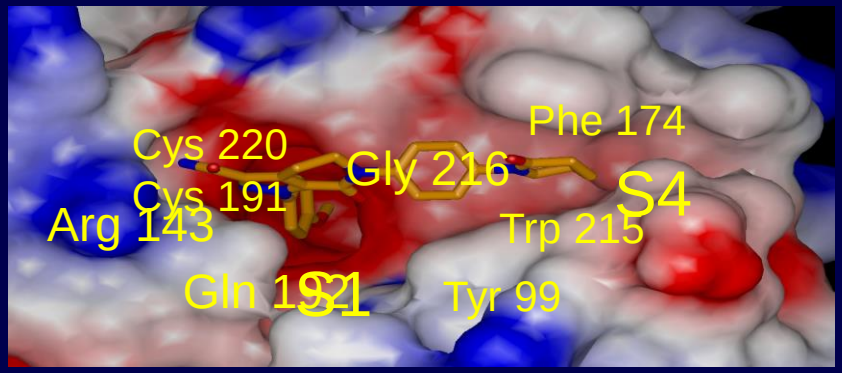
Apiksaban



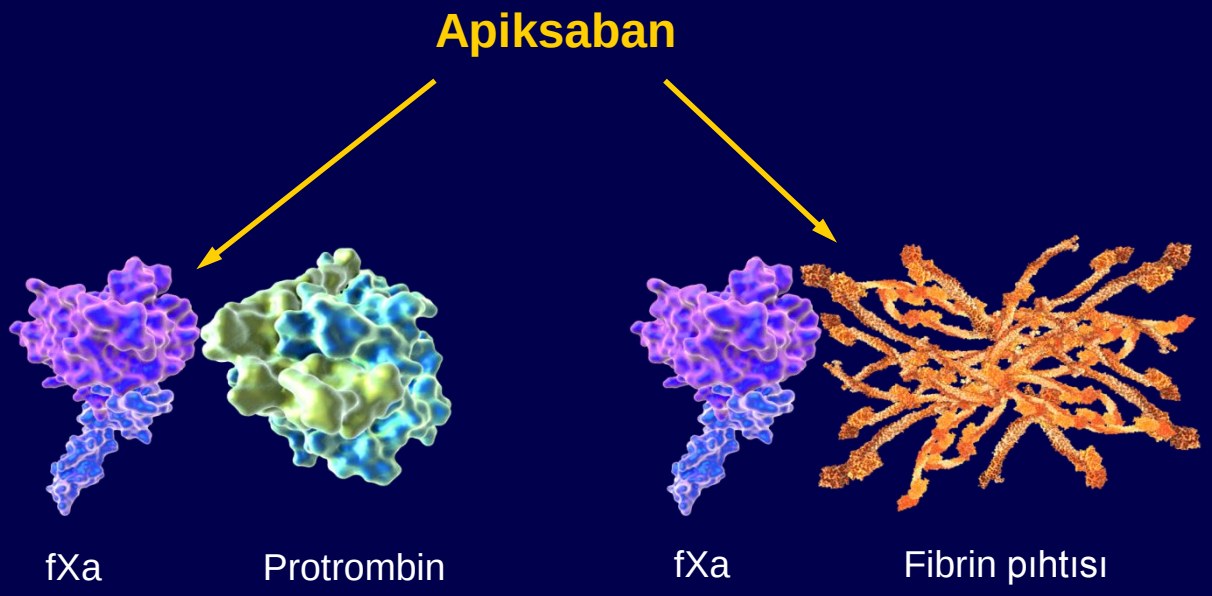
Dr. Murat Özdemir

Gazi Üniversitesi, ANKARA

AF Zirvesi, Nisan 2015, ANTALYA

Doğrudan faktör Xa inhibisyonu - apiksaban

Apiksaban pıhtıya veya protrombinaz kompleksine bağlı olan Faktör Xa'yı inhibe eder



Turpie AGG. *Arterioscler Thromb Vasc Biol* 2007;27:1238-1247.
Ansell J. *J Thromb Haemost* 2007;5(suppl1):60-64.

Apiksaban - farmakokinetik

- Emilim
  - Tüm GIS boyunca
    - Yoğun olarak distal ince barsak ve çıkan kolon
  - Zirve plazma konsantrasyonu yaklaşık 3 - 4 saatte
  - Gıda varlığından etkilenmez

Lam S. Card in Rev, 2013, e-pub ahead of print. DOI: 10.1097/CRD.0b013e318293d6e6

Apiksaban - farmakokinetik

- Metabolizma/Atılım
  - Yarılanma zamanı yaklaşık 12 saat
  - CYP3A4 tarafından metabolize edilir – aktif metaboliti yoktur
  - Renal klirens – total klirensin yaklaşık % 27'sinden sorumlu
  - P-glikoprotein substratıdır

Lam S. Card in Rev, 2013, e-pub ahead of print. DOI: 10.1097/CRD.0b013e318293d6e6

AVERROES çalışması

Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or are Unsuitable for Vitamin K Antagonist Treatment

Connolly SJ et al. *N Engl J Med* 2011;364:806–817.

AVERROES - tasarım

N=5,599

Hasta populasyonu

- Nonvalvüler AF ve en az bir inme risk faktörü
- Warfarin kullanamamış veya kullanamayacağı düşünülen olgular

Apiksaban 5 mg BD
(2.5 mg – en az ikisi varsa
Yaş≥80, VA≤60 kg, krea≥1.5mg/dL)

Aspirin 81–324 mg OD

Primer sonlanım

- İskemik inme, hemorajik inme veya sistemik emboli

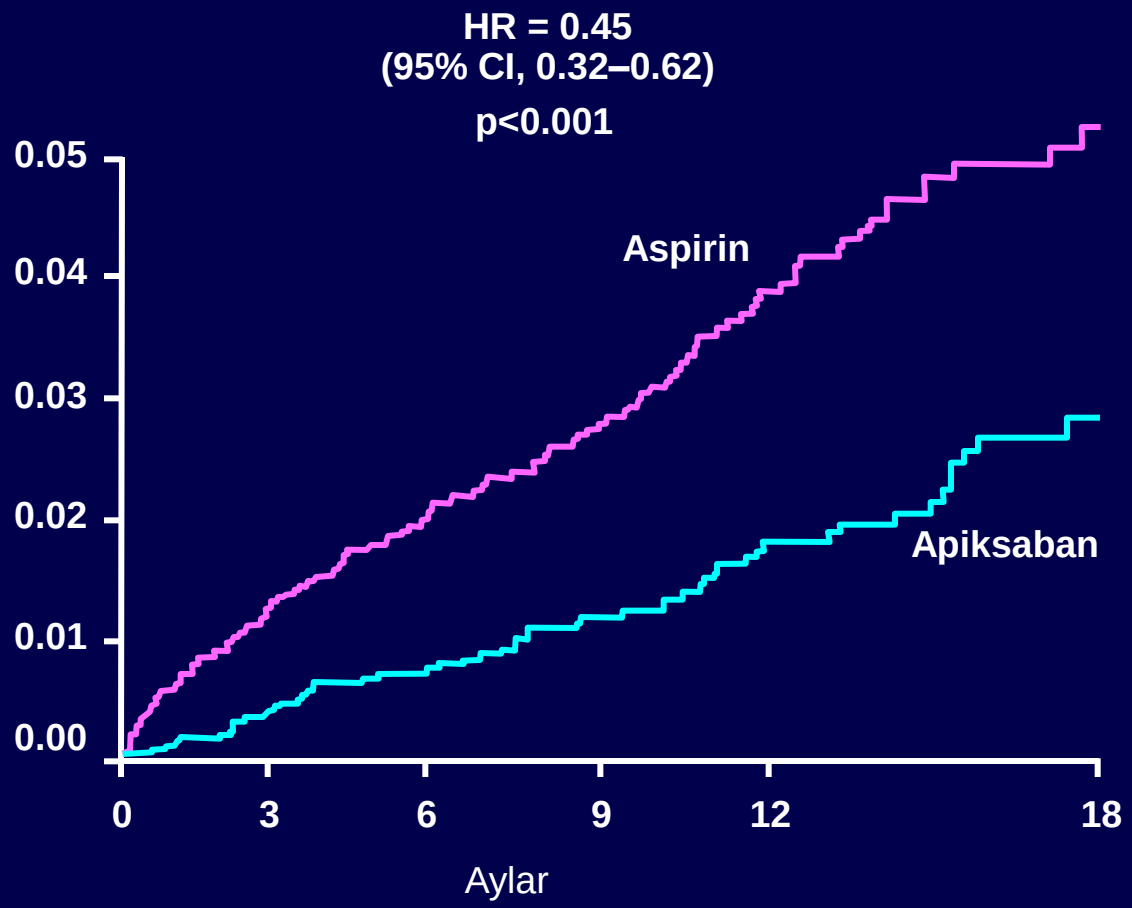
Connolly SJ et al. *N Engl J Med*. 2011;364:806–817
Eikelboom JW et al. *Am Heart J* 2010;159:348–353.e1.

AVERROES

- Ortalama $CHADS_2$ skoru = 2.1
- Medyan 1.1 yıl takip sonunda erken sonlandırıldı
- Hastaların % 94'ünde apiksaban 5 mg BID

Connolly SJ et al. *N Engl J Med* 2011;364:806–817
*Clinicaltrials.gov NCT00496769

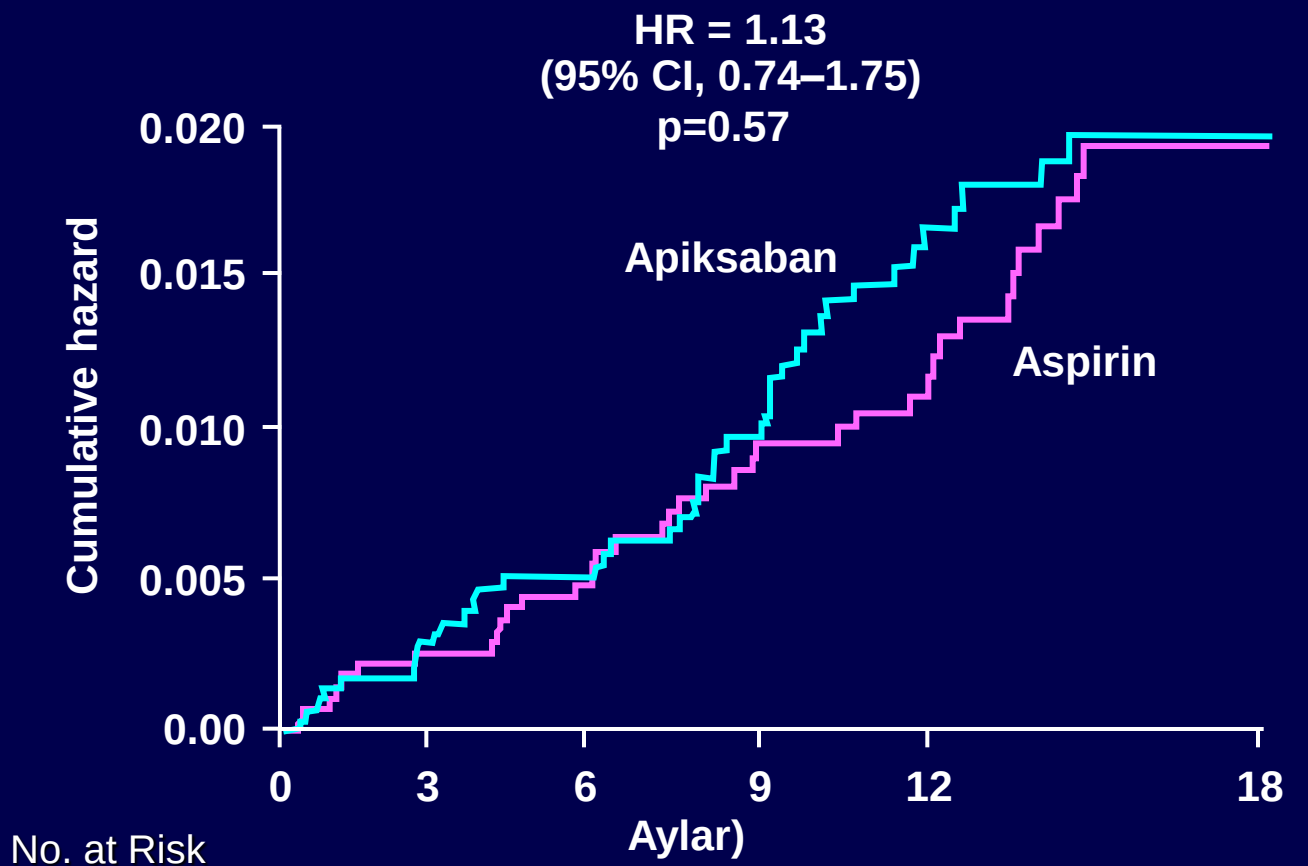
AVERROES – İnme ve sistemik emboli



No. at Risk						
Aspirin	2791	2716	2530	2112	1543	628
Apixaban	2808	2758	2566	2125	1522	615

