0.88)	0.03
	Dabigatran vs.	Warfarin		
	n=14,307	n=14,307		
S/SE	1.18	1.22	0.98 (0.76–1.26)	0.88
Ischemic	0.92	0.88	1.06 (0.79–1.42)	0.70
Hemorrhagic	0.16	0.29	0.56 (0.30–1.04)	0.07
	Rivaroxaban vs.	Warfarin		
	n=16,175	n=16,175		
S/SE	1.26	1.29	0.93 (0.72–1.19)	0.56
Ischemic	0.95	0.88	1.01 (0.75–1.36)	0.95
Hemorrhagic	0.21	0.32	0.61 (0.35–1.07)	0.08

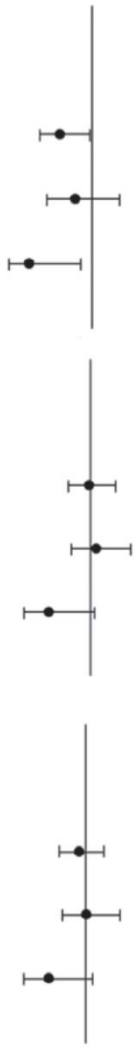


Figure 2. Forest plot depicting the hazard ratio for each pairwise propensity-matched medication comparison (dabigatran, rivaroxaban, and apixaban each vs warfarin) for stroke and systemic embolism (S/SE), ischemic stroke, and hemorrhagic stroke. NOAC, non–vitamin K oral anticoagulant.

	Event Rate per 100 person-years		Hazard Ratio (95% CI)	p value
	Apixaban vs.	Warfarin		
	n=7,695	n=7,695		
Major Bleeding	2.33	4.46	0.45 (0.34 – 0.59)	<0.001
Intracranial	0.29	1.06	0.24 (0.12 – 0.50)	<0.001
Gastrointestinal	1.78	3.04	0.51 (0.37 – 0.70)	<0.001
	Dabigatran vs.	Warfarin		
	n=14,307	n=14,307		
Major Bleeding	2.37	3.03	0.79 (0.67 – 0.94)	<0.01
Intracranial	0.28	0.79	0.36 (0.23 – 0.56)	<0.001
Gastrointestinal	1.97	1.95	1.03 (0.84 – 1.26)	0.78
	Rivaroxaban vs.	Warfarin		
	n=16,175	n=16,175		
Major Bleeding	4.04	3.64	1.04 (0.90 – 1.20)	0.60
Intracranial	0.44	0.79	0.51 (0.35 – 0.75)	<0.001
Gastrointestinal	3.26	2.53	1.21 (1.02 – 1.43)	0.03

Favor NOAC 1.0 Favor Warfarin

Figure 3. Forest plot depicting the hazard ratio for each pairwise propensity-matched medication comparison (dabigatran, rivaroxaban, and apixaban each vs warfarin) for major, intracranial, and gastrointestinal bleeding. NOAC, non–vitamin K oral anticoagulant.

The PREVAIL Trial

BACKGROUND In the PROTECT AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation) trial that evaluated patients with nonvalvular atrial fibrillation (NVAF), left atrial appendage (LAA) occlusion was noninferior to warfarin for stroke prevention, but a periprocedural safety hazard was identified.

OBJECTIVES The goal of this study was to assess the safety and efficacy of LAA occlusion for stroke prevention in patients with NVAF compared with long-term warfarin therapy.

METHODS This randomized trial further assessed the efficacy and safety of the Watchman device. Patients with NVAF who had a $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack) score ≥2 or 1 and another risk factor were eligible. Patients were randomly assigned (in a 2:1 ratio) to undergo LAA occlusion and subsequent discontinuation of warfarin (intervention group, n = 269) or receive chronic warfarin therapy (control group, n = 138). Two efficacy and 1 safety coprimary endpoints were assessed.

RESULTS At 18 months, the rate of the first coprimary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group (rate ratio 1.07 [95% credible interval (CrI): 0.57 to 1.89]) and did not achieve the prespecified criteria noninferiority (upper boundary of 95% CrI ≥1.75). The rate for the second coprimary efficacy endpoint (stroke or SE >7 days' postrandomization) was 0.0253 versus 0.0200 (risk difference 0.0053 [95% CrI: -0.0190 to 0.0273]), achieving noninferiority. Early safety events occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT AF, satisfying the pre-specified safety performance goal. Using a broader, more inclusive definition of adverse effects, these still were lower in PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial than in PROTECT AF (4.2% vs. 8.7%; p = 0.004). Pericardial effusions requiring surgical repair decreased from 1.6% to 0.4% (p = 0.027), and those requiring pericardiocentesis decreased from 2.9% to 1.5% (p = 0.36), although the number of events was small.

CONCLUSIONS In this trial, LAA occlusion was noninferior to warfarin for ischemic stroke prevention or SE >7 days' post-procedure. Although noninferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved. This trial provides additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy. (J Am Coll Cardiol 2014;64:1-12) © 2014 by the American College of Cardiology Foundation.

