Czyli co anestezjolog powinien wiedzieć o nowoczesnych doustnych antykoagulantach

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w Katowicach

Czym dysponujemy?

- Antagoniści witaminy K (VKA)
  - Acenokumarol
  - Warfaryna

Warfin
Warfarin Sodium tabletki 3 mg i 5 mg

- Bezpośredni antagoniści czynników krzepnięcia (non-VKA)
  - DaBIgatran (Pradaxa)
  - RivaroXaban (Xarelto)
  - ApiXaban (Eliquis)

Pradaxa®
dabigatran etexilate

Xarelto®
rivaroxaban

Eliquis®
(apixaban) tablets

NOAC już nie takie nowe…

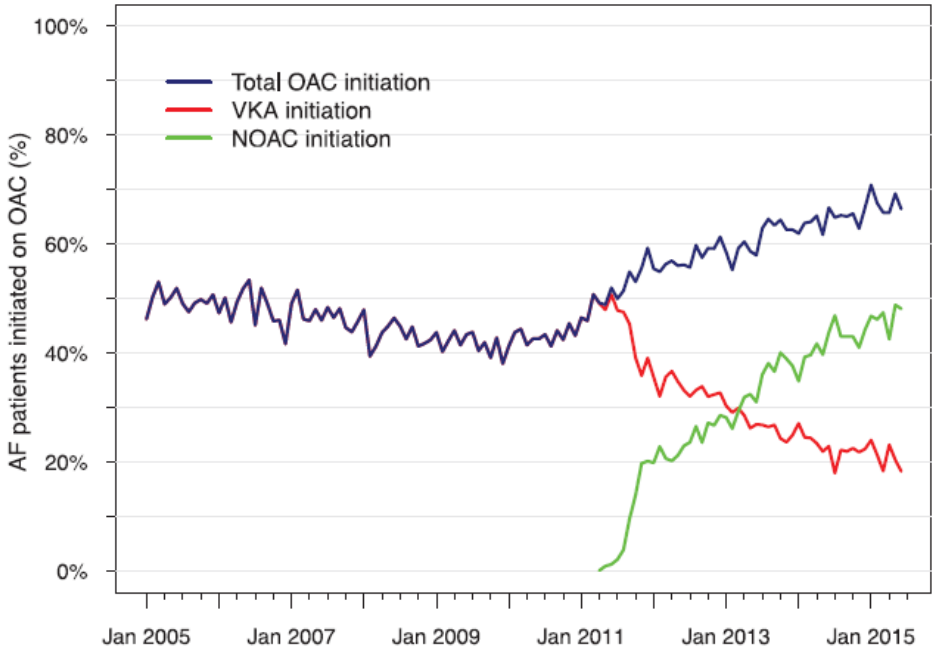
- Novel oral anticoagulants
- Non-VKA oral anticoagulants
- Direct oral anticoagulants
- Target-specific oral anticoagulants

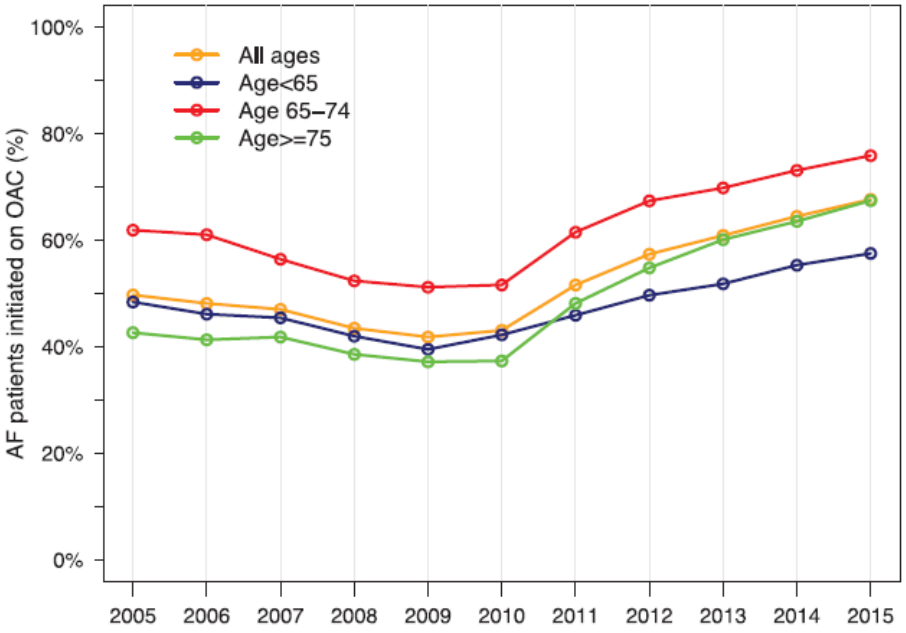
Skala zjawiska

Eur Heart J. 2017 Jan 21. pii: ehw658. doi: 10.1093/eurheartj/ehw658. [Epub ahead of print]

Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark.

Gadsbøll K[1], Staerk L[2], Fosbøl EL[3,4], Sindet-Pedersen C[2], Gundlund A[2], Lip GY[5], Gislason GH[2,4,6,7], Olesen JB[2].



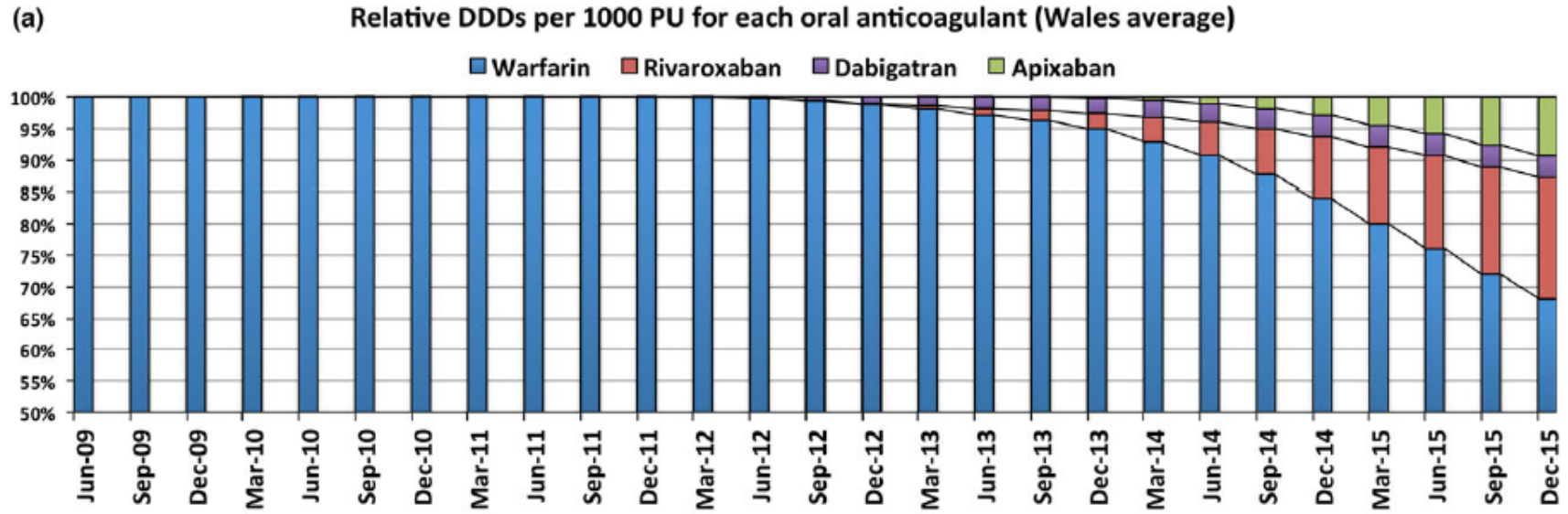


J Clin Pharm Ther. 2016 Dec 21. doi: 10.1111/jcpt.12481. [Epub ahead of print]