Connolly SJ et al. *N Engl J Med* 2011;364:806–817

AVERROES - Majör kanama



Connolly SJ et al. *N Engl J Med* 2011;364:806–817

AVERROES – Ciddi yan etkiler

	Apiksaban (%)	Aspirin (%)	p
En az 1 ciddi istenmeyen olay	**22.2**	**27.2**	**<0.001**
Kardiyak sorunlar	**11.3**	**12.1**	**0.32**
Aritmiler	**4.3**	**4.5**	**0.66**
Koroner arter sorunları	**2.2**	**2.5**	**0.46**
Kalp yetmezliği	**4.3**	**4.7**	**0.53**
Gastrointestinal sorunlar	**2.4**	**2.8**	**0.38**
Genel sorunlar	**2.4**	**2.8**	**0.38**
Enfeksiyonlar	**4.2**	**5.3**	**0.045**
Sinir sistemi sorunları	**3.0**	**6.6**	**<0.001**
Yaralanma, prosedürel komplikasyonlar	**2.2**	**2.2**	**0.97**

Connolly SJ et al. *N Engl J Med* 2011;364:806–817 in supplementary appendix

Çalışma ilacının kalıcı biçimde bırakılması

- 2 yılda :
  - Apiksaban kolunda % 17.9
  - Aspirin kolunda % 20.5
    - HR = 0.88 (95% CI 0.78-0.99, p=0.03)

Connolly SJ et al. *N Engl J Med* 2011;364:806–817

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

N Engl J Med 2011;365:981-92

ARISTOTLE - tasarım

N=18,201

Hasta populasyonu

- **Nonvalvüler AF ve en az biri :**
  - **Yaş ≥ 75**
  - **İnme/TIA/emboli öyküsü**
  - **Son 3 ayda semptomatik KY veya LVEF ≤ 0.40**
  - **Diabetes mellitus**
  - **HT**

Primer Etkinlik sonlanımı

- **İnme veya sistemik emboli**

Temel Sekonder Etkinlik sonlanımı

- **Tüm nedenlere bağlı ölüm**

Primer emniyet sonlanımı

- **Majör kanama**

Randomize
çift-kör,
double-dummy

Apiksaban 5 mg BD
(2.5 mg BD bazı olgularda)†

Warfarin
(hedef INR 2.0−3.0)

†en az ikisi: yaş ≥ 80 ; VA ≤ 60 kg; serum kreatinin ≥ 1.5 mg/dL

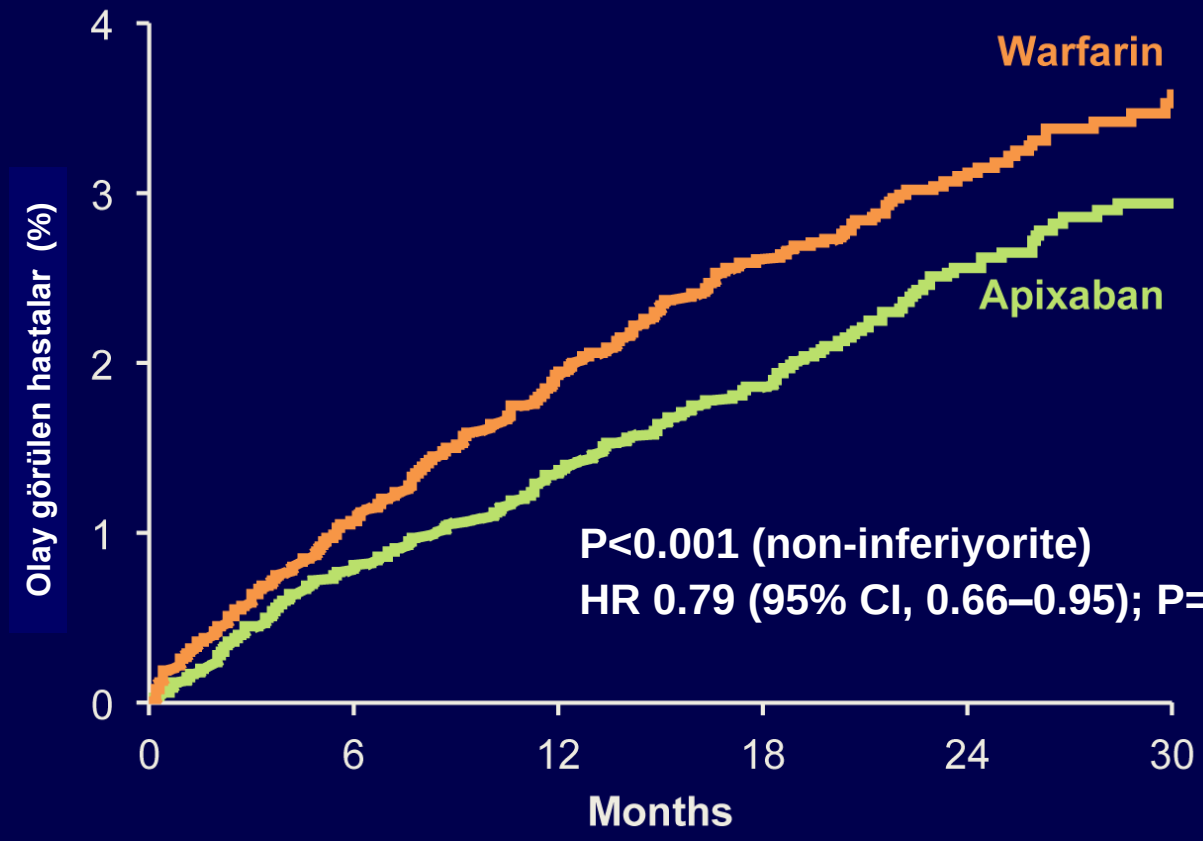
Granger CG et al. *N Engl J Med* 2011;10.1056

ARISTOTLE

- % 85 persistan/kalıcı AF
- Ortalama $CHADS_2$ skoru = 2.1
- % 5 olguda 2.5 mg doz

- Takip
  - Medyan 1.8 yıl takip
  - 69 hasta izlemde kayıp
- Warfarin kolunda TTR
  - Ortalama % 62
- İlaç bırakma oranları :
  - Warfarin % 27.5
  - Apiksaban % 25.3

ARISTOTLE – İnme veya sistemik emboli



No. at Risk						
Apiksaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

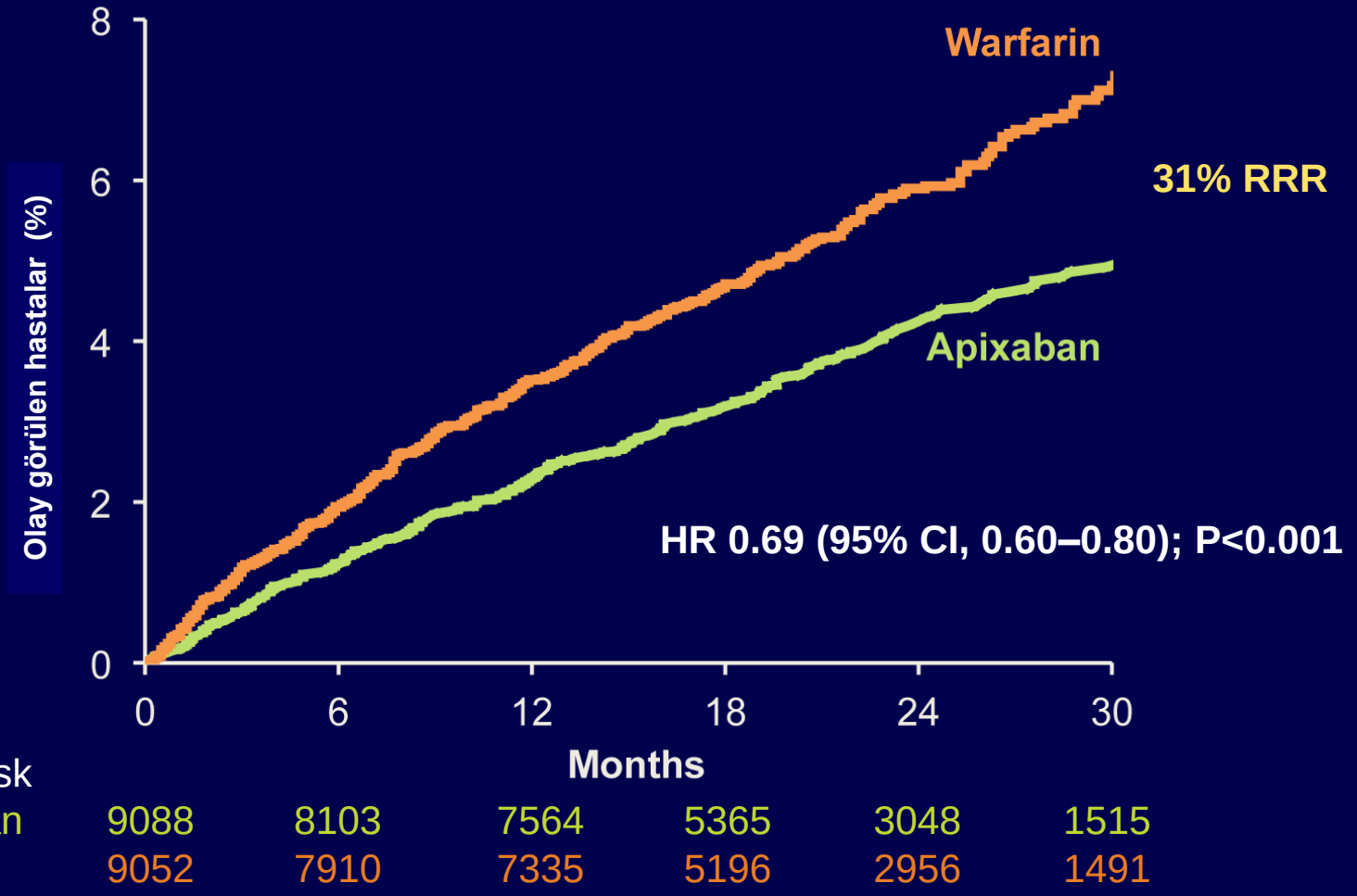
ARISTOTLE

Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

N Engl J Med 2011;365:981-92

ARISTOTLE – majör kanama



No. at Risk						
Apiksaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

ARISTOTLE – istenmeyen olaylar

N (%)	Apixaban (N=9088)	Warfarin (N=9052)
İstenmeyen olay - toplam	7406 (81.5)	7521 (83.1)
Ciddi istenmeyen olay - toplam	3182 (35.0)	3302 (36.5)
İstenmeyen olaya bağlı ilaç bırakılması	688 (7.6)	758 (8.4)