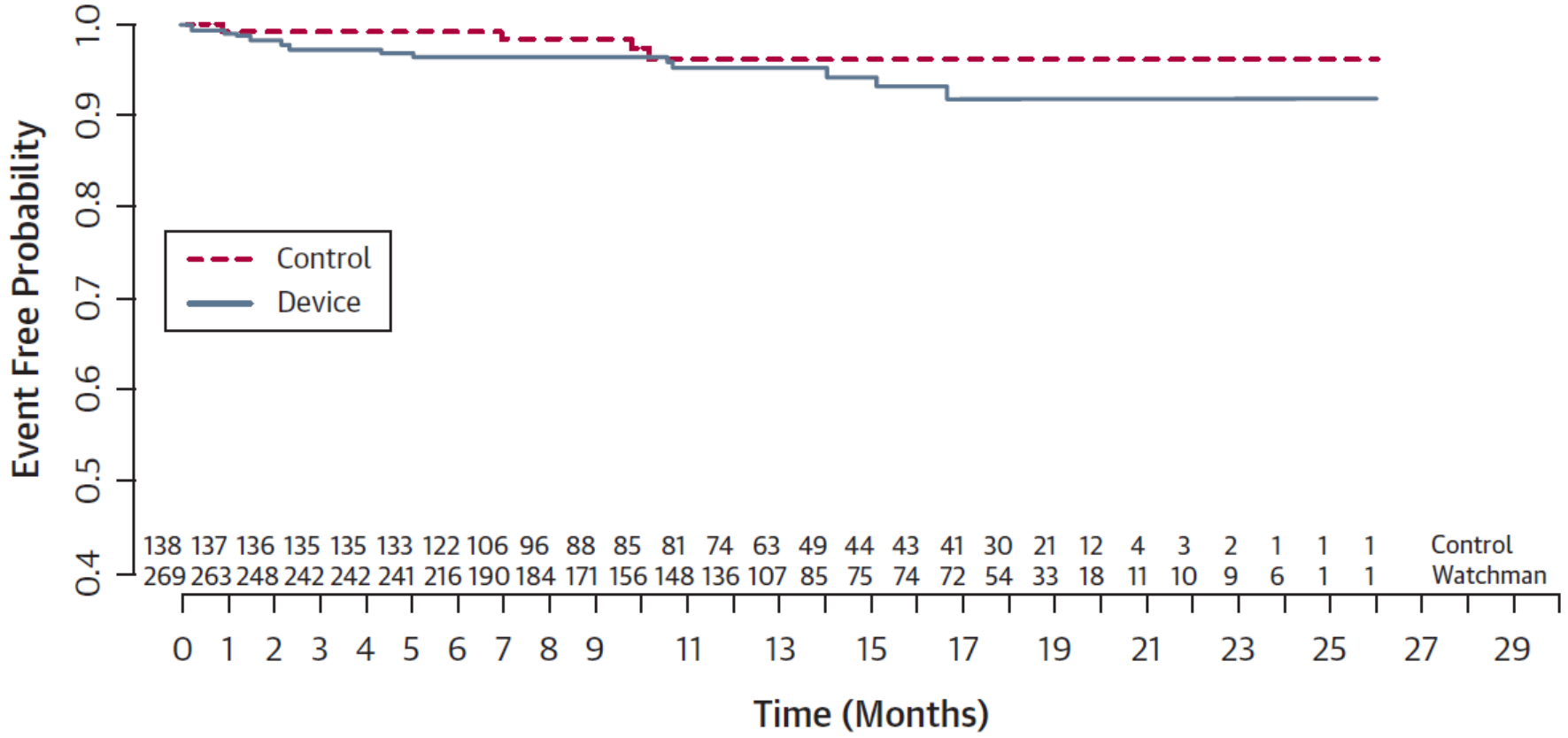


FIGURE 2 **Kaplan-Meier Curve: Freedom From First Primary Endpoint (Intention-to-Treat)**

Primary efficacy rates for Watchman **(solid line)** versus warfarin **(dotted line)** in the intention-to-treat population show similarly high 18-month event-free rates.

TABLE 5 Safety Coprimary Endpoint Results and Events by Type (Intention-to-Treat): Device Group Only

	% (n/N)	95% CrI
Safety primary endpoint results	2.2% (6/269)	2.652%
	No. of Events	**% of Subjects**
Safety events by type		
Device embolization	2	0.7
Arteriovenous fistula	1	0.4
Cardiac perforation	1	0.4
Pericardial effusion with cardiac tamponade	1	0.4
Major bleed requiring transfusion	1	0.4

TABLE 7 Comparison of Outcomes in Device Patients in PROTECT AF, CAP, and PREVAIL

	PROTECT AF	CAP	PREVAIL	p Value
Implant success	90.9	94.3	95.1	0.04
All 7-day procedural complications	8.7	4.2	4.5	0.004
Pericardial effusion requiring surgery	1.6	0.2	0.4	0.03
Pericardial effusion with pericardiocentesis	2.4	1.2	1.5	0.318
Procedure-related strokes	1.1	0.0	0.7	0.02
Device embolization	0.4	0.2	0.7	0.368

Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation

A Patient-Level Meta-Analysis

BACKGROUND The risk-benefit ratio of left atrial appendage closure (LAAC) versus systemic therapy (warfarin) for prevention of stroke, systemic embolism, and cardiovascular death in nonvalvular atrial fibrillation (NVAF) requires continued evaluation.

OBJECTIVES This study sought to assess composite data regarding left atrial appendage closure (LAAC) in 2 randomized trials compared to warfarin for prevention of stroke, systemic embolism, and cardiovascular death in patients with nonvalvular AF.

METHODS Our meta-analysis included 2,406 patients with 5,931 patient-years (PY) of follow-up from the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials, and their respective registries (Continued Access to PROTECT AF registry and Continued Access to PREVAIL registry).

RESULTS With mean follow-up of 2.69 years, patients receiving LAAC with the Watchman device had significantly fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; $p = 0.004$), cardiovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; $p = 0.006$), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; $p = 0.006$) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs. 1.87 events/100 PY; HR: 1.02; 95% CI: 0.62 to 1.7; $p = 0.94$). There were more ischemic strokes in the device group (1.6 vs. 0.9 and 0.2 vs. 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; $p = 0.05$ and 0.004, respectively). Both trials and registries identified similar event rates and consistent device effect in multiple subsets.

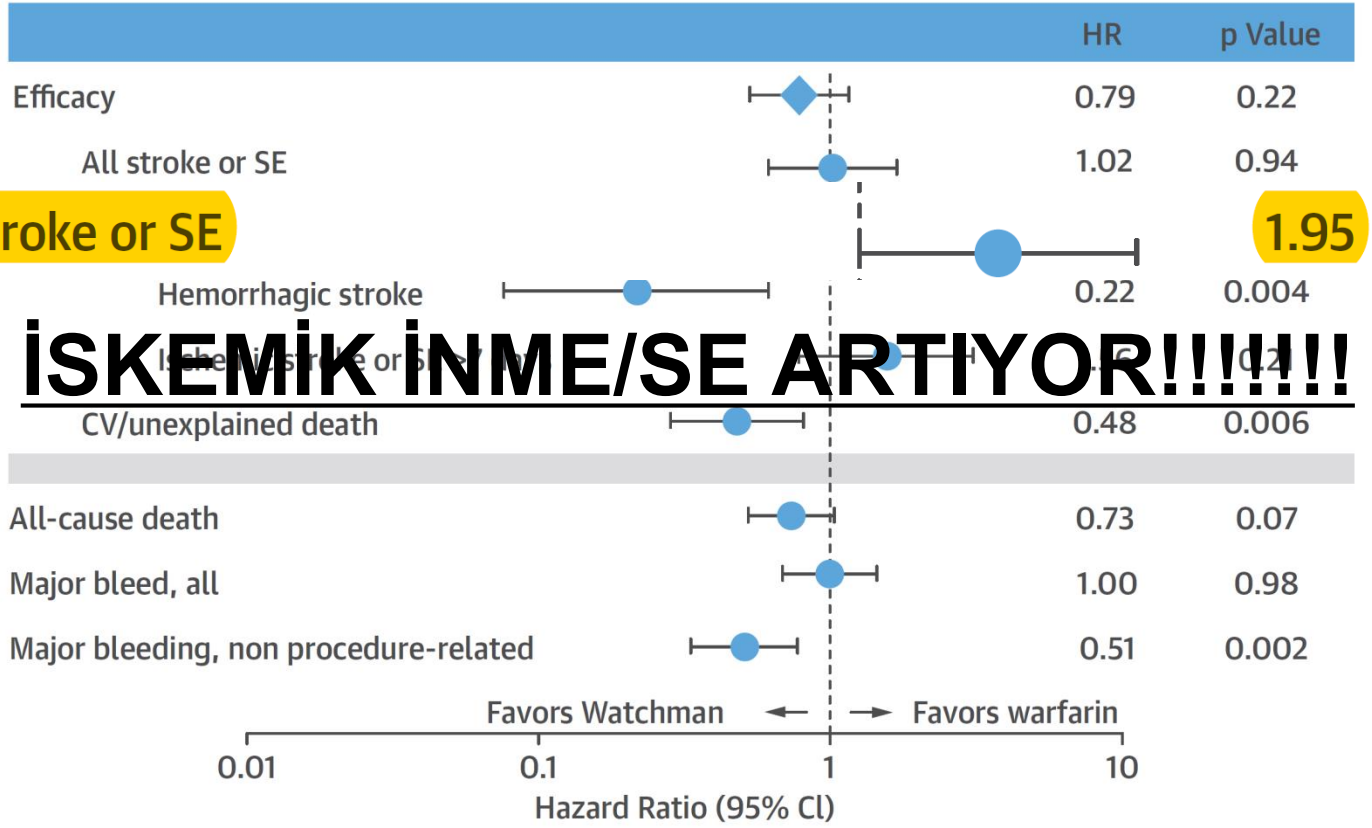
CONCLUSIONS In patients with NVAF at increased risk for stroke or bleeding who are candidates for chronic anticoagulation, LAAC resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin. (J Am Coll Cardiol 2015;65:2614–23) © 2015 by the American College of Cardiology Foundation.