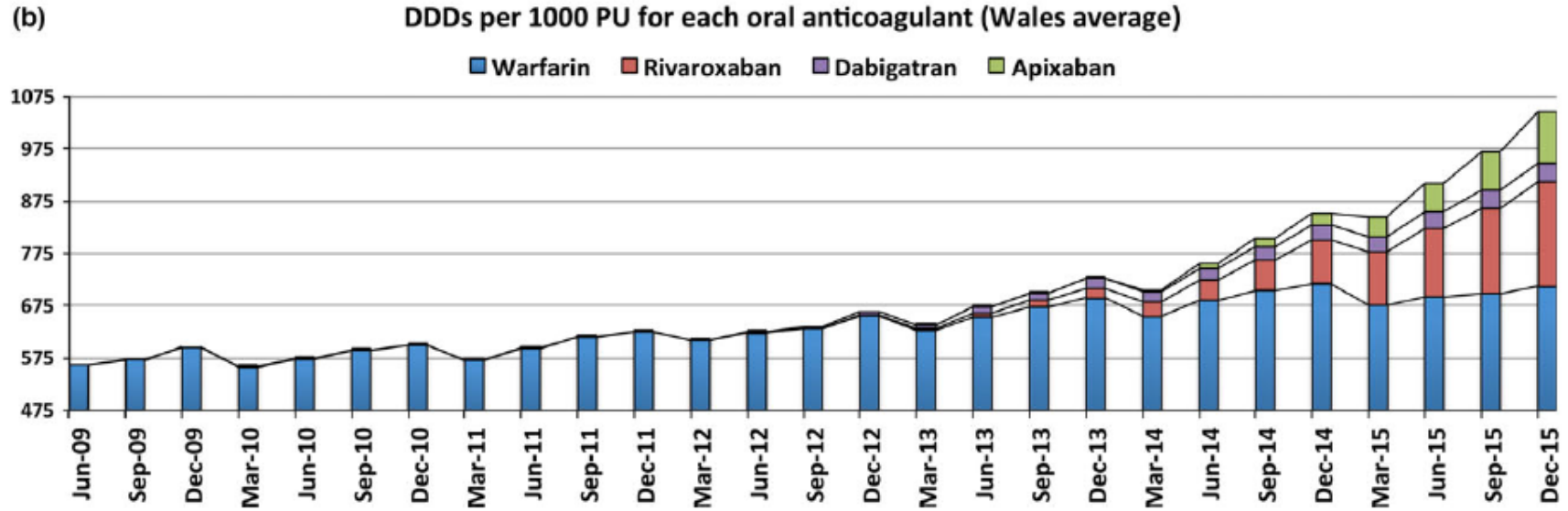
Dawn of the direct-acting oral anticoagulants: trends in oral anticoagulant prescribing in Wales 2009-2015.

Protty MB[1], Hayes J[2].

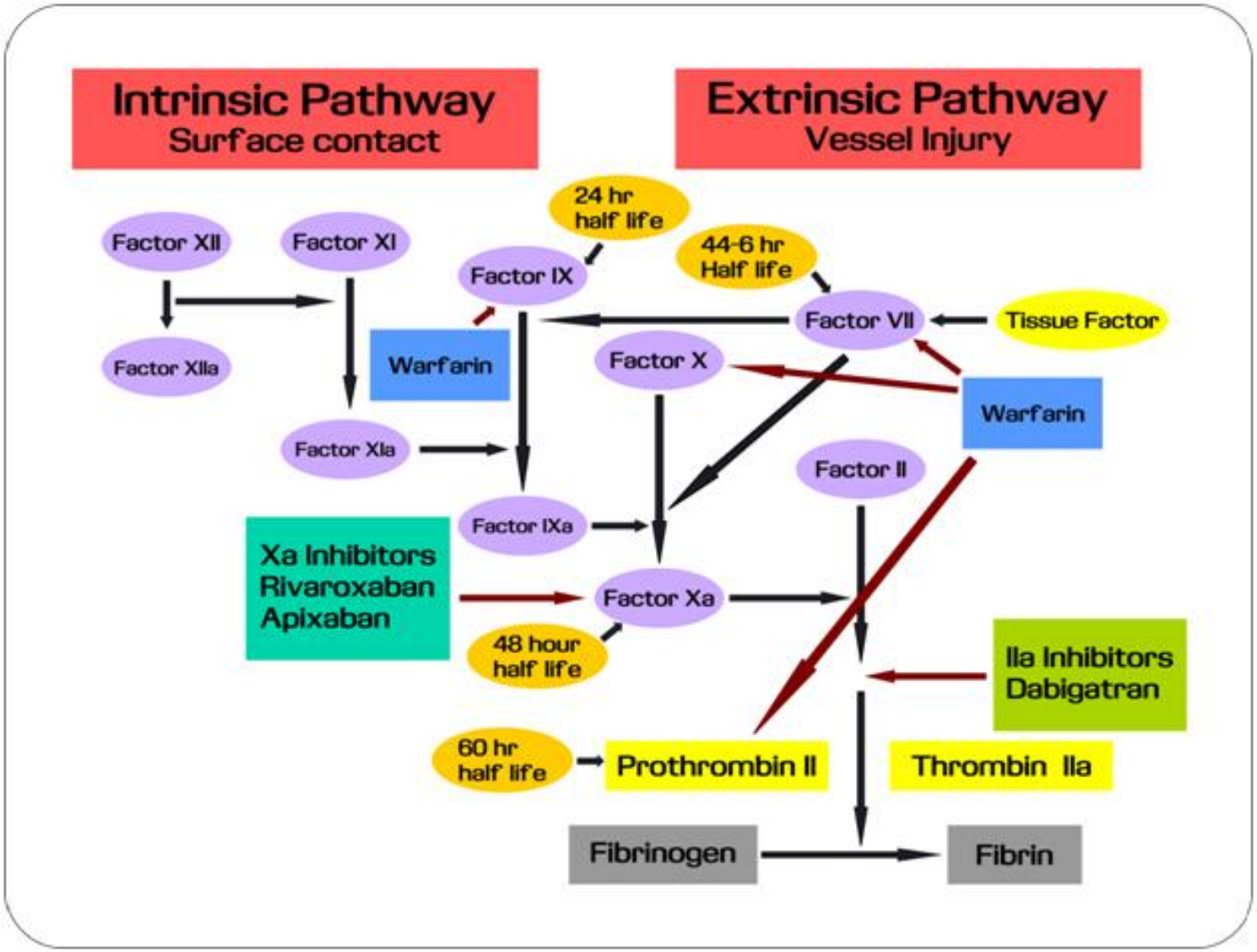
(a)



(b)



Jak one działają?



Swetha et al. OAT DOI: 10.15761/NFO.1000108

Kiedy je stosować?

Dabigatran →

A. Profilaktyka żylnych powikłań zakrzepowo-zatorowych u dorosłych chorych po planowej aloplastyce całkowitej stawu kolanowego lub biodrowego
B. Prewencja udarów i zatorowości systemowej u dorosłych pacjentów z niezastawkowym migotaniem przedsionków z punktacją $CHADS_2$ lub CHA_2DS_2-VASc ≥ 1 punkt

Kiedy je stosować?

Rywaroksaban →

A. Profilaktyka żylnej choroby zakrzepowo-zatorowej u dorosłych chorych po przebytym planowym zabiegu aloplastyki stawu biodrowego lub kolanowego
B. Profilaktyka udaru i zatorowości obwodowej u dorosłych pacjentów z niezastawkowym migotaniem przedsionków z punktacją $CHADS_2$ lub CHA_2DS_2-VASc ≥ 1 punkt
C. Leczenie zakrzepicy żył głębokich i zatorowości płucnej oraz profilaktyka nawrotowej zakrzepicy żył głębokich i zatorowości płucnej u dorosłych
D. Dla dawki 2,5 mg zarejestrowanym wskazaniem jest profilaktyka zdarzeń zakrzepowych o etiologii miażdżycowej u dorosłych chorych po przebytym ostrym zespole wieńcowym ze zwiększonymi wartościami biomarkerów sercowych (lek stosować należy w skojarzeniu z ASA lub z ASA oraz klopidogrelem)

CHADS-VASc

	Nazwa angielska	Nazwa polska	Punkty
C	Congestive heart failure / LV dysfunction	Zastoinowa niewydolność krążenia / dysfunkcja lewej komory	1
H	Hypertension	Nadciśnienie tętnicze	1
A	Age ≥75 years	Wiek ≥75 lat	2
D	Diabetes	Cukrzyca	1
S	Stroke / TIA	Przebyty incydent naczyniowo-mózgowy	2
V	Vascular disease	Choroba naczyniowa (przebyty zawał serca, miażdżycowa choroba tętnic obwodowych, blaszki miażdżycowe w aorcie)	1
A	Age 65-74 years	Wiek 65-74 lata	1
Sc	Sex category: female	Płeć żeńska	1

Jak długo je stosować?

CHARAKTERYSTYKA PACJENTA	*RUTYNOWA TERAPIA*	*CZAS PROWADZENIA TERAPII*
FA	**VKA lub Non-VKA**	**Bezterminowo**
Stabilna CHD + FA	**ASA + (VKA lub Non-VKA)**	**Bezterminowo**
PCI + FA	**ASA + klopidogrel + (VKA lub Non-VKA)**	**6–12 miesięcy / Bezterminowo**
STEMI/NSTEMI + FA	**ASA + klopidogrel + (VKA lub Non-VKA)**	**6–12 miesięcy**
DVT	**VKA lub Non-VKA**	**>3 m-ce / Bezterminowo**
CHD + DVT	**ASA + (VKA lub Non-VKA)**	**Bezterminowo**
PCI + UA + DVT	**ASA + klopidogrel + (VKA lub Non-VKA)**	**6–12 miesięcy**