Granger CG et al. *N Engl J Med* 2011;10.1056/NEJMoa1107039 supplementary appendix. NEJM.org 28 August 2011

ARISTOTLE - sonuç

- Warfarine kıyasla apiksaban :
  - İnme ve sistemik emboli riskinde % 21 (p=0.01)
  - Majör kanama riskinde % 31 (p<0.001)
  - Ölüm riskinde % 11 (p=0.047) azalmaya yol açmıştır.
- Bulgular tüm alt gruplarda benzer ve tutarlıdır
- Apiksabanın kabul edilebilir bir yan-etki profili ve warfarinden daha az ilaç bırakma oranı vardır

ARISTOTLE sonuç

1.8 yıl süreyle tedavi edilen her 1000 hastada, warfarine kıyasla apiksaban ile önlenen olaylar :

- İnme 6 hastada (hemorajik 4, iskemik 2)
- Majör kanama 15 hastada
- Ölüm 8 hastada

Granger CG et al. *N Engl J Med* 2011;10.1056/NEJMoa1107039. NEJM.org 28 August 2011

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

Nonvalvüler AF'da tromboembolinin önlenmesi için öneriler - Genel	Sınıf	Kanıt
Nonvalvüler AF'da inme riskini belirlemede CHADSVASc skoru önerilir	I	A
CHADSVASc skoru = 0 ise antitrombotik tedavi önerilmez	I	A
CHADSVASc skoru ≥ 2 ise; **Warfarin (INR=2-3) veya** **Dabigatran veya** **Apiksaban veya** **Rivaroksaban**	**I**	**A**
CHADSVASc skoru = 1 ise; **Warfarin (INR=2-3) veya** **Dabigatran veya** **Apiksaban veya** **Rivaroksaban** **Kanama riski ve hasta tercihi de dikkate alınarak**	**IIa**	**A**
Sadece cinsiyet nedeniyle CHADSVASc skoru = 1 olan olgularda antitrombotik tedavi verilmemesi düşünülmelidir	IIa	B
Hasta herhangi bir OAK kullanmayı reddediyorsa, ASA 75-100 mg + klopidogrel 75 mg (kanama riski düşükse) veya sadece ASA 75-325 mg düşünülmelidir	IIa	B

Nonvalvüler AF'da tromboembolinin önlenmesi için öneriler – Yeni oral antikoagülanlar	Sınıf	Kanıt
OAK endikasyonu olan ancak warfarin(INR=2-3) kullanamayan olgularda; Dabigatran veya Apiksaban veya Rivaroksaban	I	B
OAK endike olduğunda, olguların çoğunda warfarin(INR=2-3) yerine Dabigatran veya Apiksaban veya Rivaroksaban düşünülmelidir	**IIa**	**A**
Dabigatran kullanılacak olursa, olguların çoğunda 150 mg BD dozu düşünülmeli; 110 mg BD dozu aşağıdaki durumlarda önerilmelidir Yaş ≥ 80 İlaç etkileşimi (verapamil gibi) HASBLED skoru ≥ 3 Kreatinin klirensi 30-49 mL/dak	IIa	B
Rivaroksaban kullanılacak olursa, olguların çoğunda 20 mg OD dozu düşünülmeli; 15 mg OD dozu aşağıdaki durumlarda önerilmelidir HASBLED skoru ≥ 3 Kreatinin klirensi 30-49 mL/dak	IIa	C
Yeni oral antikoagülan kullanılan olgularda böbrek fonksiyonları başlangıçta ve izlemde yılda bir kreatinin klirensi hesaplanarak değerlendirilmelidir. Başlangıçta orta derecede böbrek fonksiyon bozukluğu olanlarda takipte yılda 2-3 değerlendirme önerilir	IIa	B
Kreatinin klirensi 30 mL/dak altında olanlarda yeni oral antikoagülanlar kullanılmamalıdır	III	A

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

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

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

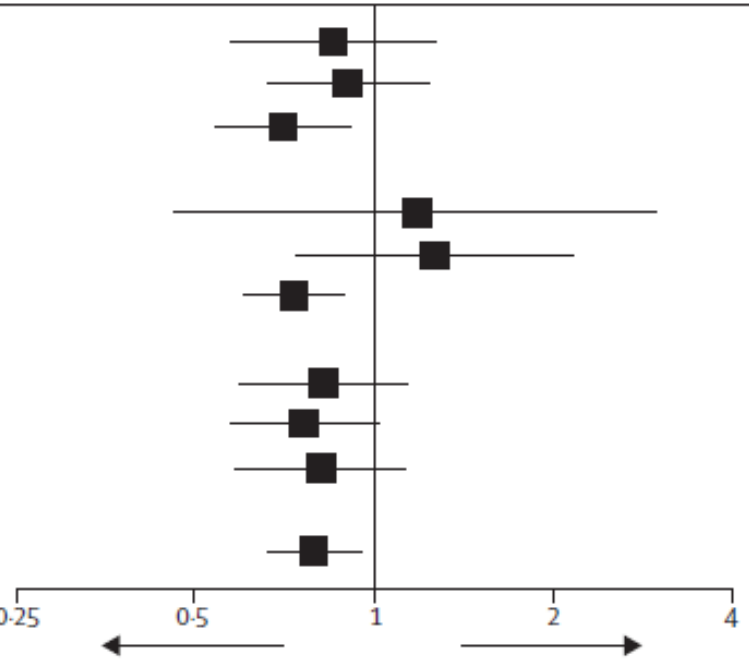
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended. Options include:		
Warfarin	I	A
Dabigatran, rivaroxaban, or apixaban	I	B

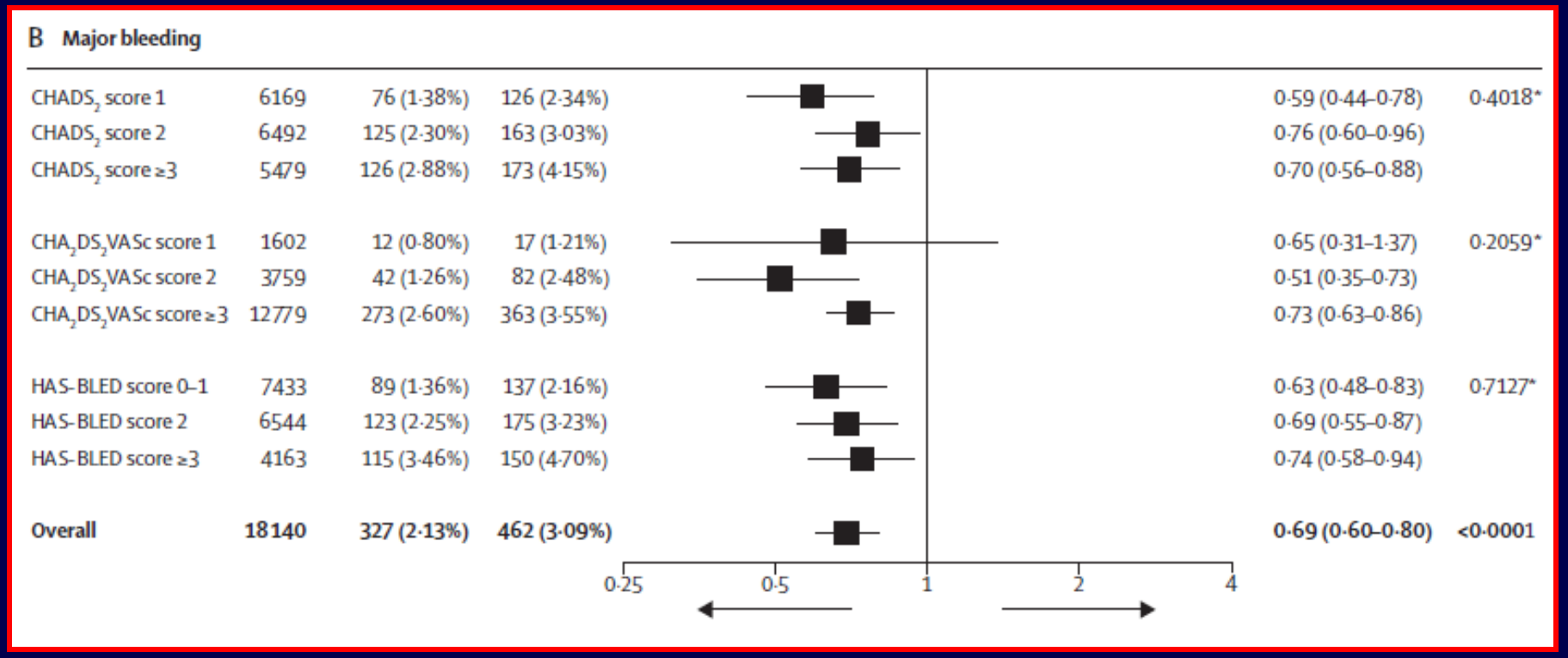
Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial

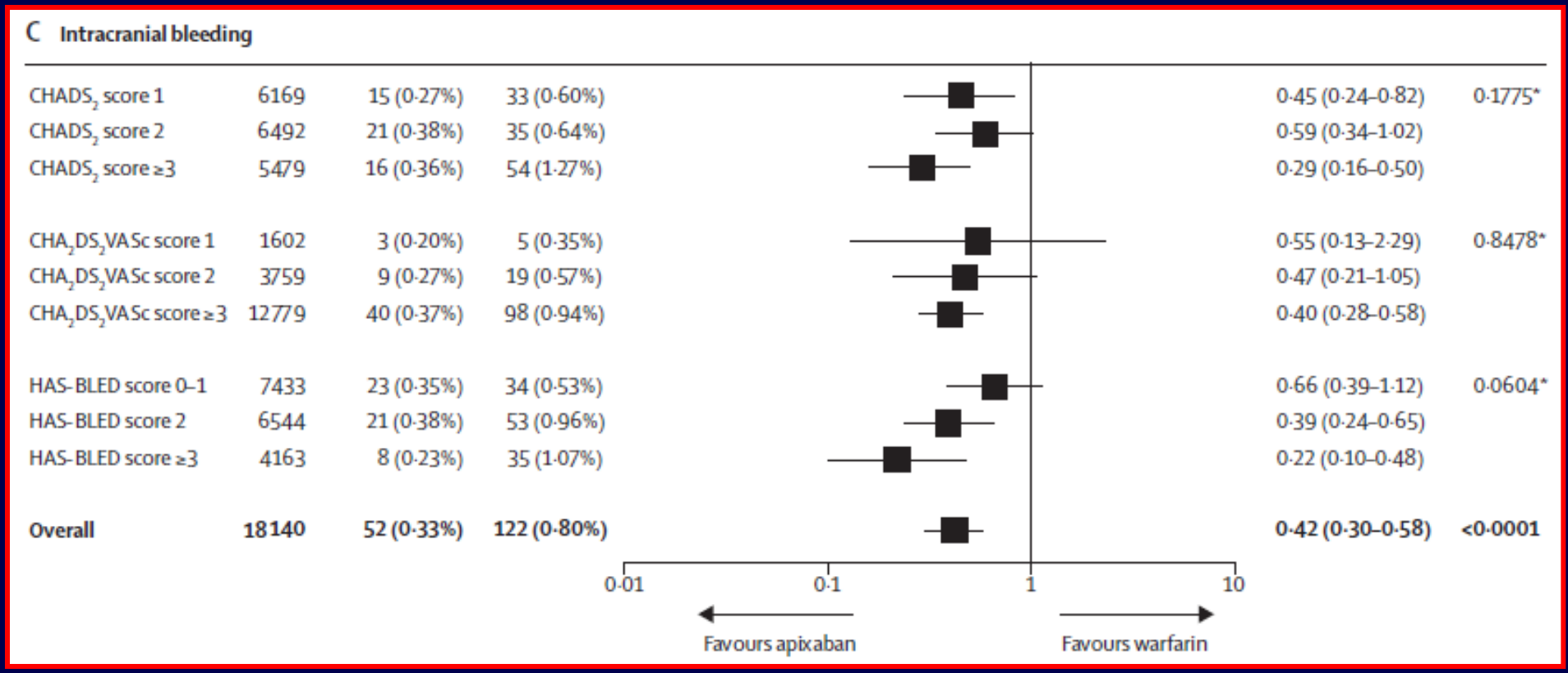
Renato D Lopes, Sana M Al-Khatib, Lars Wallentin, Hongqiu Yang, Jack Ansell, M Cecilia Bahit, Raffaele De Caterina, Paul Dorian, J Donald Easton, Cetin Erol, Justin A Ezekowitz, Bernard J Gersh, Christopher B Granger, Stefan H Hohnloser, John Horowitz, Elaine M Hylek, John J V McMurray, Puneet Mohan, Dragos Vinereanu, John H Alexander

A Stroke or systemic embolism

	Number of patients	Apixaban	Warfarin	HR (95% CI)	p value
$CHADS_2$ score 1	6183	44 (0·74%)	51 (0·87%)	0·85 (0·57–1·27)	0·4457*
$CHADS_2$ score 2	6516	74 (1·24%)	82 (1·37%)	0·90 (0·66–1·23)	
$CHADS_2$ score ≥3	5502	94 (1·95%)	132 (2·80%)	0·70 (0·54–0·91)	
CHA_2DS_2VASc score 1	1604	10 (0·62%)	8 (0·53%)	1·18 (0·46–2·98)	0·1210*
CHA_2DS_2VASc score 2	3771	30 (0·85%)	24 (0·67%)	1·26 (0·74–2·16)	
CHA_2DS_2VASc score ≥3	12826	172 (1·48%)	233 (2·03%)	0·73 (0·60–0·89)	
HAS-BLED score 0–1	7461	65 (0·92%)	79 (1·14%)	0·82 (0·59–1·13)	0·9422*
HAS-BLED score 2	6568	83 (1·39%)	109 (1·81%)	0·76 (0·57–1·02)	
HAS-BLED score ≥3	4172	64 (1·73%)	77 (2·14%)	0·81 (0·58–1·13)	
Overall	**18201**	**212 (1·27%)**	**265 (1·60%)**	**0·79 (0·66–0·95)**	**0·0114**




B Major bleeding
CHADS2 score 1 6169 76 (1·38%) 126 (2·34%) 0·59 (0·44–0·78) 0·4018*
CHADS2 score 2 6492 125 (2·30%) 163 (3·03%) 0·76 (0·60–0·96)
CHADS2 score ≥3 5479 126 (2·88%) 173 (4·15%) 0·70 (0·56–0·88)
CHA2DS2VASc score 1 1602 12 (0·80%) 17 (1·21%) 0·65 (0·31–1·37) 0·2059*
CHA2DS2VASc score 2 3759 42 (1·26%) 82 (2·48%) 0·51 (0·35–0·73)
CHA2DS2VASc score ≥3 12779 273 (2·60%) 363 (3·55%) 0·73 (0·63–0·86)
HAS-BLED score 0–1 7433 89 (1·36%) 137 (2·16%) 0·63 (0·48–0·83) 0·7127*
HAS-BLED score 2 6544 123 (2·25%) 175 (3·23%) 0·69 (0·55–0·87)
HAS-BLED score ≥3 4163 115 (3·46%) 150 (4·70%) 0·74 (0·58–0·94)
Overall 18140 327 (2·13%) 462 (3·09%) 0·69 (0·60–0·80) <0·0001
0·25
0·5
1
2
4

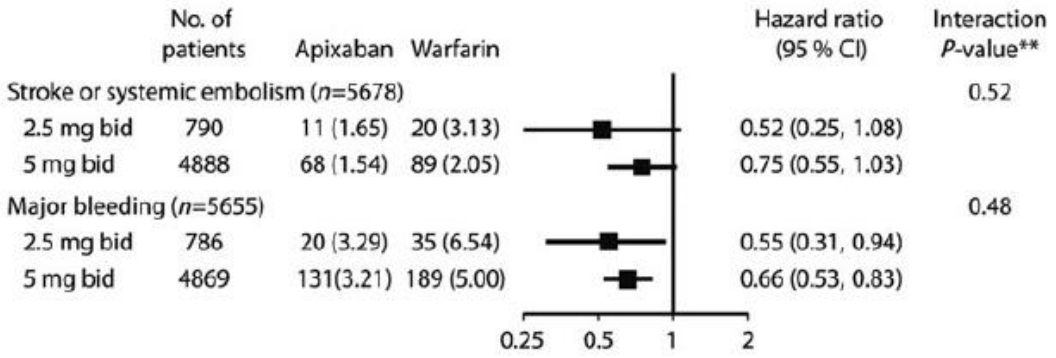

C Intracranial bleeding
CHADS2 score 1 6169 15 (0·27%) 33 (0·60%) 0·45 (0·24–0·82) 0·1775*
CHADS2 score 2 6492 21 (0·38%) 35 (0·64%) 0·59 (0·34–1·02)
CHADS2 score ≥3 5479 16 (0·36%) 54 (1·27%) 0·29 (0·16–0·50)
CHA2DS2VASc score 1 1602 3 (0·20%) 5 (0·35%) 0·55 (0·13–2·29) 0·8478*
CHA2DS2VASc score 2 3759 9 (0·27%) 19 (0·57%) 0·47 (0·21–1·05)
CHA2DS2VASc score ≥3 12779 40 (0·37%) 98 (0·94%) 0·40 (0·28–0·58)
HAS-BLED score 0–1 7433 23 (0·35%) 34 (0·53%) 0·66 (0·39–1·12) 0·0604*
HAS-BLED score 2 6544 21 (0·38%) 53 (0·96%) 0·39 (0·24–0·65)
HAS-BLED score ≥3 4163 8 (0·23%) 35 (1·07%) 0·22 (0·10–0·48)
Overall 18140 52 (0·33%) 122 (0·80%) 0·42 (0·30–0·58) <0·0001
0·01
0·1
1
10
Favours apixaban
Favours warfarin

Efficacy and Safety of Apixaban Compared With Warfarin at Different Levels of Predicted International Normalized Ratio Control for Stroke Prevention in Atrial Fibrillation

Conclusions—The benefits of apixaban compared with warfarin for stroke or systemic embolism, bleeding, and mortality appear similar across the range of centers' and patients' predicted quality of international normalized ratio control.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00412984. (***Circulation.*** **2013;127:2166-2176.**)

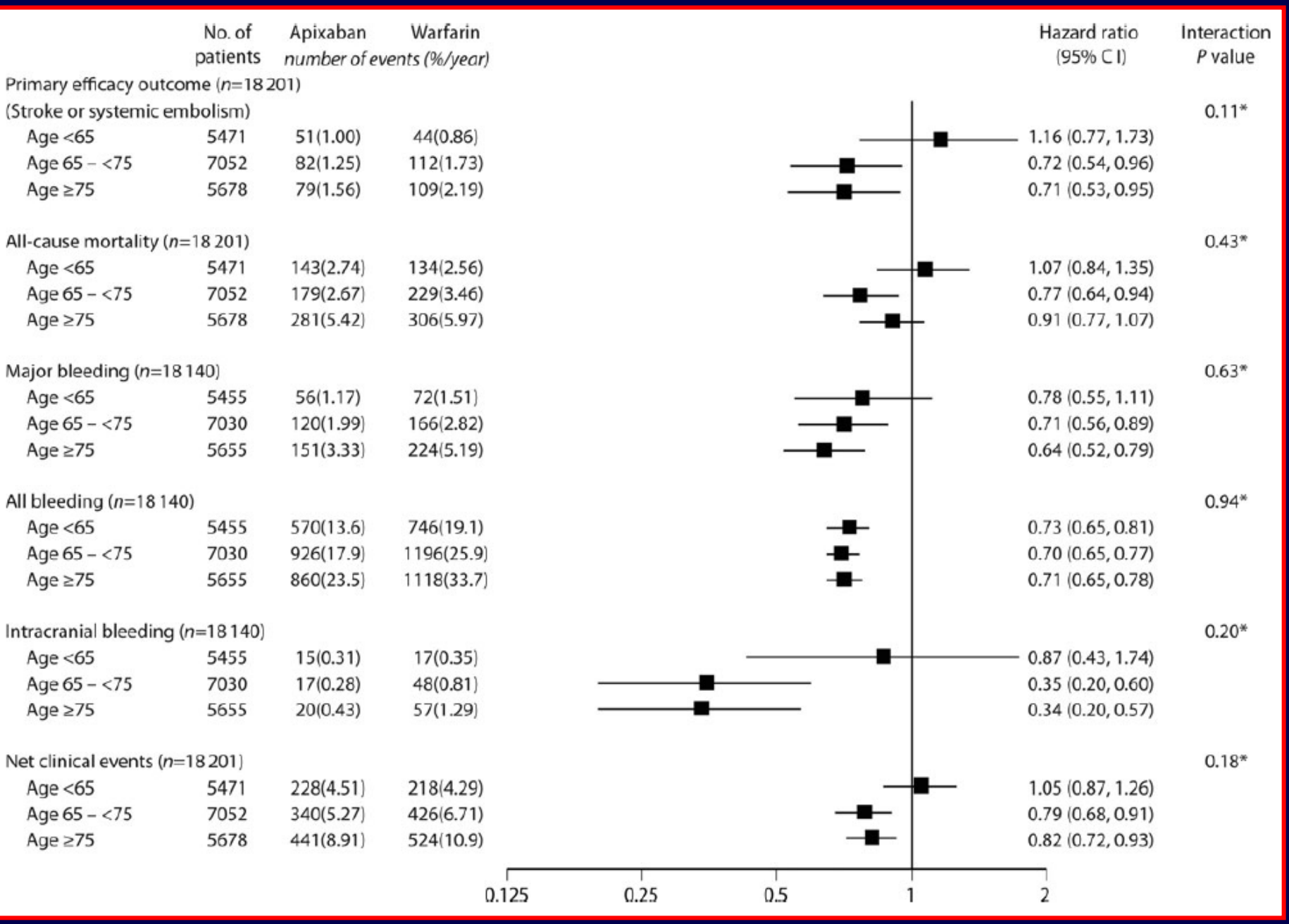
Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial



A reduced dose of 2.5 mg twice daily or placebo were administered to a total of 831 patients; 790 of these patients were ≥75 years.
** Interaction among treatment, age and dose based on randomized or treated population

Figure 3 The effect of apixaban vs. warfarin on stroke or systemic embolism and major bleeding in patients ≥75 years in relation to apixaban dose.