TABLE 1 PROTECT AF and CAP: Largest Data Sets to Evaluate Totality of Data

	PROTECT AF	PREVAIL	CAP	CAP2	Total
Enrollment	2005-2008	2010-2012	2008-2010	2012-2014	
Enrolled	800	461	566	579	2,406
Randomized	707	407	—	—	1,114
Watchman:warfarin (2:1)	463:244	269:138	566	579	1,877:382
Mean follow-up, yrs	4.0	2.2	3.7	0.58	N/A
Patient-years	2,717	860	2,022	332	5,931

CAP = Continued Access to PROTECT AF registry; CAP2 = Continued Access to PREVAIL registry; N/A = not applicable; PREVAIL = Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; PROTECT AF = Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation.

FIGURE 2 PROTECT AF/PREVAIL Combined: Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin



The combined data set of all PROTECT AF and PREVAIL Watchman patients versus chronic warfarin patients documented: 1) similarity in overall stroke or systemic embolism; 2) ischemic stroke slightly increased with Watchman but hemorrhagic stroke significantly decreased with warfarin; and 3) all-cause mortality and major nonprocedural bleeding both significantly improved with Watchman. CI = confidence interval; CV = cardiovascular; HR = hazard ratio; SE = systemic embolism; other abbreviations as in Figure 1.

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Comparative Effectiveness of Interventions for Stroke Prevention in Atrial Fibrillation: A Network Meta-Analysis

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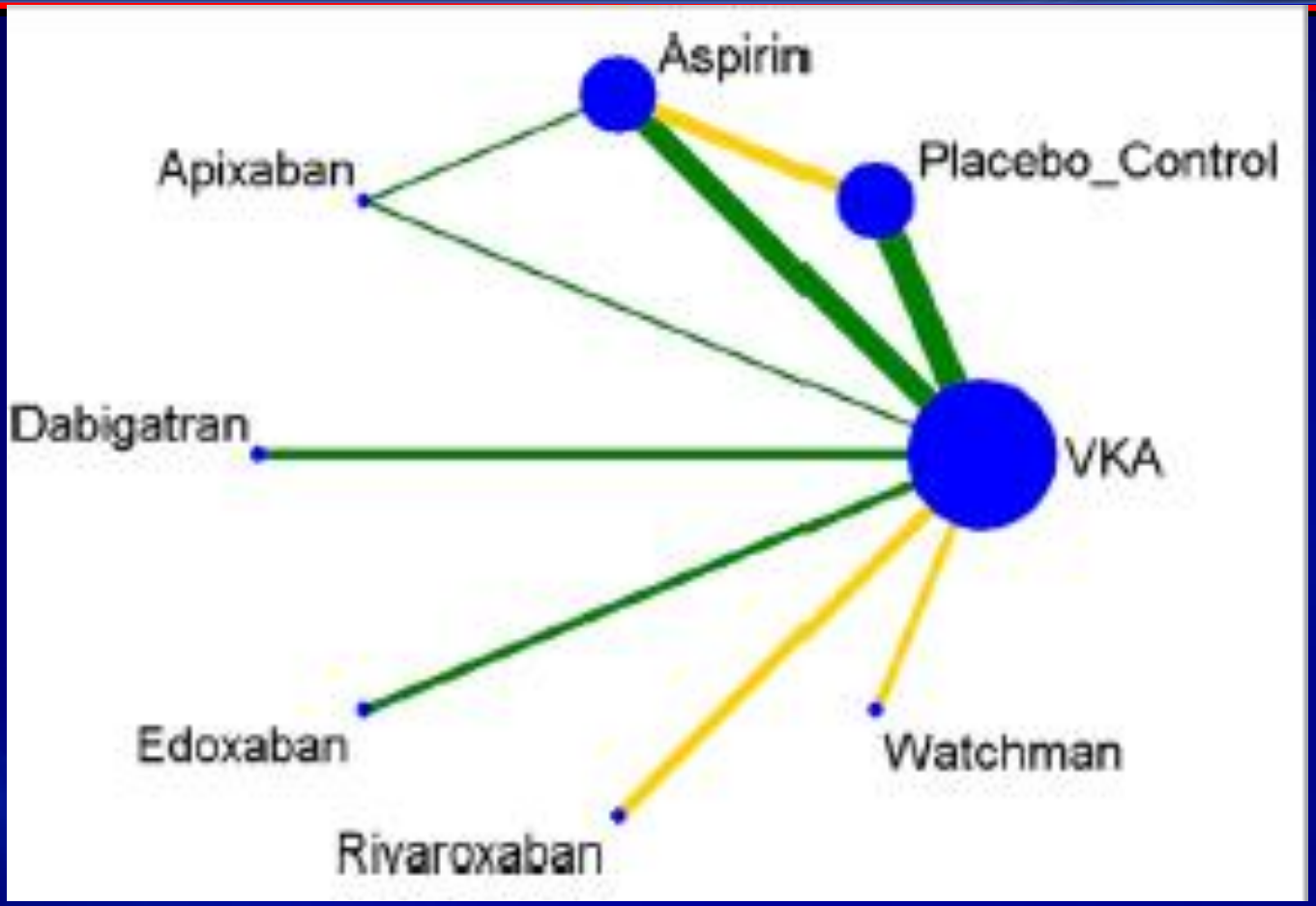
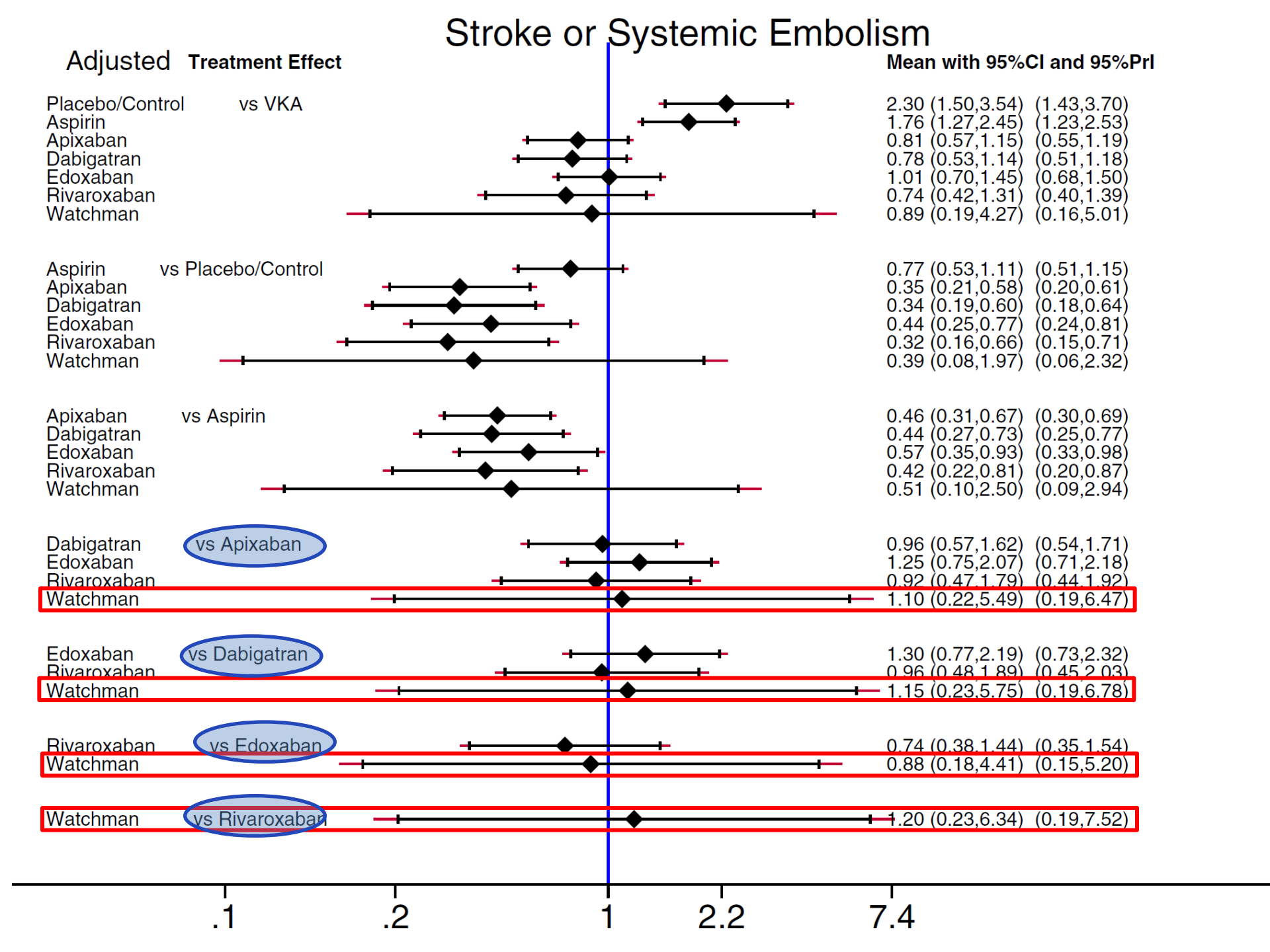
***Background*—**The goal of this study was to compare the safety and effectiveness of individual antiembolic interventions in nonvalvular atrial fibrillation (AF): novel oral anticoagulants (NOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban); vitamin K antagonists (VKA); aspirin; and the Watchman device.