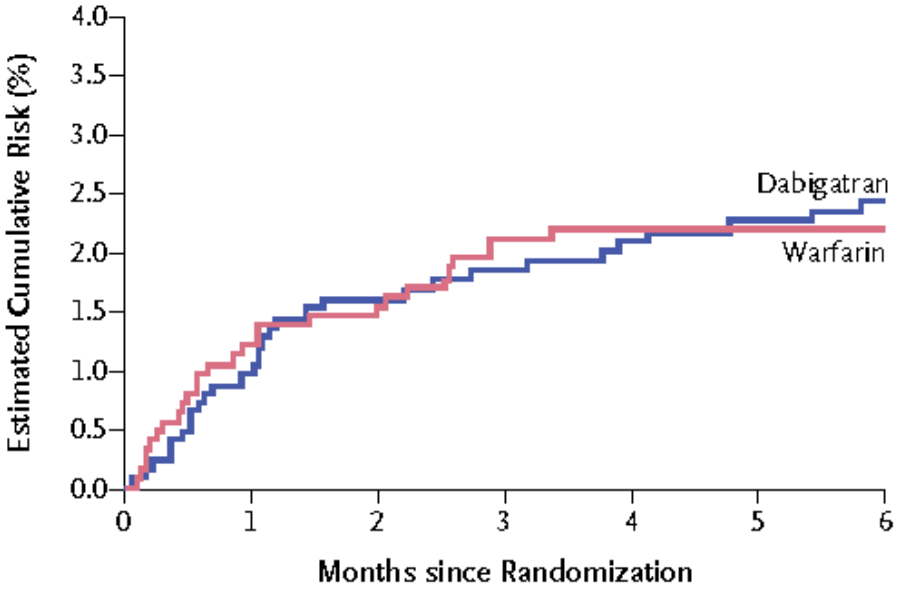
Skuteczność i bezpieczeństwo

- DVT
- AF

N Engl J Med. 2009 Dec 10;361(24):2342-52. doi: 10.1056/NEJMoa0906598.

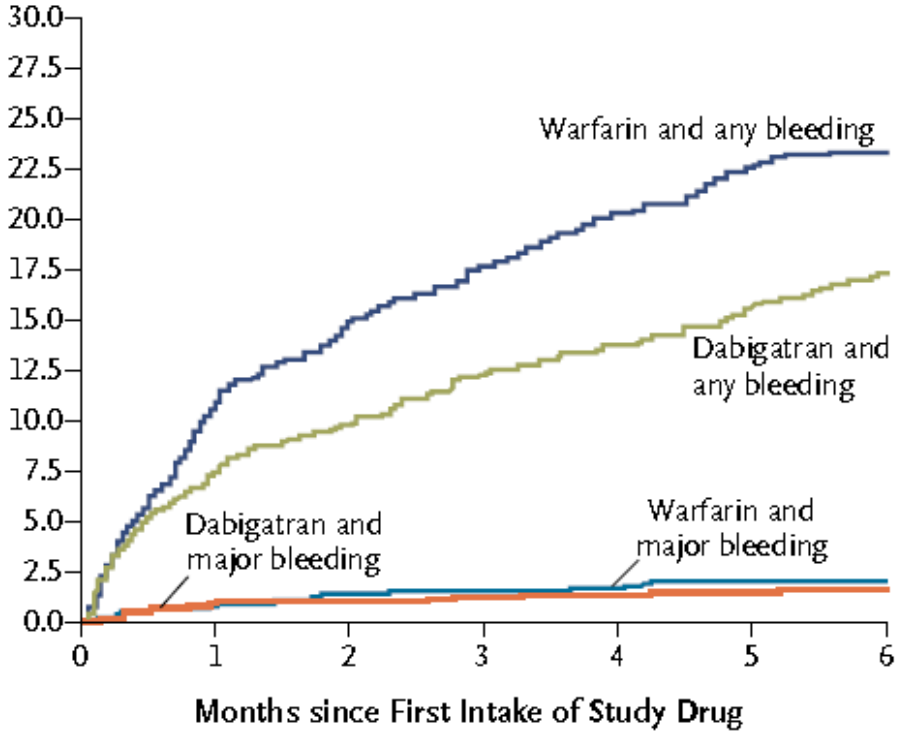
Dabigatran versus warfarin in the treatment of acute venous thromboembolism.

Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group.



Główny punkt końcowy

Risk Difference 0,4% (95%CI -0,8 do 1,5)



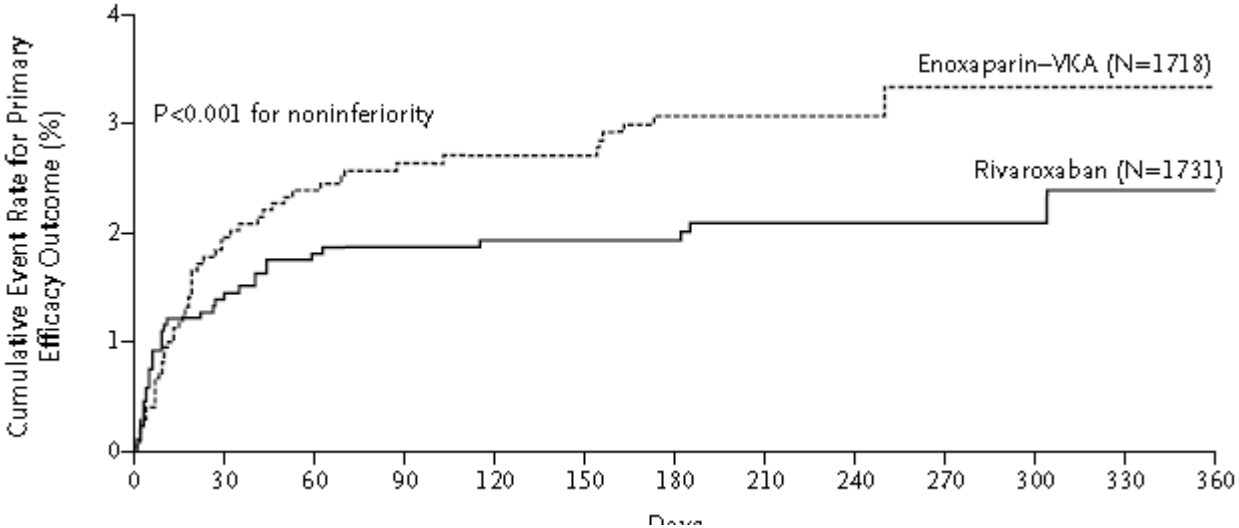
Krwawienie

HR 0,71 (95%CI 0,59-0,85)

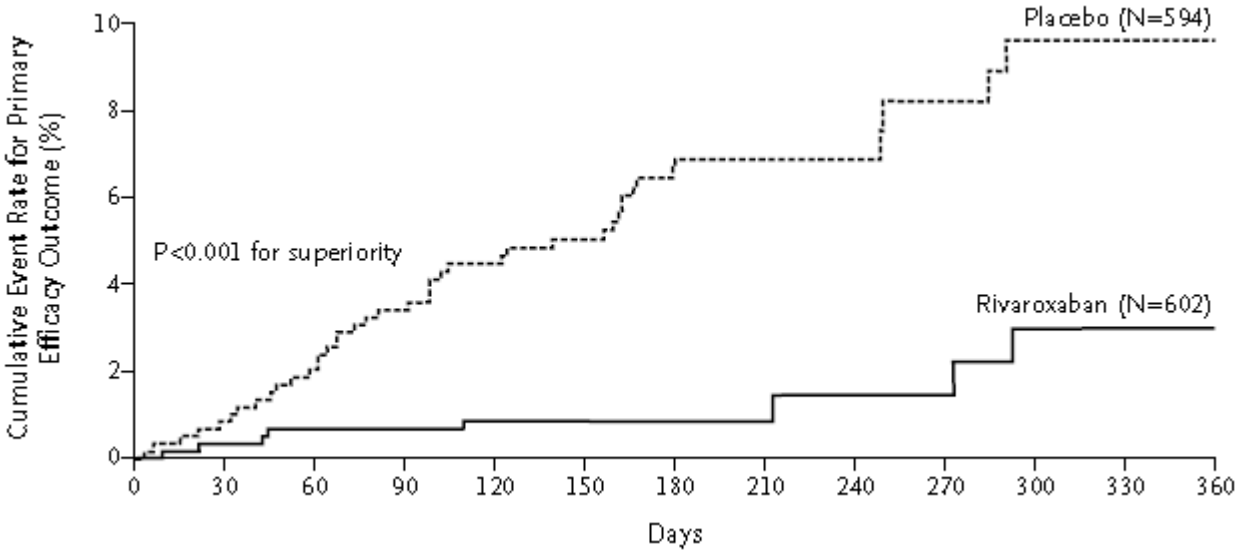
N Engl J Med. 2010 Dec 23;363(26):2499-510. doi: 10.1056/NEJMoa1007903. Epub 2010 Dec 3.

Oral rivaroxaban for symptomatic venous thromboembolism.

EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S.