European Heart Journal (2014) **35**, 1864–1872



European Heart Journal (2014) **35**, 1864–1872

Left Ventricular Systolic Dysfunction, Heart Failure, and the Risk of Stroke and Systemic Embolism in Patients With Atrial Fibrillation

Insights From the ARISTOTLE Trial

Table 3. Treatment Effect by HF/LSVD Status—Efficacy End Points

	Rate (n)			
	Apixaban	Warfarin	HR (95% CI)	Interaction *P* Value
Stroke or systemic embolism*				
LVSD	0.99 (24)	1.80 (43)	0.55 (0.34–0.91)	0.21
HF-PEF	1.51 (44)	1.54 (45)	0.98 (0.65–1.49)	
No LVSD/no HF	1.16 (95)	1.58 (129)	0.74 (0.57–0.96)	

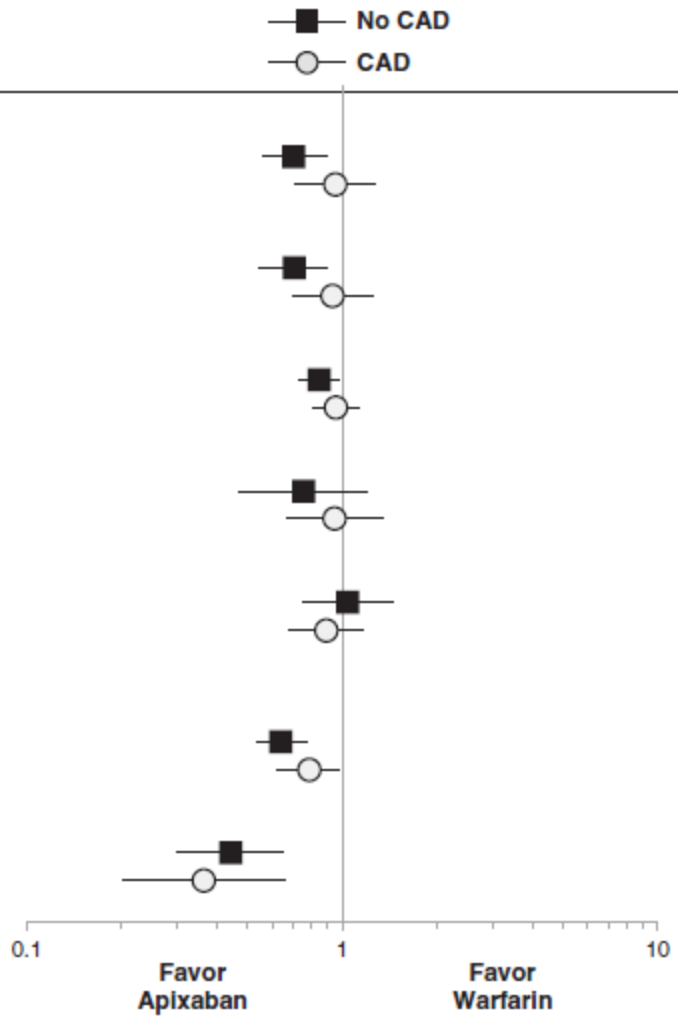
Table 4. Treatment Effect by HF/LSVD Status—Safety End Points

	Rate (n)			
	Apixaban	Warfarin	HR (95% CI)	Interaction *P* Value
ISTH major bleeding				
LVSD	2.77 (61)	3.41 (74)	0.81 (0.58–1.14)	0.50
HF-PEF	1.95 (52)	3.17 (82)	0.62 (0.44–0.88)	
No LVSD/no HF	2.17 (162)	2.83 (210)	0.77 (0.62–0.94)	

(*Circ Heart Fail.* 2013;6:451-460.)

Apixaban in patients with atrial fibrillation and prior coronary artery disease: Insights from the ARISTOTLE trial☆,☆☆

	Apixaban	Warfarin	HR (95% CI)	Interaction P-Value
Efficacy endpoints:				
Stroke or systemic embolism	1.15 (121) 1.47 (91)	1.63 (171) 1.55 (94)	0.704 (0.558, 0.889) 0.950 (0.712, 1.267)	0.11
Stroke	1.06 (112) 1.40 (87)	1.52 (159) 1.50 (91)	0.701 (0.550, 0.892) 0.937 (0.699, 1.258)	0.14
Death from any cause	3.11 (335) 4.21 (267)	3.68 (395) 4.40 (274)	0.847 (0.732, 0.979) 0.958 (0.809, 1.133)	0.28
MI	0.29 (31) 0.95 (59)	0.39 (41) 1.00 (61)	0.755 (0.473, 1.203) 0.947 (0.662, 1.354)	0.45
Revascularization (PCI/CABG)	0.70 (74) 1.69 (104)	0.67 (71) 1.89 (114)	1.040 (0.751, 1.441) 0.890 (0.682, 1.161)	0.47
Safety endpoints:				
ISTH major bleeding	1.99 (194) 2.39 (133)	3.12 (297) 3.05 (165)	0.640 (0.534, 0.766) 0.784 (0.624, 0.985)	0.17
Intracranial bleeding	0.37 (37) 0.27 (15)	0.85 (82) 0.73 (40)	0.443 (0.301, 0.654) 0.364 (0.201, 0.659)	0.59

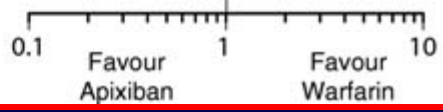


Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial

A Overall

Aspirin
No Aspirin

Outcome	Apixaban	Warfarin	HR (95% CI)	Interaction P-value
Stroke or systemic embolism	41 (1.12) 127 (1.11)	67 (1.91) 149 (1.32)	0.58 (0.39 – 0.85) 0.84 (0.66 – 1.07)	0.10
Ischaemic stroke	29 (0.79) 95 (0.83)	40 (1.14) 94 (0.83)	0.69 (0.43 – 1.11) 1.00 (0.75 – 1.33)	0.19
Myocardial infarction	33 (0.90) 46 (0.40)	26 (0.74) 58 (0.51)	1.20 (0.71 – 2.00) 0.78 (0.53 – 1.14)	0.19
Death	71 (1.93) 188 (1.64)	64 (1.82) 223 (1.97)	1.05 (0.75 – 1.47) 0.83 (0.68 – 1.00)	0.23
Major bleeding	114 (3.10) 211 (1.82)	138 (3.92) 317 (2.78)	0.77 (0.60 – 0.99) 0.65 (0.55 – 0.78)	0.29
Haemorrhagic stroke	10 (0.27) 25 (0.22)	24 (0.68) 47 (0.42)	0.40 (0.19 – 0.83) 0.53 (0.33 – 0.86)	0.52
Major or CRNM bleeding	199 (5.54) 410 (3.59)	246 (7.18) 620 (5.58)	0.76 (0.63 – 0.92) 0.65 (0.57 – 0.73)	0.15
Any bleeding	682 (22.64) 1657 (16.61)	859 (32.84) 2180 (23.72)	0.70 (0.63 – 0.77) 0.71 (0.67 – 0.76)	0.70



European Heart Journal (2014) **35**, 224–232

Efficacy and Safety of Apixaban in Patients After Cardioversion for Atrial Fibrillation

Insights From the ARISTOTLE Trial

Table 2 Clinical Outcomes After Any Cardioversion, Within 30 Days, in Patients Assigned to Either Warfarin or Apixaban

Outcomes	Warfarin (n = 412)	Apixaban (n = 331)	Total (n = 743)
Stroke or systemic embolism	0	0	0
Myocardial infarction	1 (0.2)	1 (0.3)	2 (0.2)
Major bleeding	1 (0.2)	1 (0.3)	2 (0.2)
Death	2 (0.5)	2 (0.6)	4 (0.5)

(J Am Coll Cardiol 2014;63:1082–7)

Feasibility And Safety of uninterrupted peri-procedural Apixaban administration in patients undergoing radiofrequency catheter ablation for atrial fibrillation: Results From a Multicenter Study

Results: A total of 400 patients (200 patients in each group) were included in the study. The average age was 65.9 ± 9.9 years with 286 (71.5%) male and 334 (83.5%) patients having non paroxysmal AF. There were no statistical differences in major (1% vs. 0.5%,p=1.0), minor (3.5% vs. 2.5%,p=0.56) and total bleeding complications (4.5% vs. 3%,p=0.43) between the apixaban and the warfarin group respectively. There were no symptomatic thromboembolic complications. All the dMRIs were negative for "new" SCI in the apixaban group.

Conclusions: Uninterrupted apixaban administration in patients undergoing AF ablation, appears to be feasible, and effective in preventing clinical and silent thrombo-embolic events without increasing the risk of major bleedings.

Accepted

PII: S1547-5271(15)00248-9
DOI: http://dx.doi.org/10.1016/j.hrthm.2015.02.028
Reference: HRTHM6146

To appear in: *Heart Rhythm*

Amiodarone, Anticoagulation, and Clinical Events in Patients With Atrial Fibrillation

Insights From the ARISTOTLE Trial

RESULTS In ARISTOTLE, 2,051 (11.4%) patients received amiodarone at randomization. Patients on warfarin and amiodarone had time in the therapeutic range that was lower than patients not on amiodarone (56.5% vs. 63.0%; $p < 0.0001$). More amiodarone-treated patients had a stroke or a systemic embolism (1.58%/year vs. 1.19%/year;

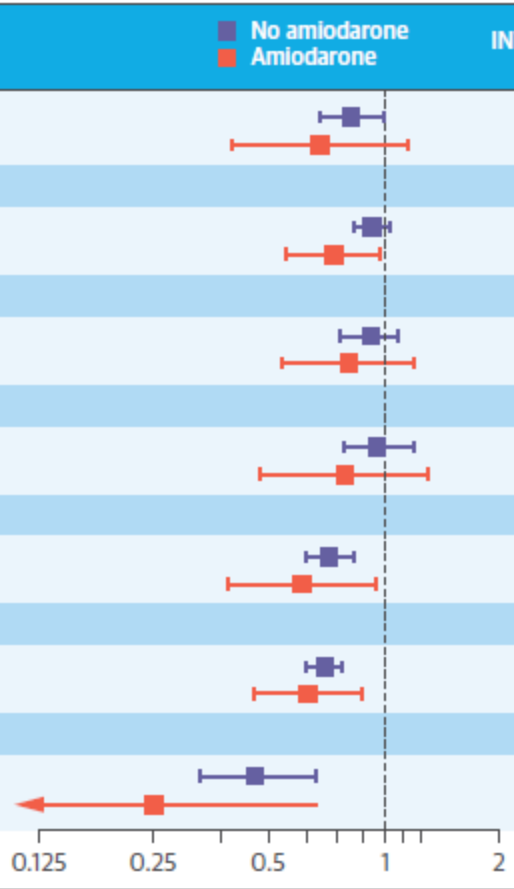
TABLE 3 Observed Rates and Number of Events in Patients Included in the Propensity-Matched Analysis*