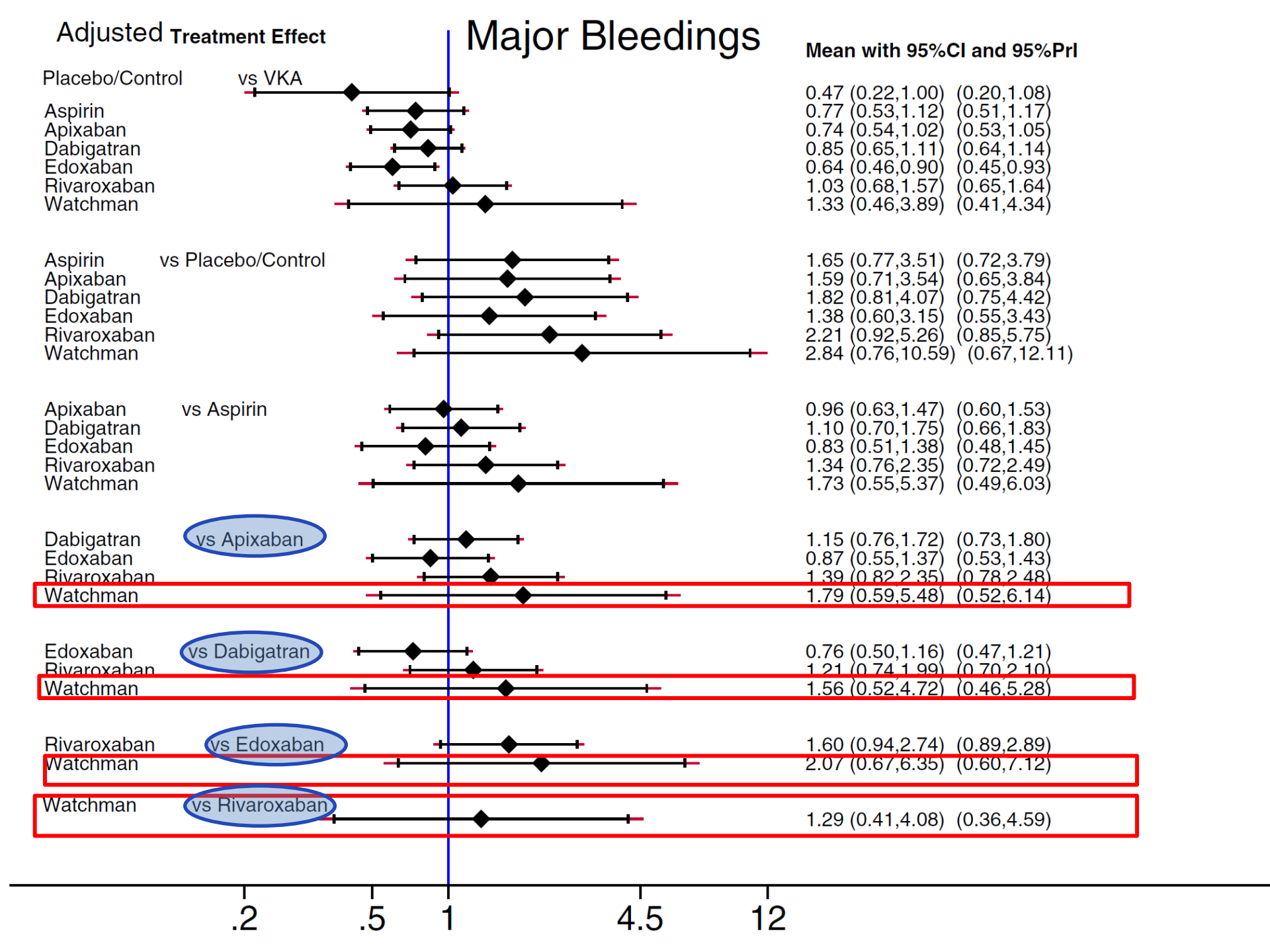
***Methods and Results*—**A network meta-analysis of randomized, clinical trials (RCTs) was performed. RCTs that included patients with prosthetic cardiac valves or mitral stenosis, mean or median follow-up <6 months, <200 participants, without published report in English language, and NOAC phase II studies were excluded. The placebo/control arm received either placebo or no treatment. The primary efficacy outcome was the combination of stroke (of any type) and systemic embolism. All-cause mortality served as a secondary efficacy outcome. The primary safety outcome was the combination of major extracranial bleeding and intracranial hemorrhage. A total of 21 RCTs (96 017 nonvalvular AF patients; median age, 72 years; 65% males; median follow-up, 1.7 years) were included. In comparison to placebo/control, use of aspirin (odds ratio [OR], 0.75 [95% CI, 0.60–0.95]), VKA (0.38 [0.29–0.49]), apixaban (0.31 [0.22–0.45]), dabigatran (0.29 [0.20–0.43]), edoxaban (0.38 [0.26–0.54]), rivaroxaban (0.27 [0.18–0.42]), and the Watchman device (0.36 [0.16–0.80]) significantly reduced the risk of any stroke or systemic embolism in nonvalvular AF patients, as well as all-cause mortality (aspirin: OR, 0.82 [0.68–0.99]; VKA: 0.69 [0.57–0.85]; apixaban: 0.62 [0.50–0.78]; dabigatran: 0.62 [0.50–0.78]; edoxaban: 0.62 [0.50–0.77]; rivaroxaban: 0.58 [0.44–0.77]; and the Watchman device: 0.47 [0.25–0.88]). Apixaban (0.89 [0.80–0.99]), dabigatran (0.90 [0.82–0.99]), and edoxaban (0.89 [0.82–0.96]) reduced risk of all-cause death as compared to VKA.