HR 0,68
(95%CI 0,44-1,04)



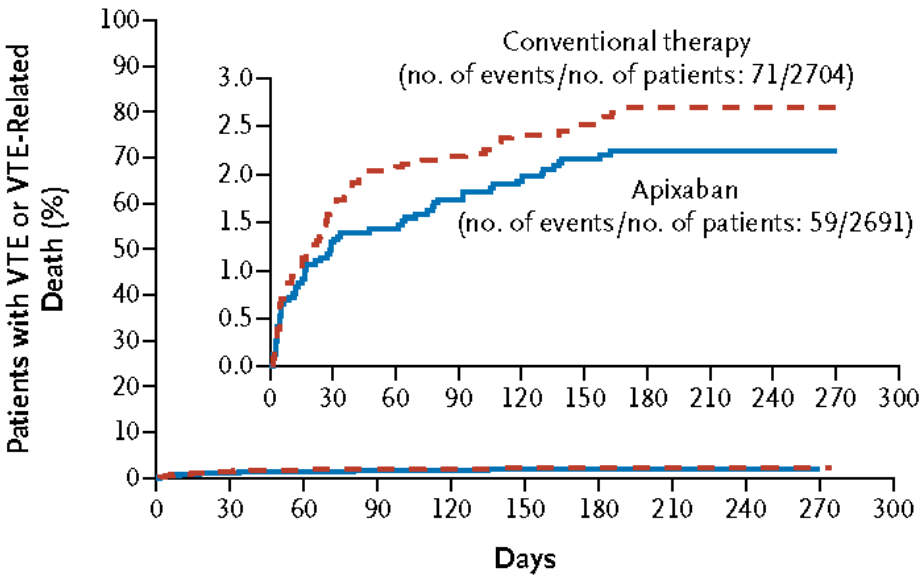
HR 0,18
(95%CI 0,09-0,39)

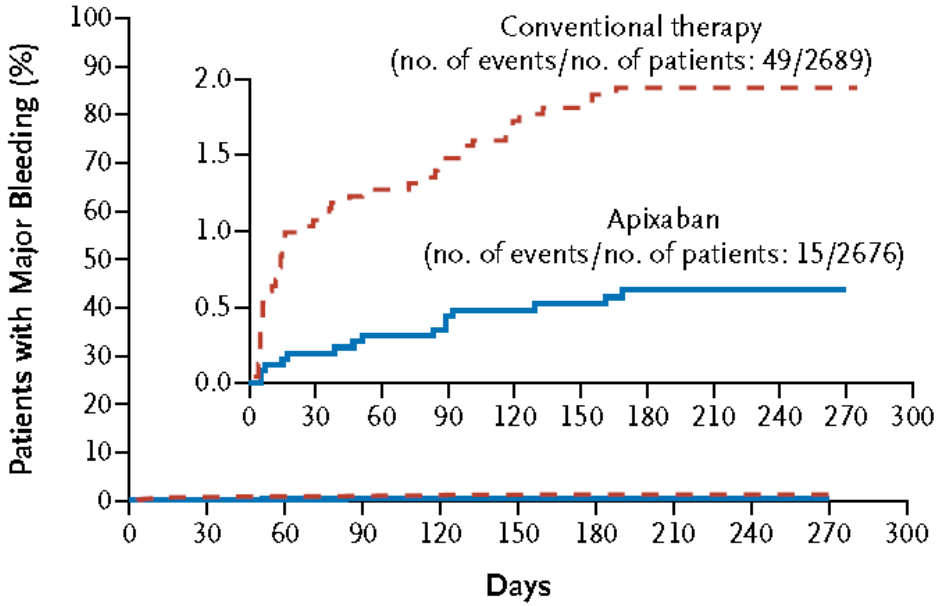
82%

N Engl J Med. 2013 Aug 29;369(9):799-808. doi: 10.1056/NEJMoa1302507. Epub 2013 Jul 1.

Oral apixaban for the treatment of acute venous thromboembolism.

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators.





Główny punkt końcowy
Risk Difference -0,4% (95%CI -1,3 do 0,4)

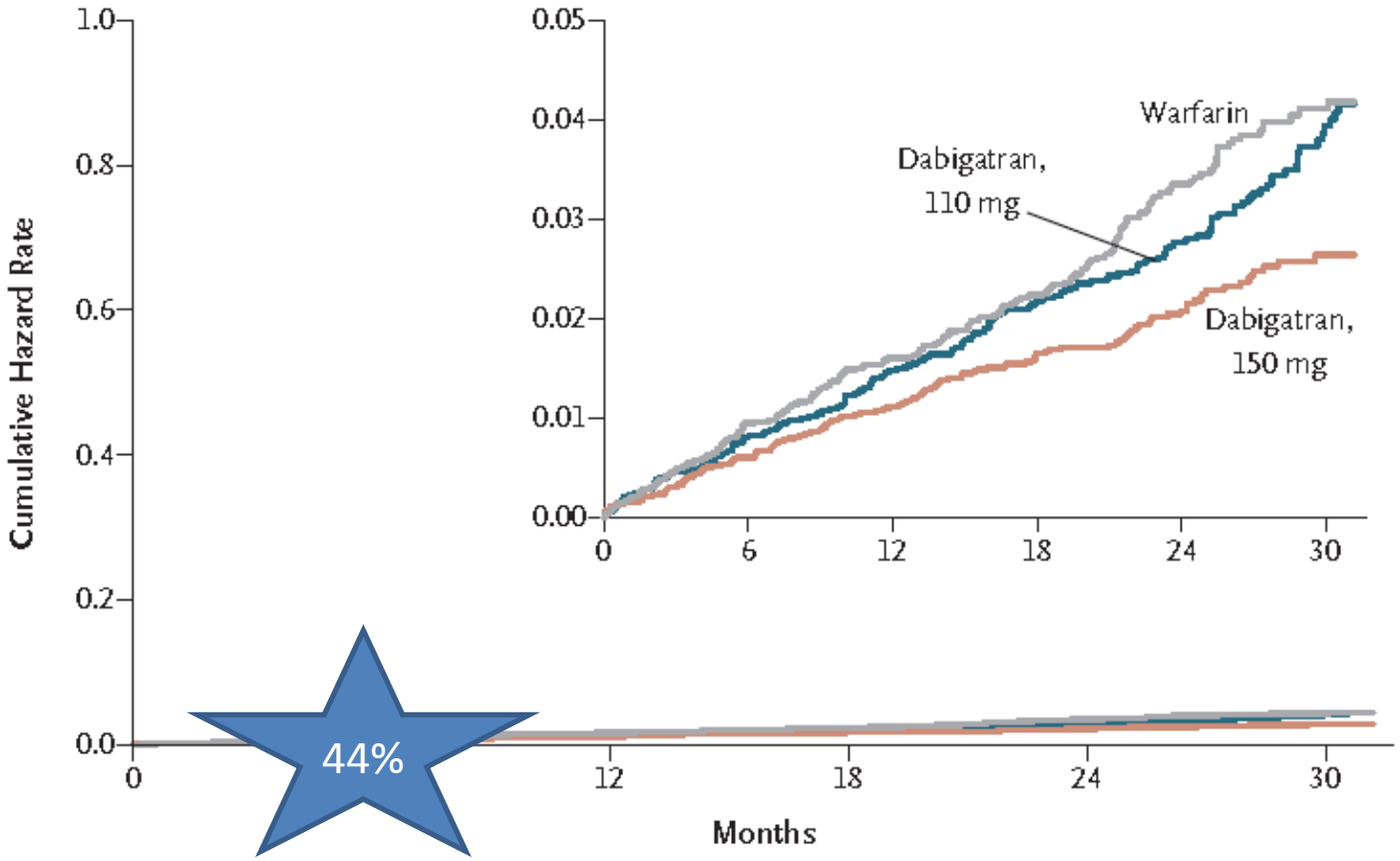
Krwawienie
HR 0,44 (95%CI 0,36-0,55)

N Engl J Med. 2009 Sep 17;361(12):1139-51. doi: 10.1056/NEJMoa0905561. Epub 2009 Aug 30.

Dabigatran versus warfarin in patients with atrial fibrillation.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators.