Endpoint	Amiodarone Rates (Events)	No Amiodarone Rates (Events)	HR (95% CI)†	p Value
Stroke/SE	1.58 (50)	1.19 (115)	1.47 (1.03–2.10)	0.0322
All-cause death‡	4.76 (156)	4.09 (409)	1.16 (0.95–1.41)	0.1577
CV death‡	2.65 (87)	2.26 (226)	1.19 (0.91–1.55)	0.2104
Non-CV death‡	1.49 (49)	1.09 (109)	1.27 (0.88–1.82)	0.1964
MI	0.30 (10)	0.51 (51)	0.58 (0.27–1.25)	0.1646
Major bleeding	2.40 (74)	2.09 (199)	1.15 (0.85–1.53)	0.3656

(J Am Coll Cardiol 2014;64:1541–50)

Hazard Ratio

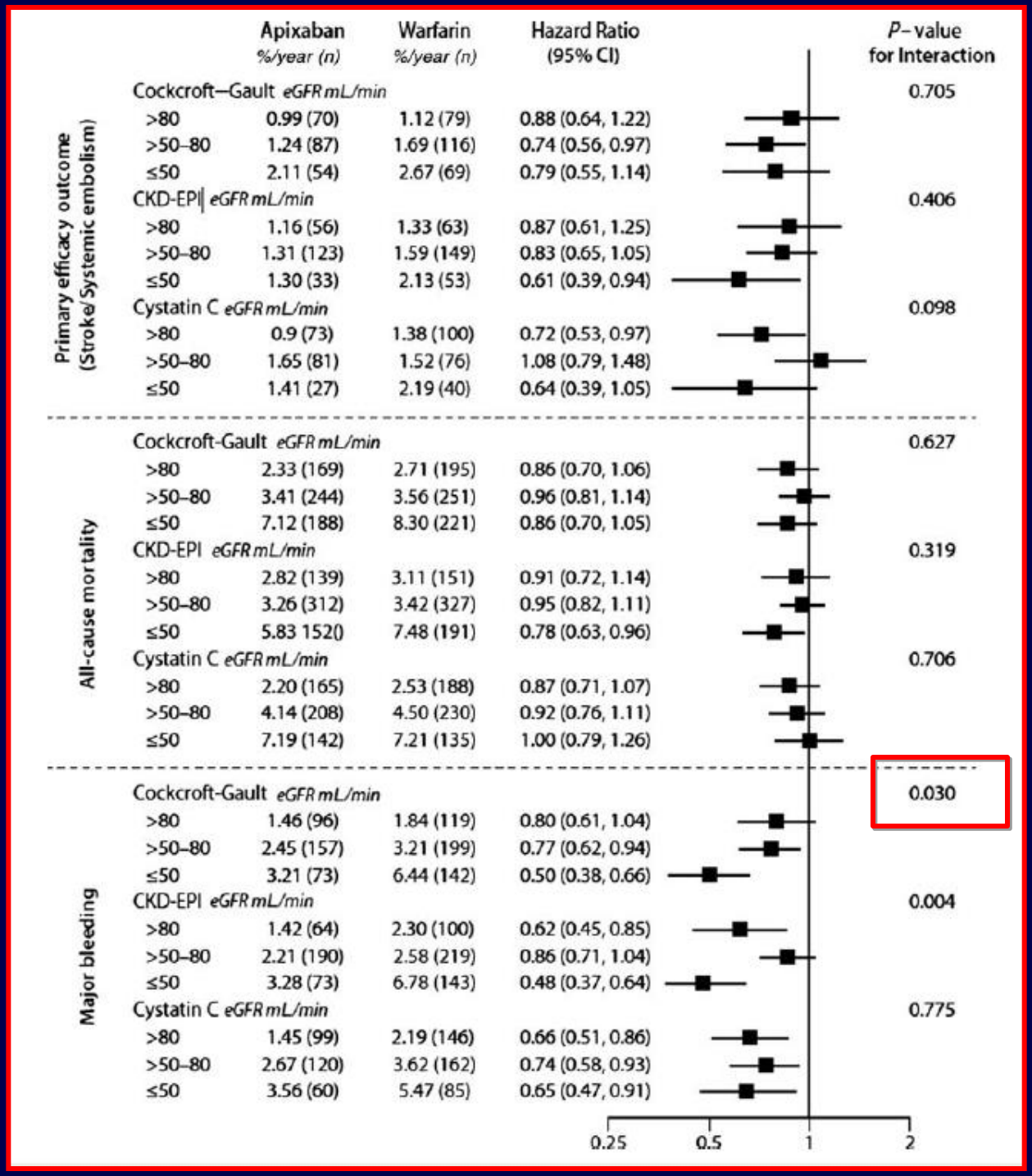
	EVENTS (RATE % PER YEAR) APIXABAN	WARFARIN	HR	INTERACTION P
Stroke or SE	1.29 (189) 1.24 (23)	1.57 (227) 1.85 (35)	0.82 (0.68 - 1.00) 0.68 (0.40 - 1.15)	0.48
Death	3.43 (514) 4.15 (78)	3.68 (546) 5.65 (109)	0.93 (0.83 - 1.05) 0.74 (0.55 - 0.98)	0.14
CV Death	1.74 (260) 2.34 (44)	1.90 (281) 2.90 (56)	0.92 (0.77 - 1.09) 0.81 (0.54 - 1.20)	0.56
Non-CV Death	1.10 (165) 1.38 (26)	1.15 (170) 1.76 (34)	0.96 (0.78 - 1.19) 0.79 (0.47 - 1.31)	0.47
Major Bleeding	2.18 (293) 1.86 (31)	3.03 (397) 3.06 (51)	0.72 (0.62 - 0.84) 0.61 (0.39 - 0.96)	0.49
Major/ Clinically Relevant Non-major Bleeding	4.10 (542) 3.92 (64)	5.92 (756) 6.31 (103)	0.70 (0.62 - 0.78) 0.63 (0.46 - 0.87)	0.52
Intracranial Bleeding	0.35 (47) 0.30 (5)	0.74 (99) 1.19 (20)	0.46 (0.33 - 0.66) 0.25 (0.10 - 0.67)	0.25



(J Am Coll Cardiol 2014;64:1541-50)

Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial

Stefan H. Hohnloser[1*], Ziad Hijazi[2,3], Laine Thomas[4], John H. Alexander[4], John Amerena[5], Michael Hanna[6], Matyas Keltai[7], Fernando Lanas[8], Renato D. Lopes[4], Jose Lopez-Sendon[9], Christopher B. Granger[4], and Lars Wallentin[2]


Apixaban %/year (n)
Warfarin %/year (n)
Hazard Ratio (95% CI)
P–value for Interaction
Primary efficacy outcome (Stroke/Systemic embolism)
Cockcroft–Gault eGFR mL/min
0.705
>80 0.99 (70) 1.12 (79) 0.88 (0.64, 1.22)
>50–80 1.24 (87) 1.69 (116) 0.74 (0.56, 0.97)
≤50 2.11 (54) 2.67 (69) 0.79 (0.55, 1.14)
CKD-EPI eGFR mL/min
0.406
>80 1.16 (56) 1.33 (63) 0.87 (0.61, 1.25)
>50–80 1.31 (123) 1.59 (149) 0.83 (0.65, 1.05)
≤50 1.30 (33) 2.13 (53) 0.61 (0.39, 0.94)
Cystatin C eGFR mL/min
0.098
>80 0.9 (73) 1.38 (100) 0.72 (0.53, 0.97)
>50–80 1.65 (81) 1.52 (76) 1.08 (0.79, 1.48)
≤50 1.41 (27) 2.19 (40) 0.64 (0.39, 1.05)
All-cause mortality
Cockcroft-Gault eGFR mL/min
0.627
>80 2.33 (169) 2.71 (195) 0.86 (0.70, 1.06)
>50–80 3.41 (244) 3.56 (251) 0.96 (0.81, 1.14)
≤50 7.12 (188) 8.30 (221) 0.86 (0.70, 1.05)
CKD-EPI eGFR mL/min
0.319
>80 2.82 (139) 3.11 (151) 0.91 (0.72, 1.14)
>50–80 3.26 (312) 3.42 (327) 0.95 (0.82, 1.11)
≤50 5.83 152() 7.48 (191) 0.78 (0.63, 0.96)
Cystatin C eGFR mL/min
0.706
>80 2.20 (165) 2.53 (188) 0.87 (0.71, 1.07)
>50–80 4.14 (208) 4.50 (230) 0.92 (0.76, 1.11)
≤50 7.19 (142) 7.21 (135) 1.00 (0.79, 1.26)
Major bleeding
Cockcroft-Gault eGFR mL/min
0.030
>80 1.46 (96) 1.84 (119) 0.80 (0.61, 1.04)
>50–80 2.45 (157) 3.21 (199) 0.77 (0.62, 0.94)
≤50 3.21 (73) 6.44 (142) 0.50 (0.38, 0.66)
CKD-EPI eGFR mL/min
0.004
>80 1.42 (64) 2.30 (100) 0.62 (0.45, 0.85)
>50–80 2.21 (190) 2.58 (219) 0.86 (0.71, 1.04)
≤50 3.28 (73) 6.78 (143) 0.48 (0.37, 0.64)
Cystatin C eGFR mL/min
0.775
>80 1.45 (99) 2.19 (146) 0.66 (0.51, 0.86)
>50–80 2.67 (120) 3.62 (162) 0.74 (0.58, 0.93)
≤50 3.56 (60) 5.47 (85) 0.65 (0.47, 0.91)
0.25
0.5
1
2

Meta-Analysis on Risk of Bleeding With *Apixaban* in Patients With Renal Impairment

Study or Subgroup	Apixaban Events	Apixaban Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADVANCE-2 & 3	7	1289	11	1328	4.5%	0.66 [0.25, 1.69]
AMPLIFY	5	549	10	544	4.2%	0.50 [0.17, 1.44]
AMPLIFY-EXT	7	168	3	193	1.2%	2.68 [0.70, 10.20]
ARISTOTLE	157	3817	199	3770	83.1%	0.78 [0.64, 0.96]
AVERROES	17	1188	17	1188	7.1%	1.00 [0.51, 1.95]
Total (95% CI)		**7011**		**7023**	**100.0%**	**0.80 [0.66, 0.96]**
Total events	193		240			

Heterogeneity: Chi² = 4.58, df = 4 (P = 0.33); I² = 13%

Test for overall effect: Z = 2.37 (P = 0.02)

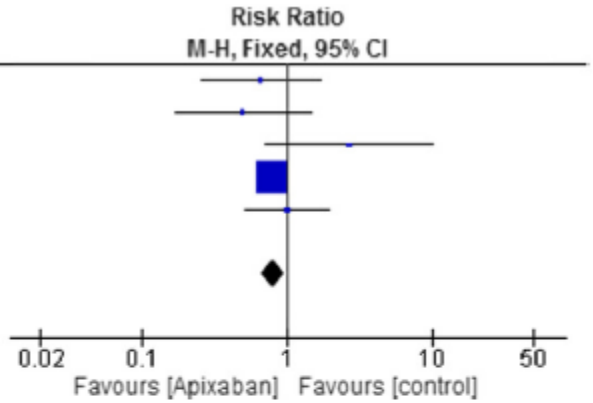


Figure 2. Meta-analysis of bleeding rates in mild renal impairment. Comparator: apixaban versus control.