Conclusions*—**The entire spectrum of therapy to prevent thromboembolism in nonvalvular AF significantly reduced stroke/systemic embolism events and mortality. (J Am Heart Assoc.* 2016;5:e003206 doi: 10.1161/JAHA.116.003206)

Key Words: anticoagulation • atrial fibrillation • comparative effectiveness • left atrial appendage • nonvalvular • oral anticoagulants • stroke • vitamin K antagonists • watchman


Aspirin
Apixaban
Placebo_Control
Dabigatran
VKA
Edoxaban
Watchman
Rivaroxaban


Stroke or Systemic Embolism
Adjusted Treatment Effect
Mean with 95%CI and 95%PrI
Placebo/Control vs VKA
Aspirin 2.30 (1.50,3.54) (1.43,3.70)
Apixaban 1.76 (1.27,2.45) (1.23,2.53)
Dabigatran 0.81 (0.57,1.15) (0.55,1.19)
Edoxaban 0.78 (0.53,1.14) (0.51,1.18)
Rivaroxaban 1.01 (0.70,1.45) (0.68,1.50)
Watchman 0.74 (0.42,1.31) (0.40,1.39)
0.89 (0.19,4.27) (0.16,5.01)
Aspirin vs Placebo/Control
Apixaban 0.77 (0.53,1.11) (0.51,1.15)
Dabigatran 0.35 (0.21,0.58) (0.20,0.61)
Edoxaban 0.34 (0.19,0.60) (0.18,0.64)
Rivaroxaban 0.44 (0.25,0.77) (0.24,0.81)
Watchman 0.32 (0.16,0.66) (0.15,0.71)
0.39 (0.08,1.97) (0.06,2.32)
Apixaban vs Aspirin
Dabigatran 0.46 (0.31,0.67) (0.30,0.69)
Edoxaban 0.44 (0.27,0.73) (0.25,0.77)
Rivaroxaban 0.57 (0.35,0.93) (0.33,0.98)
Watchman 0.42 (0.22,0.81) (0.20,0.87)
0.51 (0.10,2.50) (0.09,2.94)
Dabigatran vs Apixaban
Edoxaban 0.96 (0.57,1.62) (0.54,1.71)
Rivaroxaban 1.25 (0.75,2.07) (0.71,2.18)
Watchman 0.92 (0.47,1.79) (0.44,1.92)
1.10 (0.22,5.49) (0.19,6.47)
Edoxaban vs Dabigatran
Rivaroxaban 1.30 (0.77,2.19) (0.73,2.32)
Watchman 0.96 (0.48,1.89) (0.45,2.03)
1.15 (0.23,5.75) (0.19,6.78)
Rivaroxaban vs Edoxaban
Watchman 0.74 (0.38,1.44) (0.35,1.54)
0.88 (0.18,4.41) (0.15,5.20)
Watchman vs Rivaroxaban
1.20 (0.23,6.34) (0.19,7.52)
.1
.2
1
2.2
7.4


Adjusted Treatment Effect
Major Bleedings
Mean with 95%CI and 95%PrI
Placebo/Control vs VKA
Aspirin 0.47 (0.22,1.00) (0.20,1.08)
Apixaban 0.77 (0.53,1.12) (0.51,1.17)
Dabigatran 0.74 (0.54,1.02) (0.53,1.05)
Edoxaban 0.85 (0.65,1.11) (0.64,1.14)
Rivaroxaban 0.64 (0.46,0.90) (0.45,0.93)
Watchman 1.03 (0.68,1.57) (0.65,1.64)
1.33 (0.46,3.89) (0.41,4.34)
Aspirin vs Placebo/Control
Apixaban 1.65 (0.77,3.51) (0.72,3.79)
Dabigatran 1.59 (0.71,3.54) (0.65,3.84)
Edoxaban 1.82 (0.81,4.07) (0.75,4.42)
Rivaroxaban 1.38 (0.60,3.15) (0.55,3.43)
Watchman 2.21 (0.92,5.26) (0.85,5.75)
2.84 (0.76,10.59) (0.67,12.11)
Apixaban vs Aspirin
Dabigatran 0.96 (0.63,1.47) (0.60,1.53)
Edoxaban 1.10 (0.70,1.75) (0.66,1.83)
Rivaroxaban 0.83 (0.51,1.38) (0.48,1.45)
Watchman 1.34 (0.76,2.35) (0.72,2.49)
1.73 (0.55,5.37) (0.49,6.03)
Dabigatran vs Apixaban
Edoxaban 1.15 (0.76,1.72) (0.73,1.80)
Rivaroxaban 0.87 (0.55,1.37) (0.53,1.43)
Watchman 1.39 (0.82,2.35) (0.78,2.48)
1.79 (0.59,5.48) (0.52,6.14)
Edoxaban vs Dabigatran
Rivaroxaban 0.76 (0.50,1.16) (0.47,1.21)
Watchman 1.21 (0.74,1.99) (0.70,2.10)
1.56 (0.52,4.72) (0.46,5.28)
Rivaroxaban vs Edoxaban
Watchman 1.60 (0.94,2.74) (0.89,2.89)
2.07 (0.67,6.35) (0.60,7.12)
Watchman vs Rivaroxaban
1.29 (0.41,4.08) (0.36,4.59)
.2
.5
1
4.5
12

- Watchman vs NOAC: maliyet etkin mi

Time to Cost-Effectiveness Following Stroke Reduction Strategies in AF

Warfarin Versus NOACs Versus LAA Closure

Vivek Y. Reddy, MD,* Ronald L. Akehurst, MFPHM,† Shannon O. Armstrong, BA,‡ Stacey L. Amorosi, MA,§ Stephen M. Beard, MSc,‖ David R. Holmes, Jr, MD¶

ABSTRACT

BACKGROUND Left atrial appendage closure (LAAC) and nonwarfarin oral anticoagulants (NOACs) have emerged as safe and effective alternatives to warfarin for stroke prophylaxis in patients with nonvalvular atrial fibrillation (AF).