Złożony punkt końcowy → udar + powikłania zakrzepowe

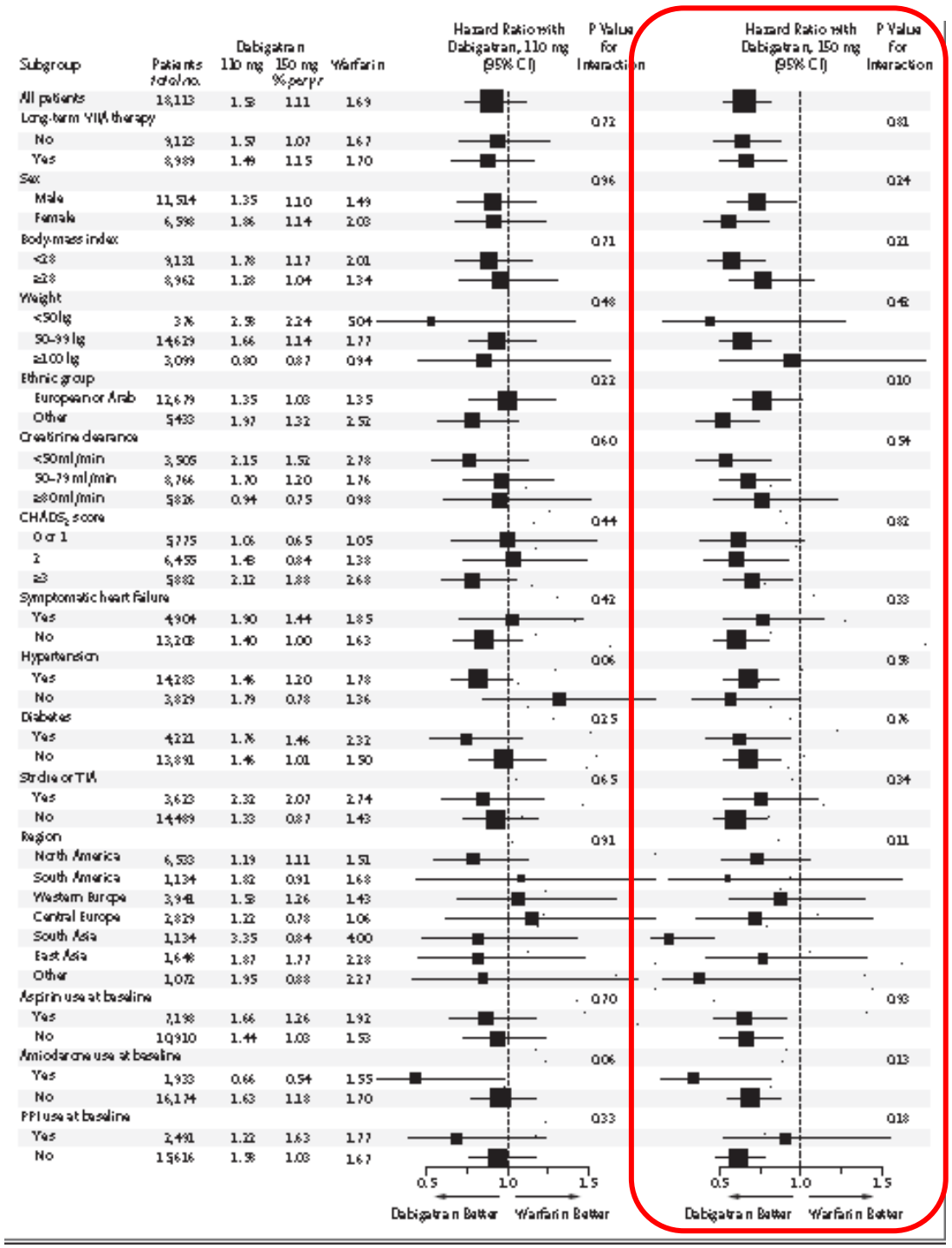


HR(110) 0,91 (95%CI 0,74-1,11)

HR(150) 0,66 (95%CI 0,53-0,82)

Przy częstości krwawień:

(W) 3,36% vs. (110) 2,71% vs. (150) 3,11%



D150 lepszy we wszystkich podgrupach!

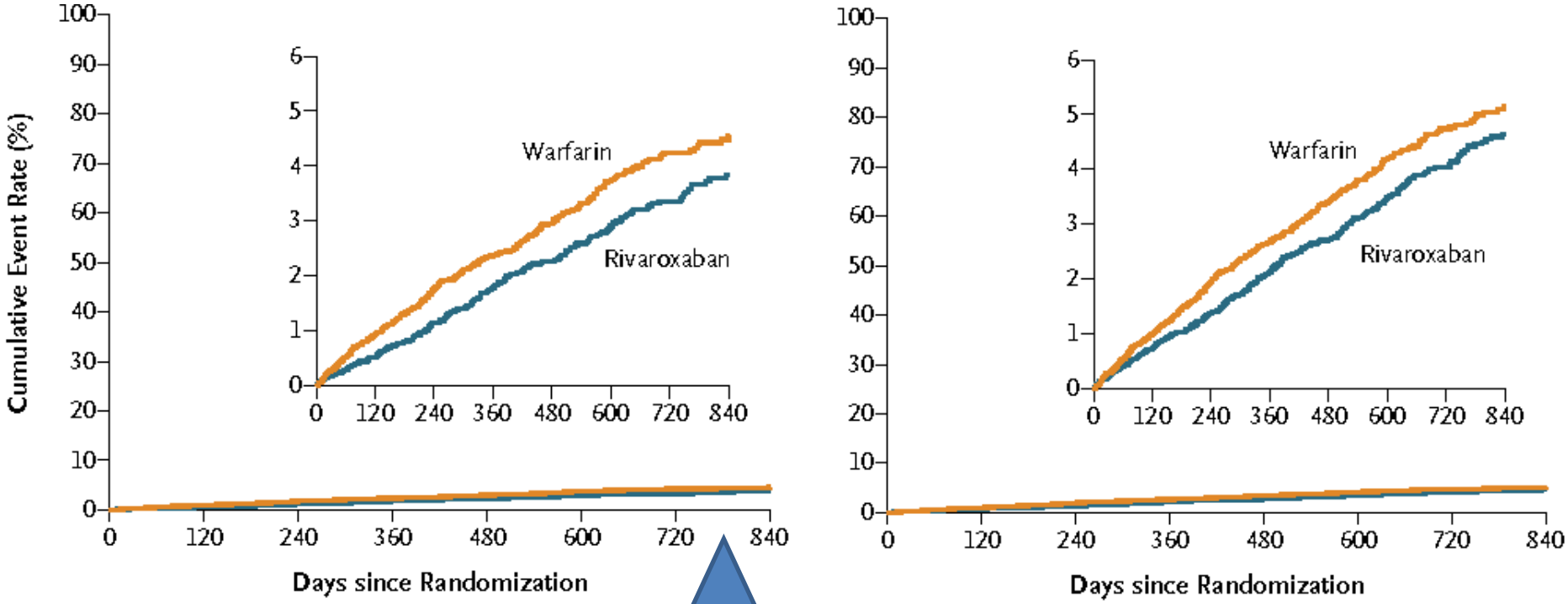
Connolly et al. NEJM 2009

N Engl J Med. 2011 Sep 8;365(10):883-91. doi: 10.1056/NEJMoa1009638. Epub 2011 Aug 10.

Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators.

Złożony punkt końcowy → udar + powikłania zakrzepowe



21%

Per protocol population
HR 0,79 (95%CI 0,66-0,96)

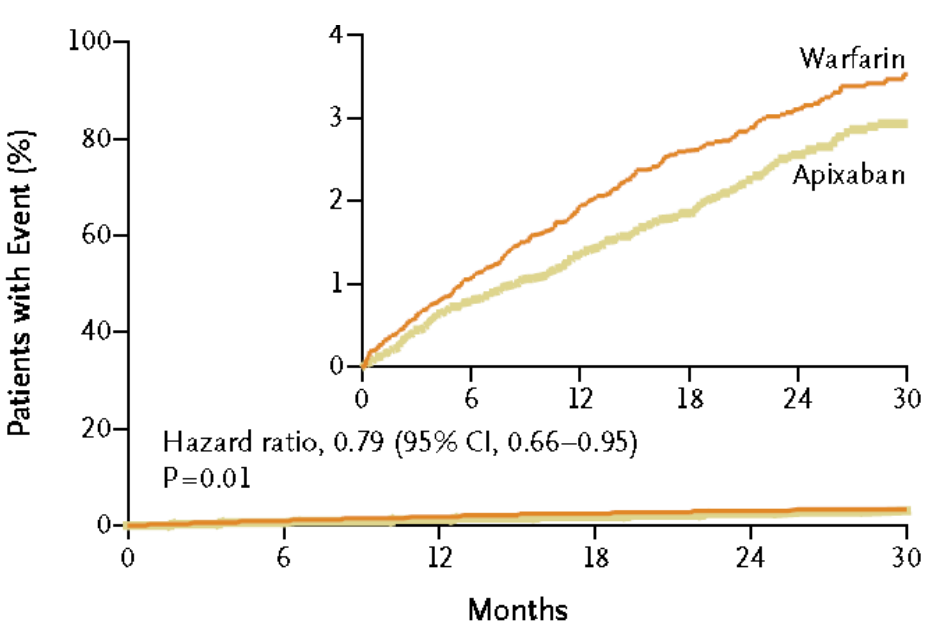
Intention-to-treat
HR 0,88 (95%CI 0,74-1,03)

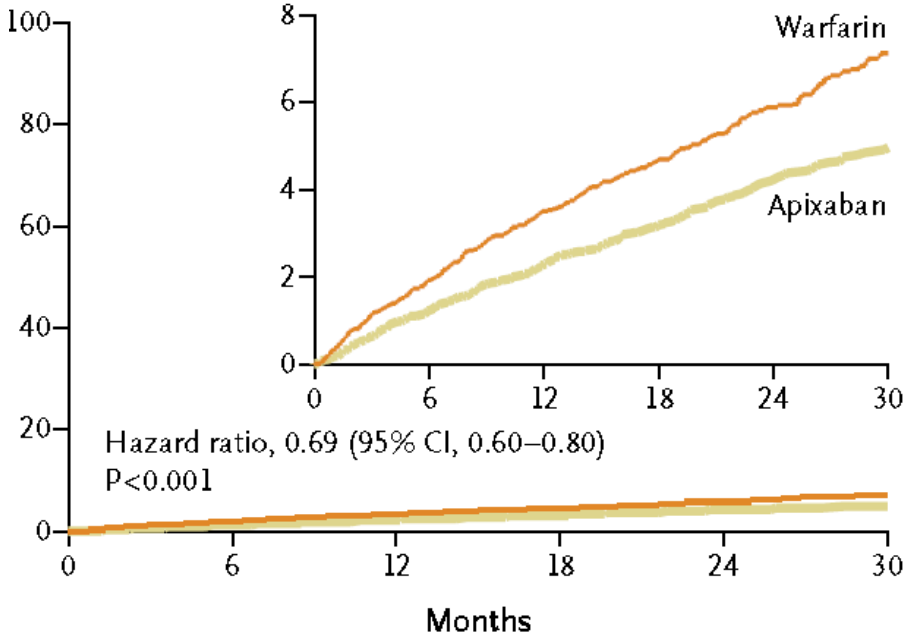
Krwawienie: HR 1,03(95%CI 0,96-1,11)

N Engl J Med. 2011 Sep 15;365(11):981-92. doi: 10.1056/NEJMoa1107039. Epub 2011 Aug 27.