Study or Subgroup	Favours [experimental] Events	Favours [experimental] Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ADVANCE-2 & 3	5	209	1	217	8.6%	5.19 [0.61, 44.06]
AMPLIFY	5	175	9	163	19.4%	0.52 [0.18, 1.51]
AMPLIFY-EXT	6	43	2	46	13.3%	3.21 [0.68, 15.05]
ARISTOTLE	73	1502	142	1515	32.1%	0.52 [0.39, 0.68]
AVERROES	20	568	16	561	26.5%	1.23 [0.65, 2.36]
Total (95% CI)		**2497**		**2502**	**100.0%**	**1.01 [0.49, 2.10]**
Total events	109		170			

Heterogeneity: Tau² = 0.41; Chi² = 14.27, df = 4 (P = 0.006); I² = 72%

Test for overall effect: Z = 0.04 (P = 0.97)

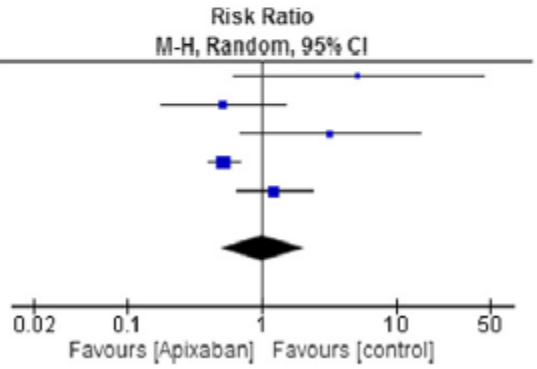
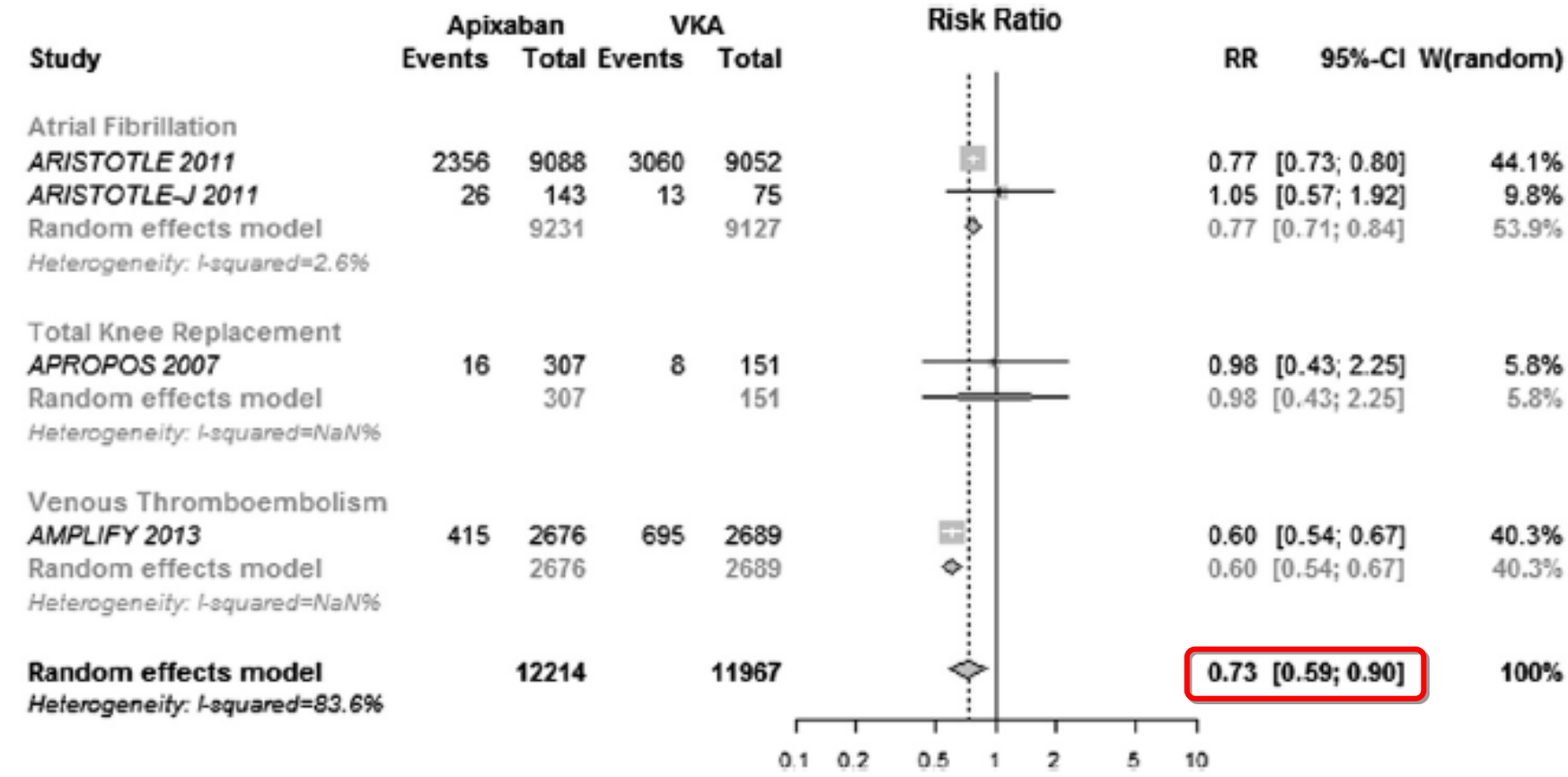


Figure 3. Meta-analysis of bleeding rates in moderate to severe renal impairment. Comparator: apixaban versus control.

(Am J Cardiol 2015;115:323–327)

A Meta-Analysis of Randomized Controlled Trials of the Risk of Bleeding With *Apixaban* Versus Vitamin K Antagonists

Tüm kanamalar



(Am J Cardiol 2015;115:533–541)

Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin

The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes

Table 3 Characteristics of Major Extracranial Hemorrhage

	Overall (n = 18,140)	Apixaban (n = 9088)	Warfarin (n = 9052)	Apixaban vs. Warfarin HR (95% CI)	p Value*
Led to hospitalization	1.23 (374)	1.05 (162)	1.41 (212)	0.75 (0.61–0.92)	0.0052
Fall in hemoglobin ≥2 g/dl	1.25 (381)	1.06 (164)	1.44 (217)	0.74 (0.60–0.91)	0.0035
Led to transfusion	1.06 (325)	0.89 (137)	1.25 (188)	0.71 (0.57–0.89)	0.0025
Required medical or surgical consultation	1.74 (527)	1.54 (236)	1.94 (291)	0.79 (0.67–0.94)	0.0080
Required medical or surgical intervention to stop	0.77 (236)	0.65 (100)	0.90 (136)	0.72 (0.56–0.93)	0.012
Associated with hemodynamic compromise	0.32 (97)	0.26 (40)	0.38 (57)	0.69 (0.46–1.029)	0.069
Caused changed in antithrombotic therapy	1.31 (398)	1.14 (176)	1.47 (222)	0.78 (0.64–0.95)	0.012

(J Am Coll Cardiol 2014;63:2141–7)

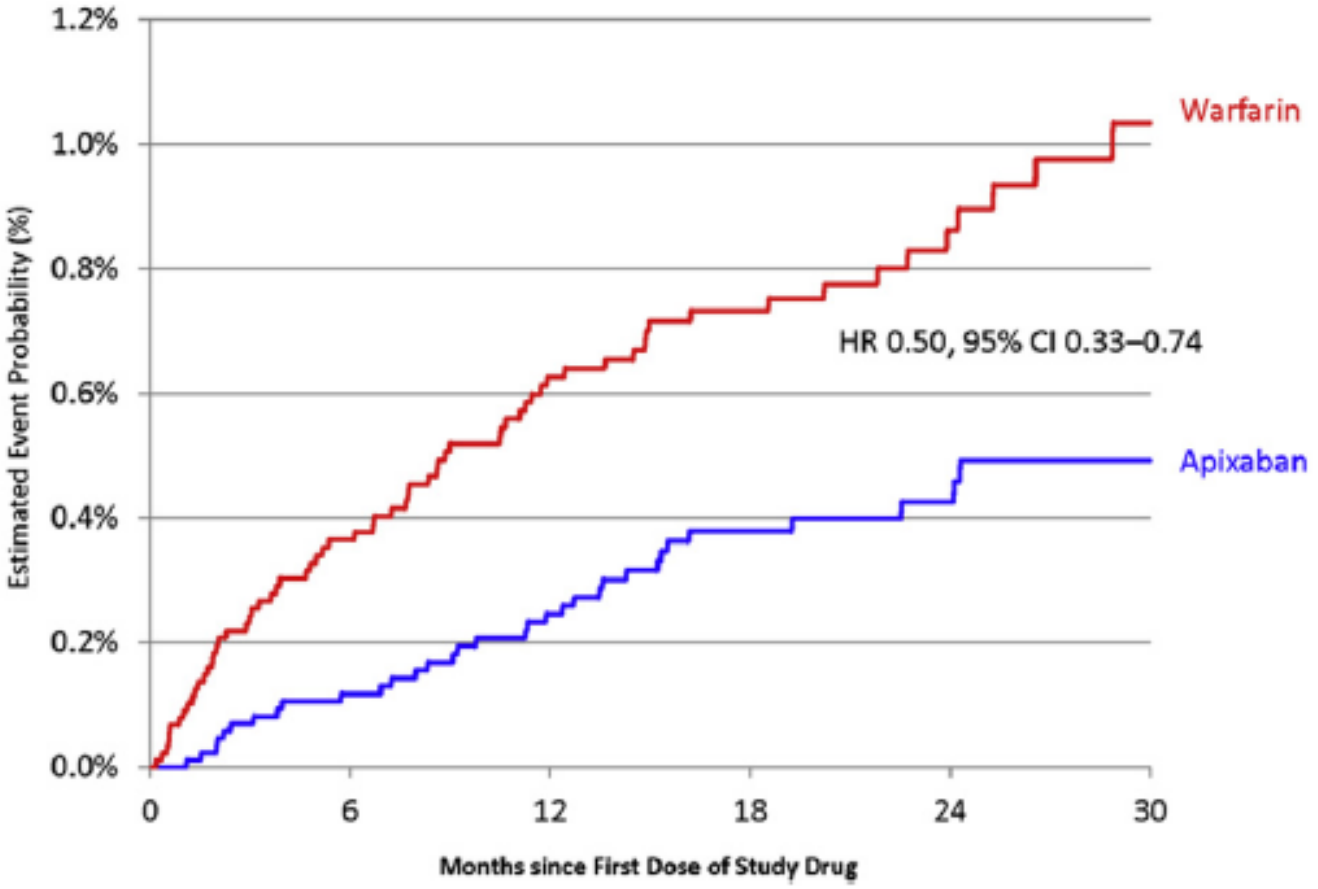


Figure 1 **Major Bleeding Following by Death Within 30 Days**

CI = confidence interval; HR = hazard ratio.