OBJECTIVES This analysis assessed the cost-effectiveness of warfarin, NOACs, and LAAC with the Watchman device (Boston Scientific, Marlborough, Massachusetts) for stroke risk reduction in patients with nonvalvular AF at multiple time points over a lifetime horizon.

METHODS A Markov model was developed to assess the cost-effectiveness of LAAC, NOACs, and warfarin from the perspective of the Centers for Medicare & Medicaid Services over a lifetime (20-year) horizon. Patients were 70 years of age and at moderate risk for stroke and bleeding. Clinical event rates, stroke outcomes, and quality of life information were drawn predominantly from PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) 4-year data and meta-analyses of warfarin and NOACs. Costs for stroke risk reduction therapies, treatment of associated acute events, and long-term care following disabling stroke were presented in 2015 U.S. dollars.

RESULTS Relative to warfarin, LAAC was cost-effective at 7 years ($42,994/quality-adjusted life-years [QALY]), and NOACs were cost-effective at 16 years ($48,446/QALY). LAAC was dominant over NOACs by year 5 and warfarin by year 10. At 10 years, LAAC provided more QALYs than warfarin and NOACs (5.855 vs. 5.601 vs. 5.751, respectively). In sensitivity analyses, LAAC remained cost-effective relative to warfarin ($41,470/QALY at 11 years) and NOACs ($21,964/QALY at 10 years), even if procedure costs were doubled.

CONCLUSIONS Both NOACs and LAAC with the Watchman device were cost-effective relative to warfarin, but LAAC was also found to be cost-effective and to offer better value relative to NOACs. The results of this analysis should be considered when formulating policy and practice guidelines for stroke prevention in AF. (J Am Coll Cardiol 2015;66:2728–39)

TABLE 4 QALY and Cost Results at 5, 10, 15, and 20 Years

	Total QALYs	Incremental QALYs (Relative to Warfarin)	Total Costs	Incremental Costs (Relative to Warfarin)	Incremental Cost per QALY Versus Warfarin	Incremental Cost per QALY Versus NOAC
5 yrs						
LAAC	3.455	0.068	$20,892	$10,128	$149,468	Dominant
Warfarin	3.387	–	$10,764	–	–	–
NOAC	3.448	0.061	$20,924	$10,160	$167,446	–
10 yrs						
LAAC	5.855	0.254	$25,425	-$1,409	Dominant	Dominant
Warfarin	5.601	–	$26,834	–	–	–
NOAC	5.751	0.150	$39,260	$12,426	$82,684	–
15 yrs						
LAAC	7.309	0.466	$29,075	-$12,251	Dominant	Dominant
Warfarin	6.843	–	$41,326	–	–	–
NOAC	7.077	0.234	$53,431	$12,105	$51,755	–
20 yrs						
LAAC	8.031	0.638	$31,198	-$18,748	Dominant	Dominant
Warfarin	7.392	–	$49,946	–	–	–
NOAC	7.682	0.290	$61,701	$11,755	$40,602	–

QALY = quality-adjusted life-year; other abbreviations as in Table 1.

Yıllık maliyet:
3780 Dolar
Watchman/NOAC:
4,26

TABLE 3 Cost Inputs

Acute Events	Costs	Code (Ref. #)
LAAC procedure (including 2 TEEs)*	$16,109	DRG 273/274 (43)
Fatal ischemic stroke	$8,854	DRG 063 (38)
Severe ischemic stroke	$48,539	DRG 061/CMG 108-110 (38,39)
Moderate ischemic stroke	$33,235	DRG 062/CMG 101-104 (38,39)
Minor ischemic stroke	$23,236	DRG 063/CMG 105-107 (38,39)
Transient ischemic attack	$4,097	DRG 069 (38)
Systemic embolism (nonfatal)	$4,924	DRG 068 (38)
Systemic embolism (fatal)	$8,520	DRG 067 (38)
Fatal hemorrhagic stroke	$10,194	DRG 064 (38)
Severe hemorrhagic stroke	$42,562	DRG 064/CMG 108-110 (38,39)
Moderate hemorrhagic stroke	$28,595	DRG 065/CMG 101-104 (38,39)
Minor hemorrhagic stroke	$18,797	DRG 066/CMG 105-107 (38,39)
Major extracranial hemorrhage (nonfatal)	$5,877	DRG 377 (38)
Major extracranial hemorrhage (fatal)	$10,425	DRG 378 (38)
Minor bleeding	$427	CPT 42970 (44)
Myocardial infarction (nonfatal)	$6,862	DRG 280, 281, 282 (38)
Myocardial infarction (fatal)	$5,771	DRG 283, 284, 285 (38)
Quarterly costs		
Warfarin + INR monitoring	$91	CPT 85610, 99211 (44,45)
NOAC	$945	(45)
Independent post-stroke	$108	CPT 99214 (44)
Moderately disabled post-stroke	$9,293	(40–42)
Severely disabled post-stroke	$15,131	(40–42)

TÜRKİYE

NOAC Yıllık maliyet:
960 TL

Watchman implantasyon maliyeti:
13000 TL

Watchman/NOAC:
13,56

Türkiye için cost-efektivite eşitlik noktası: Yaklaşık 13-14 yıl

TABLE 4 QALY and Cost Results at 5, 10, 15, and 20 Years

	Total QALYs	Incremental QALYs (Relative to Warfarin)	Total Costs	Incremental Costs (Relative to Warfarin)	Incremental Cost per QALY Versus Warfarin	Incremental Cost per QALY Versus NOAC
5 yrs						
LAAC	3.455	0.068	$20,892	$10,128	$149,468	Dominant
Warfarin	3.387	–	$10,764	–	–	–
NOAC	3.448	0.061	$20,924	$10,160	$167,446	–
10 yrs						
LAAC	5.855	0.254	$25,425	-$1,409	Dominant	Dominant
Warfarin	5.601	–	$26,834	–	–	–
NOAC	5.751	0.150	$39,260	$12,426	$82,684	–
15 yrs						
LAAC	7.309	0.466	$29,075	-$12,251	Dominant	Dominant
Warfarin	6.843	–	$41,326	–	–	–
NOAC	7.077	0.234	$53,431	$12,105	$51,755	–
20 yrs						
LAAC	8.031	0.638	$31,198	-$18,748	Dominant	Dominant
Warfarin	7.392	–	$49,946	–	–	–
NOAC	7.682	0.290	$61,701	$11,755	$40,602	–

QALY = quality-adjusted life-year; other abbreviations as in Table 1.