Apixaban versus warfarin in patients with atrial fibrillation.

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators.





Udar + embolizm

HR 0,79 (95%CI 0,66-0,95)

21%

Krwawienia

HR 0,69 (95%CI 0,60-0,80)

31%

Int J Cardiol. 2015 Jan 20;179:279-87. doi: 10.1016/j.ijcard.2014.11.101. Epub 2014 Nov 13.

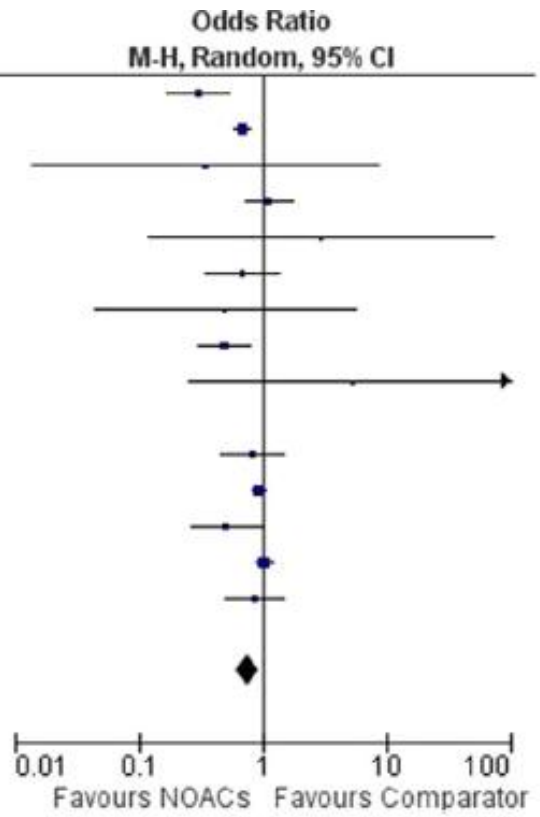
Risk of major bleeding in different indications for new oral anticoagulants: insights from a meta-analysis of approved dosages from 50 randomized trials.

Sardar P[1], Chatterjee S[2], Lavie CJ[3], Giri JS[4], Ghosh J[5], Mukherjee D[6], Lip GY[7].

Study or Subgroup	NOACs Events	NOACs Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
AMPLIFY 2013	15	2676	49	2689	6.8%	0.30 [0.17, 0.54]
ARISTOTLE 2011	327	9088	462	9052	16.1%	0.69 [0.60, 0.80]
ARISTOTLE J 2011	0	71	1	75	0.4%	0.35 [0.01, 8.67]
AVERROES 2011	44	2808	39	2791	9.3%	1.12 [0.73, 1.73]
Botticelli DVT 2008	1	128	0	126	0.4%	2.98 [0.12, 73.76]
EINSTEIN 2010	14	1718	20	1711	5.5%	0.69 [0.35, 1.38]
EINSTEIN DVT Dose 2008	1	135	2	137	0.6%	0.50 [0.05, 5.62]
EINSTEIN PE 2012	26	2412	52	2405	8.6%	0.49 [0.31, 0.79]
ODIXa DVT 2007	2	119	0	126	0.4%	5.38 [0.26, 113.29]
PETRO 2007	0	166	0	70		Not estimable
RE-COVER 2009	20	1274	24	1265	6.5%	0.82 [0.45, 1.50]
RE-LY 2009	399	6076	421	6022	16.2%	0.94 [0.81, 1.08]
RE-MEDY 2013	13	1430	25	1426	5.6%	0.51 [0.26, 1.01]
ROCKET AF 2011	395	7061	386	7082	16.2%	1.03 [0.89, 1.19]
ROCKET AF J 2012	26	639	30	639	7.5%	0.86 [0.50, 1.47]
Total (95% CI)		**35801**		**35616**	**100.0%**	**0.76 [0.63, 0.92]**
Total events	1283		1511			

Heterogeneity: Tau² = 0.05; Chi² = 39.59, df = 13 (P = 0.0002); I² = 67%

Test for overall effect: Z = 2.79 (P = 0.005)



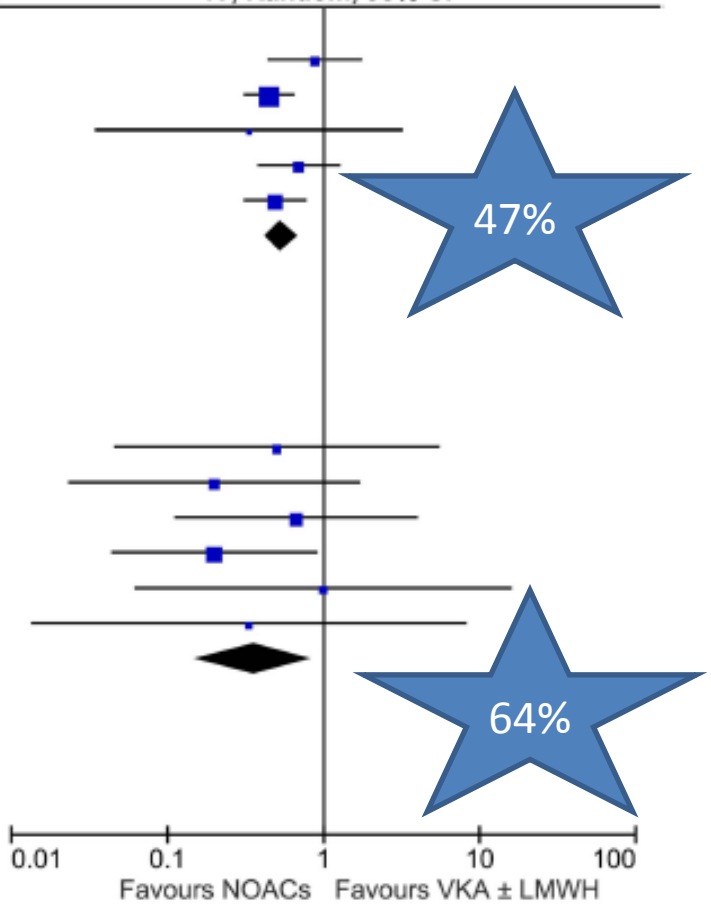
Heart. 2015 Aug;101(15):1204-11. doi: 10.1136/heartjnl-2015-307489. Epub 2015 Jun 2.

Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis.

Caldeira D[1], Rodrigues FB[2], Barra M[2], Santos AT[2], de Abreu D[2], Gonçalves N[2], Pinto FJ[3], Ferreira JJ[2], Costa J[4].

Study or Subgroup	NOACs Events	NOACs Total	VKA ± LMWH Events	VKA ± LMWH Total	Weight	Odds Ratio IV, Random, 95% CI
AF						
ARISTOTLE	15	9120	17	9081	12.3%	0.88 [0.44, 1.76]
ENGAGE-AF	53	14069	59	7036	42.8%	0.45 [0.31, 0.65]
J-ROCKET	1	639	3	639	1.2%	0.33 [0.03, 3.20]
RE-LY	25	12091	18	6022	16.1%	0.69 [0.38, 1.27]
ROCKET-AF	27	7131	55	7133	27.8%	0.49 [0.31, 0.78]
Subtotal (95% CI)		**43050**		**29911**	**100.0%**	**0.53 [0.42, 0.68]**
Total events	121		152			
Heterogeneity: $I^2 = 0\%$						
Test for overall effect: Z = 5.08 (P < 0.00001)						
VTE						
AMPLIFY	1	2676	2	2689	12.7%	0.50 [0.05, 5.54]
EINSTEIN-DVT	1	1718	5	1711	15.9%	0.20 [0.02, 1.70]
EINSTEIN-PE	2	2412	3	2405	22.9%	0.66 [0.11, 3.98]
Hokusai-VTE	2	4118	10	4122	31.8%	0.20 [0.04, 0.91]
RE-COVER	1	1274	1	1265	9.5%	0.99 [0.06, 15.89]
RE-MEDY	0	1430	1	1426	7.2%	0.33 [0.01, 8.16]
Subtotal (95% CI)		**13628**		**13618**	**100.0%**	**0.36 [0.15, 0.84]**
Total events	7		22			
Heterogeneity: $I^2 = 0\%$						
Test for overall effect: Z = 2.36 (P = 0.02)						