(J Am Coll Cardiol 2014;63:2141–7)

Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial

Table III. Clinical outcomes during 30 days after study drug discontinuation at end of trial

Clinical outcome and time interval	Apixaban		Warfarin	
	n/N	%/year	n/N	%/year
Stroke or systemic embolism				
Day 1-30	21/6791	4.02	5/6569	0.99
Day 1-2	1/6791	2.69	1/6569	2.78
Day 3-7	4/6787	4.31	0/6566	0
Day 8-14	5/6780	3.85	1/6559	0.80
Day 15-30	11/6771	4.18	3/6548	1.18
Major bleeding				
Day 1-30	26/6791	4.97	10/6569	1.97
Day 1-2	0/6791	0	2/6569	5.56
Day 3-7	1/6787	1.08	3/6566	3.34
Day 8-14	7/6780	5.39	0/6559	0
Day 15-30	18/6771	6.84	5/6548	1.96
Death				
Day 1-30	24/6796	4.58	18/6573	3.55
Day 1-2	1/6796	2.69	1/6573	2.78
Day 3-7	3/6789	3.23	6/6568	6.68
Day 8-14	5/6782	3.85	7/6560	5.57
Day 15-30	15/6772	5.68	4/6549	1.56

Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial

Table III. Clinical outcomes during 30 days after study drug discontinuation at end of trial

Conclusions The excess in thrombotic and bleeding events in the apixaban group after study drug discontinuation appears to be related to an increased risk associated with the initiation of a VKA rather than a direct effect of apixaban. Whether ≥2 days of apixaban bridging improves outcomes during VKA transition is unknown and deserves further evaluation. (Am Heart J 2015;169:25-30.)

Stroke or systemic embolism				
Day 1-30	21/6791	4.02	5/6569	0.99
Day 1-2	1/6791	2.69	1/6569	2.78
Day 3-7	4/6787	4.31	0/6566	0
Day 8-14	5/6780	3.85	1/6559	0.80
Day 15-30	11/6771	4.18	3/6548	1.18
Major bleeding				
Day 1-30	26/6791	4.97	10/6569	1.97
Day 1-2	0/6791	0	2/6569	5.56
Day 3-7	1/6787	1.08	3/6566	3.34
Day 8-14	7/6780	5.39	0/6559	0
Day 15-30	18/6771	6.84	5/6548	1.96
Death				
Day 1-30	24/6796	4.58	18/6573	3.55
Day 1-2	1/6796	2.69	1/6573	2.78
Day 3-7	3/6789	3.23	6/6568	6.68
Day 8-14	5/6782	3.85	7/6560	5.57
Day 15-30	15/6772	5.68	4/6549	1.56

İlaç etkileşmeleri

- Kuvvetli CYP3A4 ve P-Gp inhibitörü alanlarda doz 2.5 mg olmalı
  - Ketokonazol, itrakonazol, ritonavir, klaritromisin
- Kuvvetli CYP3A4 ve P-Gp indükleyicilerinden uzak durulmalı
  - Rifampin, karbamezapin, fenitoin
- Kanama riskinin artabileceği durumlar
  - ASA, diğer antikoagülanlar, DAPT, NSAID
- Önemli etkileşim yok
  - Famotidin, atenolol, digoksin, amiodaron

Lam S. Card in Rev, 2013, e-pub ahead of print. DOI: 10.1097/CRD.0b013e318293d6e6

Uyarılar

- Ciddi KC yetmezliğinde kullanılmamalı
- Gebelikte kategori B
- Kr klirensi < 15 mL/dak veya diyaliz – kullanılmamalı

Lam S. Card in Rev, 2013, e-pub ahead of print. DOI: 10.1097/CRD.0b013e318293d6e6

Kontrendikasyonlar

- Valvüler AF
- Protez kapak
- Allerji
- Aktif kanama

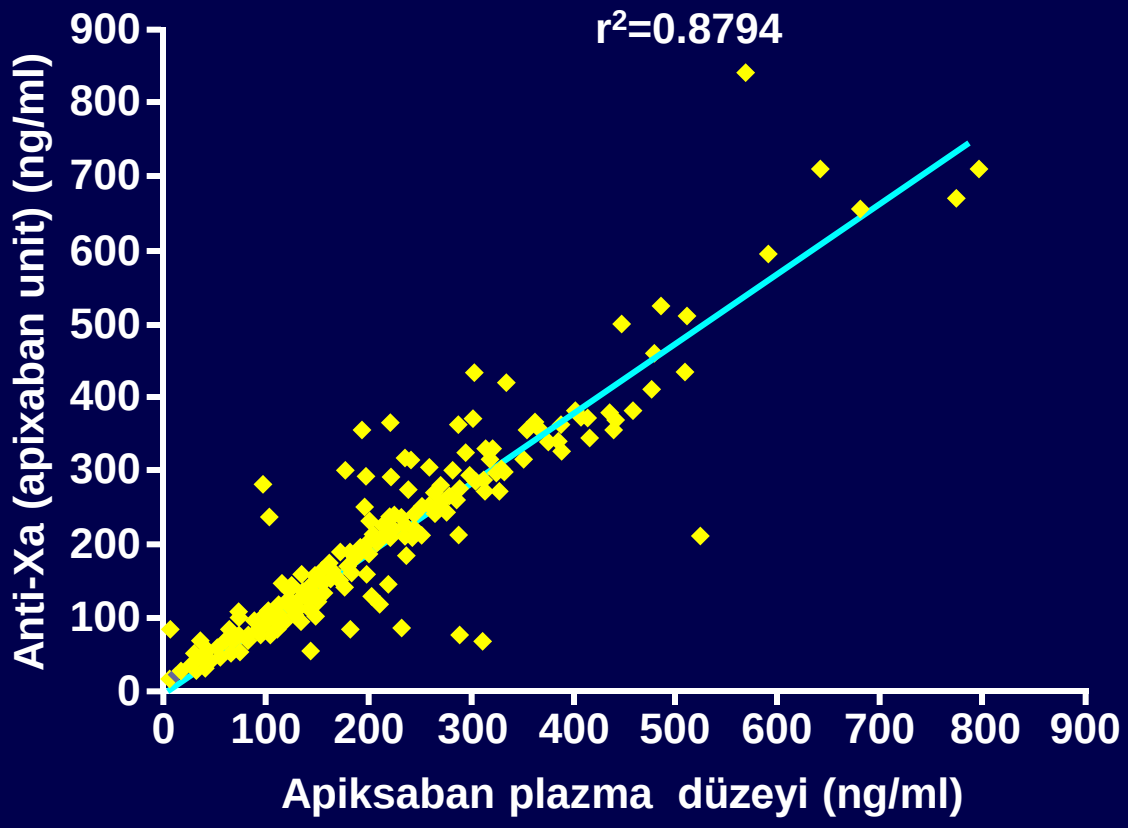
Lam S. Card in Rev, 2013, e-pub ahead of print. DOI: 10.1097/CRD.0b013e318293d6e6

Koagülasyon izlemi - Lab

- INR uygun değil
- aPTT uygun değil
- Anti Fxa aktivitesi ?

Anti FXa aktivitesi apiksabanın plasma düzeyleri ile yakın direkt ilişki gösterir

Anti-faktör Xa chromogenic assay (Diagnostica Stago Rotachrom® Heparin) apiksabanın plazma düzeylerini değerlendirmek için uygun olabilir



Barrett et al. *Thromb Haemost* 2010;104:1263-71

Anti- FXa aktivitesi

- Klinik olaylarla korelasyon net değil
- Doz modifikasyonuna kılavuzluk edemez
- Kullanılabileceği durumlar
  - Kompliyansın kontrolü
  - Doz aşımı
  - Acil durumlar – kanama, acil cerrahi gereksinimi gibi

Jimenez D. Adv Ther 2012;29:187

Doz aşımı veya kanama

- Antidot yok
  - PCC
  - aFVII
  - TDP
- Antikoagülan etki son dozdan sonra 24 saat devam eder
- Diyaliz faydalı değil
- Aktif kömür

Lam S. Card in Rev, 2013, e-pub ahead of print. DOI: 10.1097/CRD.0b013e318293d6e6

Pratik ipuçları

- Girişim öncesi ne zaman kesilmeli ?
  - Yüksek kanama riskli girişim – 48 saat
  - Düşük kanama riskli girişim - 24 saat

- Warfarinden geçiş – INR < 2.0 olunca

Lam S. Card in Rev, 2013, e-pub ahead of print. DOI: 10.1097/CRD.0b013e318293d6e6

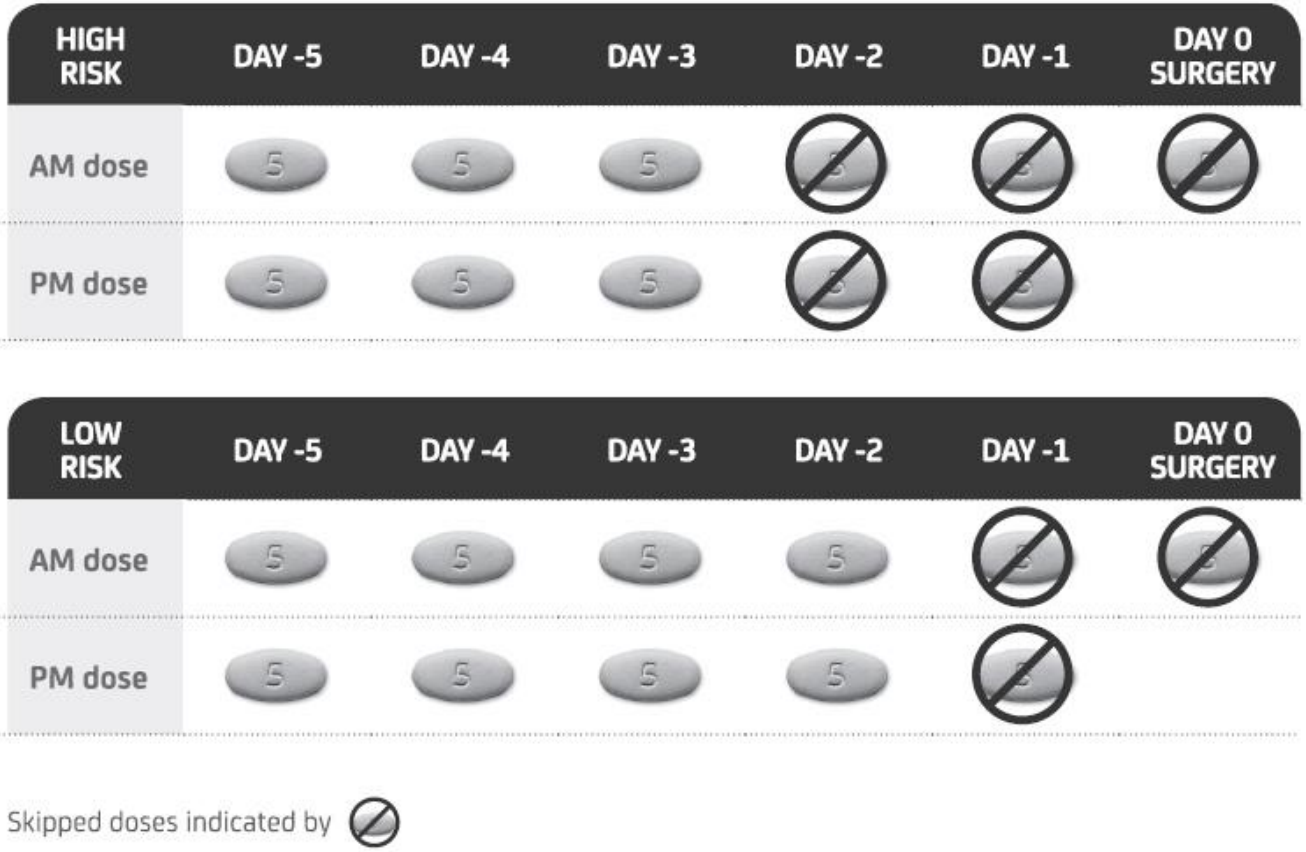


Figure 2 Perioperative dosing/elimination.