Türkiye için cost-efektivite üstünlük noktası:
> 20 yıl
(yaklaşık 30. yılda kesin dominant)

TABLE 4 QALY and Cost Results at 5, 10, 15, and 20 Years

	Total QALYs	Incremental QALYs (Relative to Warfarin)	Total Costs	Incremental Costs (Relative to Warfarin)	Incremental Cost per QALY Versus Warfarin	Incremental Cost per QALY Versus NOAC
5 yrs						
LAAC	3.455	0.068	$20,892	$10,128	$149,468	Dominant
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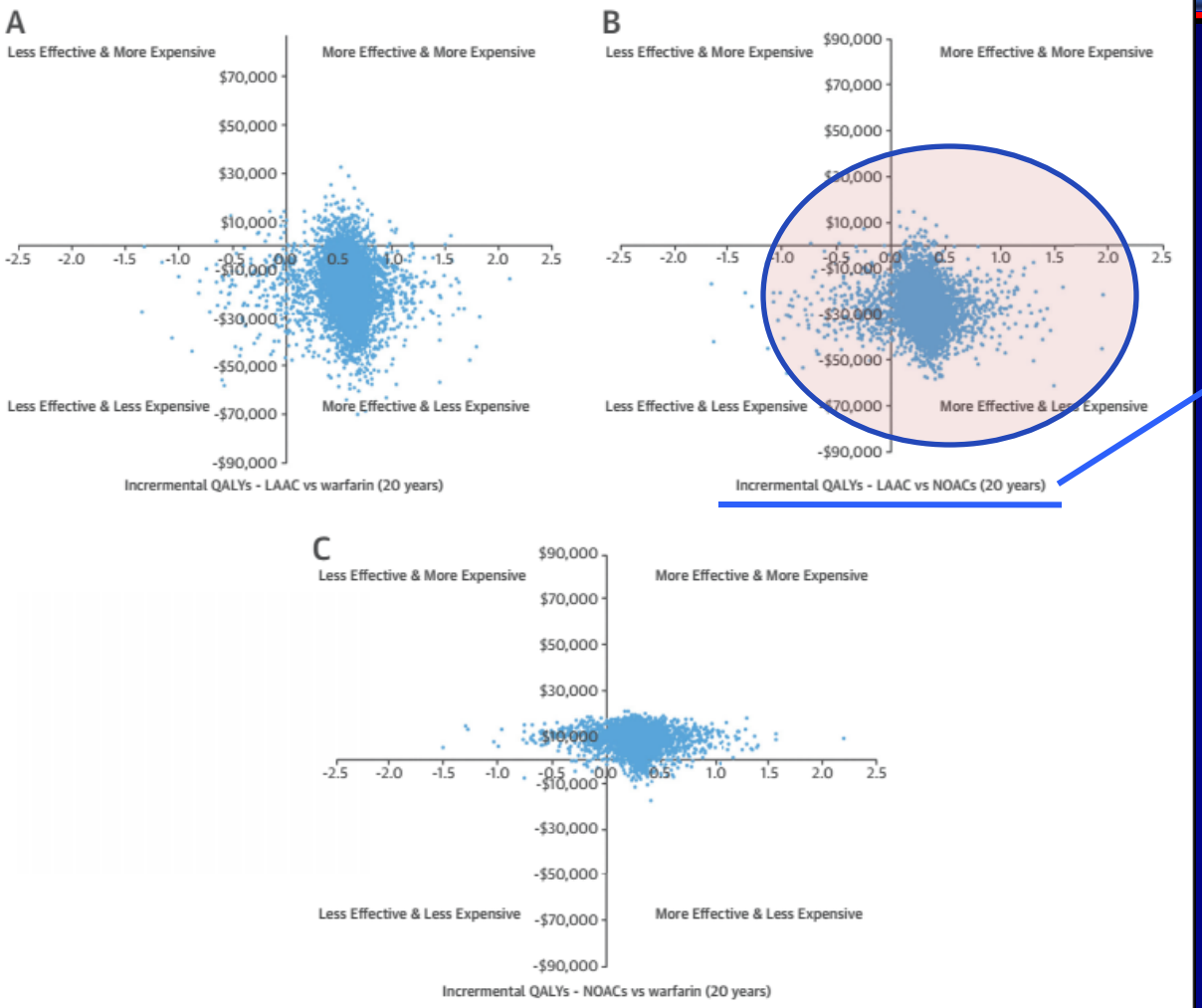
LAAC	8.031	0.638	$31,198	-$18,748	Dominant	Dominant
Warfarin	7.392	–	$49,946	–	–	–
NOAC	7.682	0.290	$61,701	$11,755	$40,602	–

QALY = quality-adjusted life-year; other abbreviations as in Table 1.

FIGURE 3 Scatter Plots of Incremental Costs and Incremental QALYs at 20 Years for LAAC Versus Warfarin, LAAC Versus NOACs, and NOACs Versus Warfarin



Probabilistic sensitivity analysis results reflect 5,000 model simulations to estimate the effect of uncertainty on model results. QALYs = quality-adjusted life-years; other abbreviations as in Figures 1 and 2.

20 Yıl !!

Türkiye için: 50 yıl

Learning Curve Assessment for Percutaneous Left Atrial Appendage Closure With the WATCHMAN Occluder

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Objectives: *We sought to evaluate the effect of increasing experience with left atrial appendage (LAA) closure on short-term outcome.*

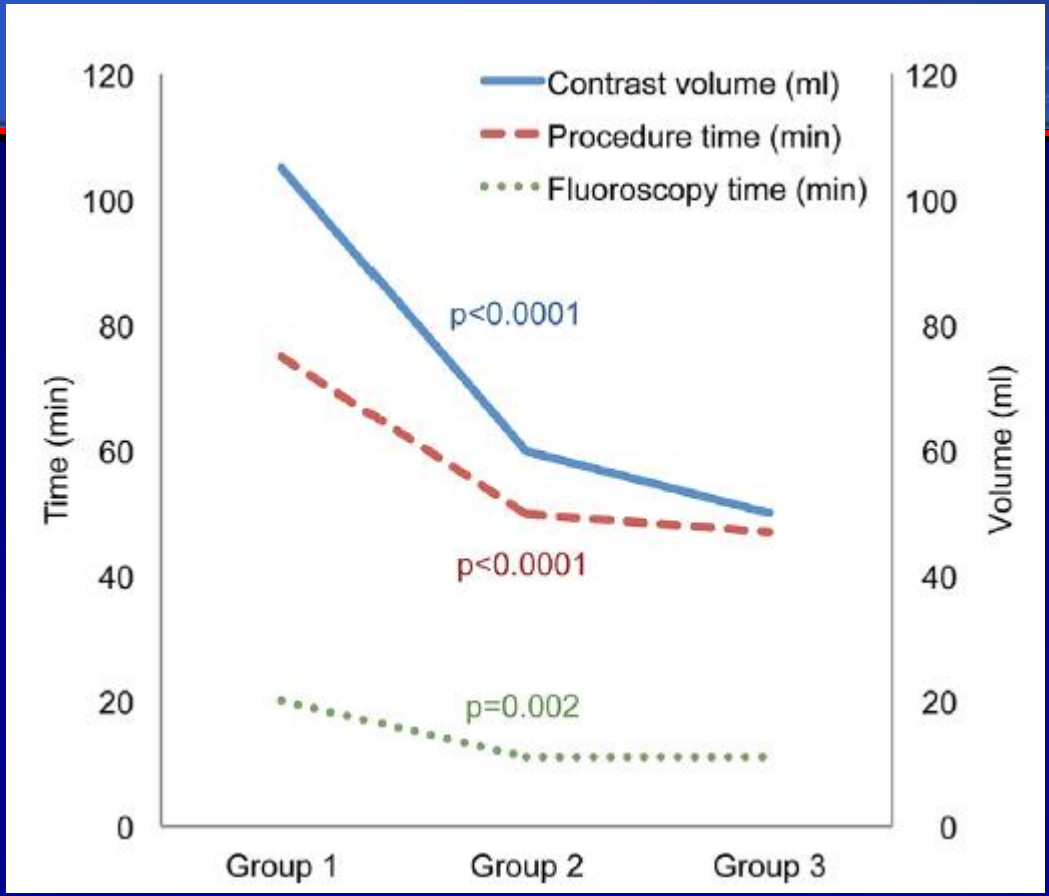
Background: *Data regarding the impact of the learning curve of LAA closure—particularly regarding technical aspects of the procedure—are lacking.*