Test for subgroup differences: P = 0.38), $I^2 = 0\%$

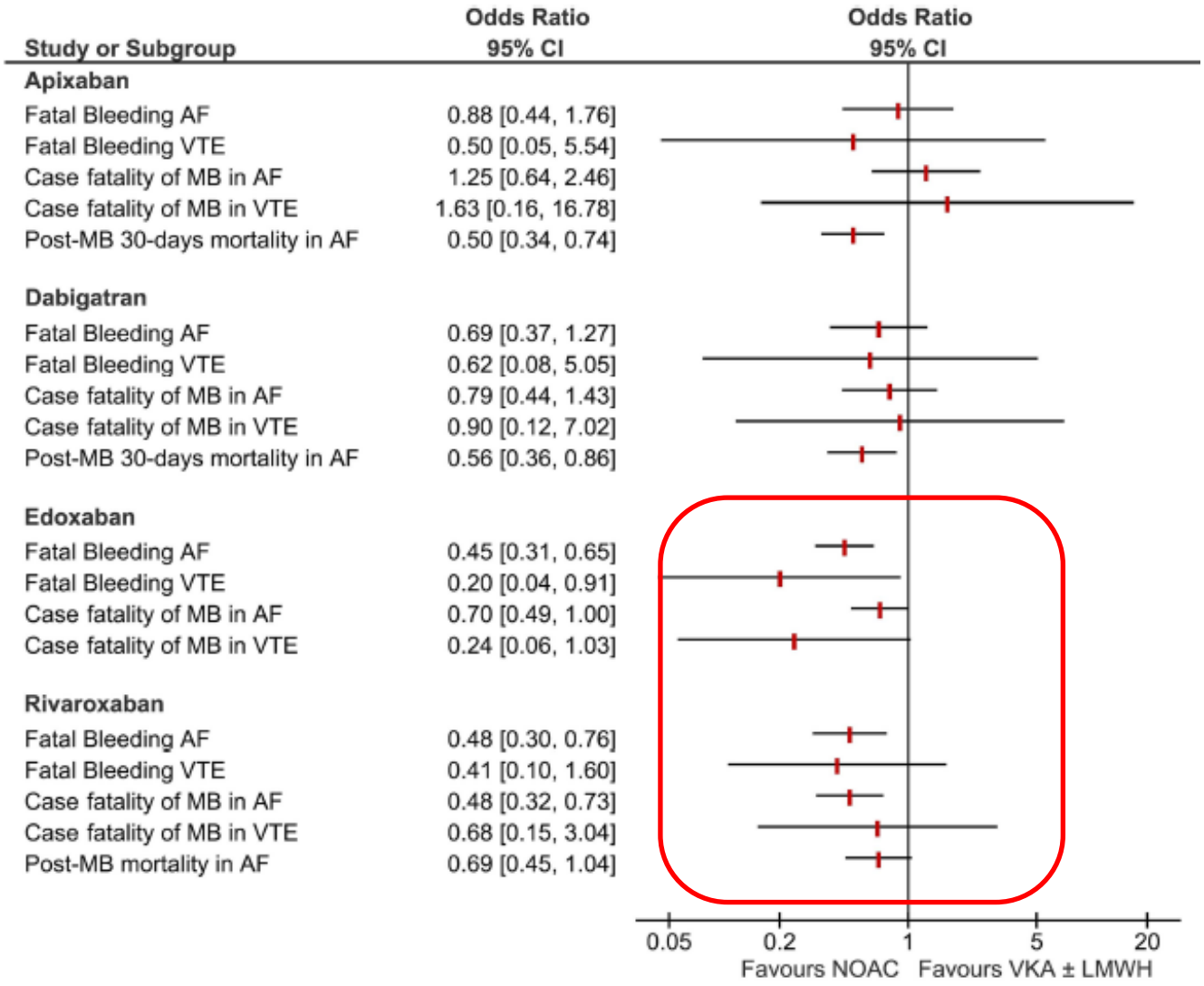


Prawdopodobieństwo śmiertelnego krwawienia

Heart. 2015 Aug;101(15):1204-11. doi: 10.1136/heartjnl-2015-307489. Epub 2015 Jun 2.

Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis.

Caldeira D[1], Rodrigues FB[2], Barra M[2], Santos AT[2], de Abreu D[2], Gonçalves N[2], Pinto FJ[3], Ferreira JJ[2], Costa J[4].



Heart. 2015 Aug;101(15):1204-11. doi: 10.1136/heartjnl-2015-307489. Epub 2015 Jun 2.

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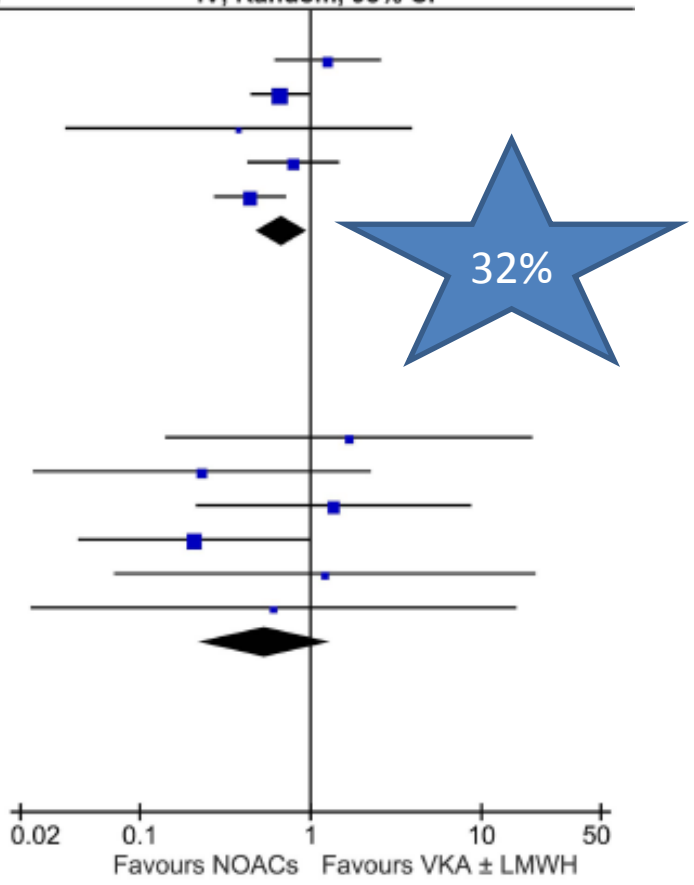
Study or Subgroup	NOACs Events	NOACs Total	VKA ± LMWH Events	VKA ± LMWH Total	Weight	Odds Ratio IV, Random, 95% CI
AF						
ARISTOTLE	15	327	17	462	17.0%	1.26 [0.62, 2.56]
ENGAGE-AF	52	672	59	524	33.1%	0.66 [0.45, 0.98]
J-ROCKET	1	23	3	28	2.2%	0.38 [0.04, 3.91]
RE-LY	25	741	18	426	20.5%	0.79 [0.43, 1.47]
ROCKET-AF	27	395	55	386	27.2%	0.44 [0.27, 0.72]
Subtotal (95% CI)		**2158**		**1826**	**100.0%**	**0.68 [0.48, 0.96]**
Total events	120		152			
Heterogeneity: I^2 = 37%						
Test for overall effect: Z = 2.18 (P = 0.03)						
VTE						
AMPLIFY	1	15	2	49	12.8%	1.68 [0.14, 19.91]
EINSTEIN-DVT	1	14	5	20	15.2%	0.23 [0.02, 2.24]
EINSTEIN-PE	2	26	3	52	22.8%	1.36 [0.21, 8.70]
Hokusai-VTE	2	56	10	66	32.1%	0.21 [0.04, 0.99]
RE-COVER	1	20	1	24	9.7%	1.21 [0.07, 20.67]
RE-MEDY	0	13	1	25	7.3%	0.60 [0.02, 15.90]
Subtotal (95% CI)		**144**		**236**	**100.0%**	**0.54 [0.22, 1.32]**
Total events	7		22			
Heterogeneity: I^2 = 0%						
Test for overall effect: Z = 1.35 (P = 0.18)						
Test for subgroup differences: P = 0.65						



Prawdopodobieństwo zgonu

J Neurol. 2015 Mar;262(3):516-22. doi: 10.1007/s00415-014-7462-0. Epub 2014 Aug 14.

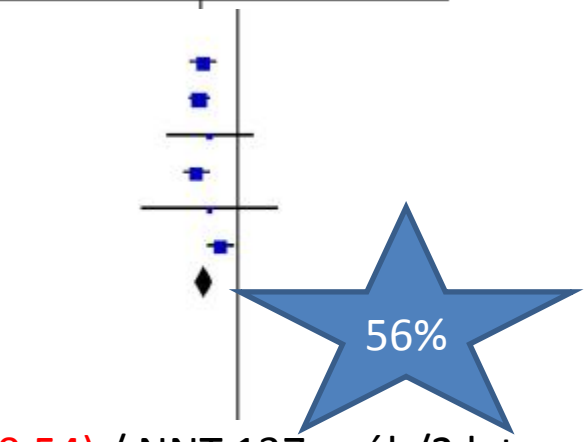
Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis.