Methods: *The present analysis represents first data from a single-center all-comer registry. The population was divided into 3 groups according to treatment time (group 1: patients 1–30; group 2: patients 31–60; group 3: patients 61–90).*

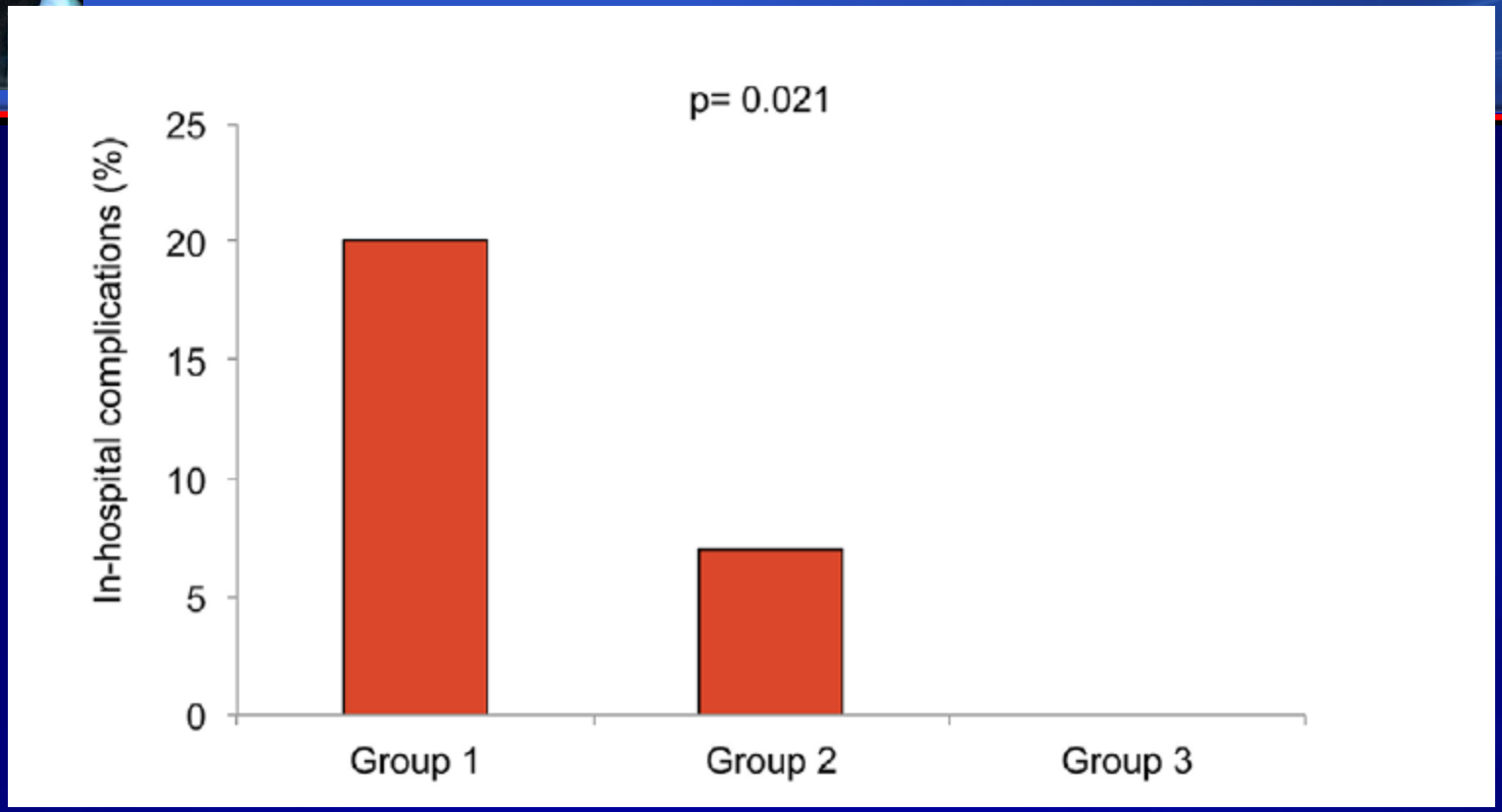
Results: *The mean age of the population was 77 years. Median CHA_2DS_2VASC Score and HAS-BLED were 5 (IQR 3–5) and 3 (IQR 3–4), respectively. Implantation success was 90% with a slight but not statistically significant increase during the course of the registry. Procedure time (75 [62–108] vs. 50 [43–66] vs. 47 [41–61] minutes; $P < 0.0001$), fluoroscopy time (20 [15–30] vs. 11 [8−19] vs. 11 [9–18] minutes; $P = 0.002$), and contrast volume (105 [70–170] vs. 60 [50–75] vs. 50 [50–73] ml; $P < 0.0001$) were reduced across the 3 groups. In-hospital complications decreased significantly (20 vs. 7% vs. 0%; $P = 0.021$). The compression grade of the occluder was chosen higher with increasing learning curve (15 [11–25] vs. 25 [17–29] vs. 21 [14–26] %; $P = 0.05$).*

Conclusions: *With increasing operator experience the performance and safety of percutaneous LAA closure improved continuously.* (J Interven Cardiol 2016;29:393–399)

- Tek operator:
- Grup 1: 1-30.hastalar
- Grup 2: 31-60. hastalar
- Grup 3: 61-90.hastalar



30 vakadan sonra öğrenme eğrisi düzleşiyor



Komplikasyonlar:

Grup 1: %20 (1 ruptür)

Grup 2: %7

Grup 3: % 0

- Sonuç:
- Öğrenme eğrisi en az 60 olgu
- Öğrenildikten sonra işlem süresi hasta başına 1 saat’e yakın
- Öğrenme sürecinde komplikasyonlar ciddi

- İyi bir laboratuar ve ekiple günde en fazla 8-10 vaka yapılabilir.
- Tek laboratuar tam zamanlı bu işe ayrılsa senede 1500-2000 olgu
- Uygun tüm hastalara implantasyon için 1000 laboratuar'ın tam zamanlı bu işe ayrılması gerekir (yaklaşık 10 yılda stasyoner implantasyon temposuna ulaşılabilir).
- Bu süreçte en az 30.000 hasta öğrenme eğrisinde komplikasyonla karşılacaktır
- Hastaların bir kısmı (>CHADS-VASC hastaları) cost efektif zaman yakalanamadan başka sebepler ile ölmeye aday

- Bence “epidemik” bir sorun için fazla “butik” bir çözüm

Recommendations for occlusion or exclusion of the left atrial appendage

Recommendations	Class[a]	Level[b]	Ref[c]
After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention.	I	B	461, 462
LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause).	IIb	B	449, 453, 454
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.	IIb	B	463
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery.	IIb	B	468

AF = atrial fibrillation; LAA = left atrial appendage.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.