Caldeira D[1], Barra M, Pinto FJ, Ferreira JJ, Costa J.

Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
VKA						
ARISTOTLE	52	9088	122	9052	22.6%	0.42 [0.31, 0.59]
ENGAGE-AF	102	14014	132	7012	28.3%	0.39 [0.30, 0.50]
J-ROCKET	5	639	10	639	3.5%	0.50 [0.17, 1.45]
RE-LY	63	12091	87	6022	22.6%	0.36 [0.26, 0.50]
RE-MEDY	2	1430	4	1426	1.5%	0.50 [0.09, 2.72]
ROCKET-AF	55	7111	84	7125	21.5%	0.66 [0.47, 0.92]
Subtotal (95% CI)		**44373**		**31276**	**100.0%**	**0.44 [0.36, 0.54]**
Total events	279		439			

Heterogeneity: Tau² = 0.02; Chi² = 7.88, df = 5 (P = 0.16); I² = 37%

Test for overall effect: Z = 7.72 (P < 0.00001)

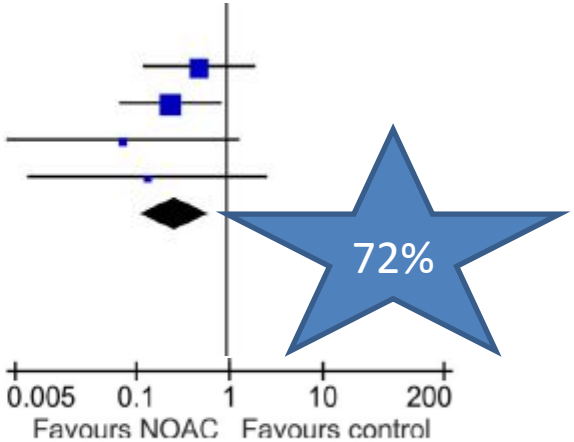


HR 0,44 (95%CI 0,36-0,54) / NNT 137 osób/2 lata

LMWH-VKA						
AMPLIFY	3	2676	6	2689	37.7%	0.50 [0.13, 2.01]
EINSTEIN-PE	3	2412	12	2405	45.3%	0.25 [0.07, 0.88]
Hokusai-VTE	0	4118	6	4122	8.7%	0.08 [0.00, 1.37]
RE-COVER	0	1274	3	1265	8.2%	0.14 [0.01, 2.74]
Subtotal (95% CI)		**10480**		**10481**	**100.0%**	**0.28 [0.12, 0.65]**
Total events	6		27			

Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 3 (P = 0.64); I² = 0%

Test for overall effect: Z = 2.94 (P = 0.003)



HR 0,28 (95%CI 0,12-0,65) / NNT 463 osób/7 m-cy

Jak ocenić zagrożenie?

Litera akronimu	Nazwa angielska	Nazwa polska	Liczba punktów
H	Hypertension	Nadciśnienie tętnicze (ciśnienie skurczowe >160 mmHg)	1
A	Abnormal renal and/or liver function	Nieprawidłowa czynność nerek (przewlekła dializoterapia, stan po przeszczepieniu nerki lub stężenie kreatyniny w surowicy >200 µmol/l) i/lub wątroby (przewlekła choroba wątroby (np. marskość) lub cechy biochemiczne istotnego uszkodzenia wątroby)	1 lub 2
S	Stroke / TIA	Przebyty udar lub TIA	1
B	Bleeding	Incydent krwawienia w wywiadzie i/lub predyspozycja do krwawień (np. skaza krwotoczna, niedokrwistość)	1
L	Labile INRs	Niestabilne wartości INR (wahające się duże wartości lub często poza przedziałem terapeutycznym)	1
E	Elderly	Starszy wiek (>65 lat)	1
D	Drugs or alcohol	Stosowanie leków wpływających na układ krzepnięcia (przeciwpłytkowych, NLPZ) lub nadużywanie alkoholu	1 lub 2

Jak ocenić zagrożenie?

- Zabiegi dużego ryzyka: KCH, chirurgia naczyń, NCH, ortopedia, urologia, onkologia głowy i szyi, T>45 min
- Wywiad rodzinny
- Wywiad dotyczący poprzednich procedur/ krwawień

Ale dla NOAC to nie zawsze wykonalne…

Pharmacotherapy. 2015 Jul;35(7):e115-7. doi: 10.1002/phar.1602. Epub 2015 Jun 10.

Spontaneous Hemopericardium in a Patient Receiving Apixaban Therapy: First Case Report.

Siqawy C[1,2], Apter S[2,3], Vine J[1,2], Grossman E[1,2].

⊕ **Author information**

Abstract

Apixaban, a direct factor Xa inhibitor, is a novel oral anticoagulant (NOAC) indicated for prevention of embolic events in patients with nonvalvular atrial fibrillation. The agent is associated with a lower risk of bleeding compared with vitamin K antagonists such as warfarin. Hemopericardium is a life-threatening bleeding event that is rarely caused by anticoagulants. We describe the case of a 76-year-old woman who was diagnosed with nonvalvular atrial fibrillation and treated with apixaban. Six weeks later, she was hospitalized after complaints of weakness and dizziness, and a chest radiograph revealed cardiomegaly. Further imaging, including a computed tomography scan and transthoracic echocardiogram, confirmed a diagnosis of hemopericardium. To our knowledge, this is the first case report of hemopericardium associated with apixaban therapy. This report, along with two previous cases reports of hemopericardium associated with dabigatran and rivaroxaban, emphasizes the need for careful use of NOACs and for further research to identify an antidote or other method for controlling hemorrhage secondary to NOACs in an acute setting. Furthermore, clinicians should consider hemopericardium in the differential diagnosis of patients treated with anticoagulants, including NOACs, who present with cardiomegaly.

Czym się różnią w praktyce?

NOAC

- **Zbawienie dla pacjenta i lekarza POZ**
  - ✓ Brak potrzeby monitorowania
  - ✓ Brak potrzeby kłucia
  - ✓ Redukcja kosztów
  - ✓ Brak zmienności międzyosobniczej
  - ✓ Nieistotny wpływ diety
  - ✓ Doustne stosowanie

- **Przekleństwo dla chirurga i anestezjologa**
  - ✓ (Względny) brak możliwości rutynowego monitorowania (tylko ujemny wynik jest wiążący)
  - ✓ (Względny) brak swoistego antidotum

VKA – RYZYKO DODANE

- Leki → antybiotyki, alkohol etylowy ☺
- Dieta → kapusta ☺

Cardiology. 2017;136(2):115-124. doi: 10.1159/000447530. Epub 2016 Sep 6.

Practical Considerations for the Nonvitamin K Antagonist Oral Anticoagulants.

Trikha R[1], Kowey PR.

Lek	Inhibitory CYP3A4	Aktywatory CYP3A4
Dabigatran	Ketokonazol	Rifampicyna
Rivaroxaban	Ketokonazol Leki p/wirusowe (navir'y)	Karbamazepina Fenytoina Rifampicyna
Apixaban	Jw. Klarytromycyna	Karbamazepina Fenytoina Rifampicyna
	ZWIĘKSZAJĄ AKTYWNOŚĆ NOAC	ZMNIEJSZAJĄ AKTYWNOŚĆ NOAC

Cardiology. 2017;136(2):115-124. doi: 10.1159/000447530. Epub 2016 Sep 6.

Practical Considerations for the Nonvitamin K Antagonist Oral Anticoagulants.

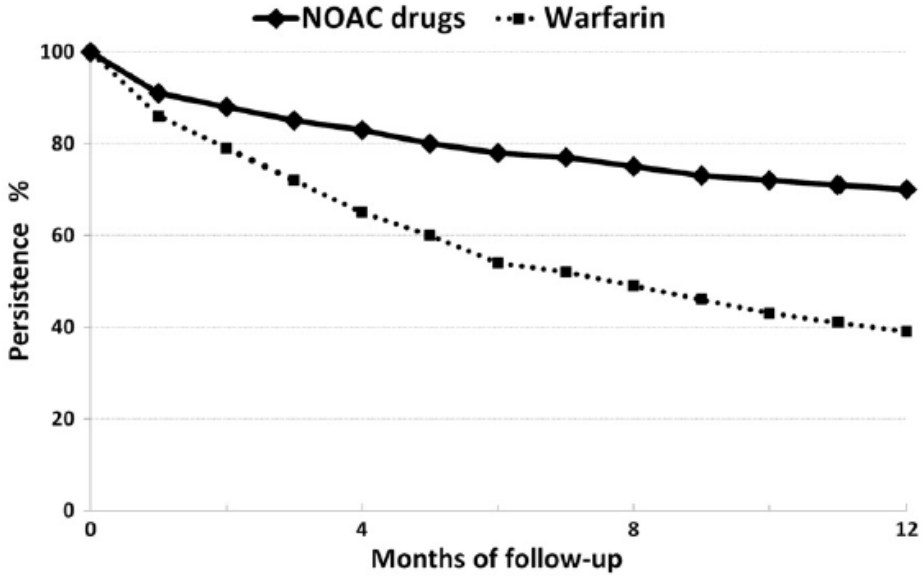
Trikha R[1], Kowey PR.

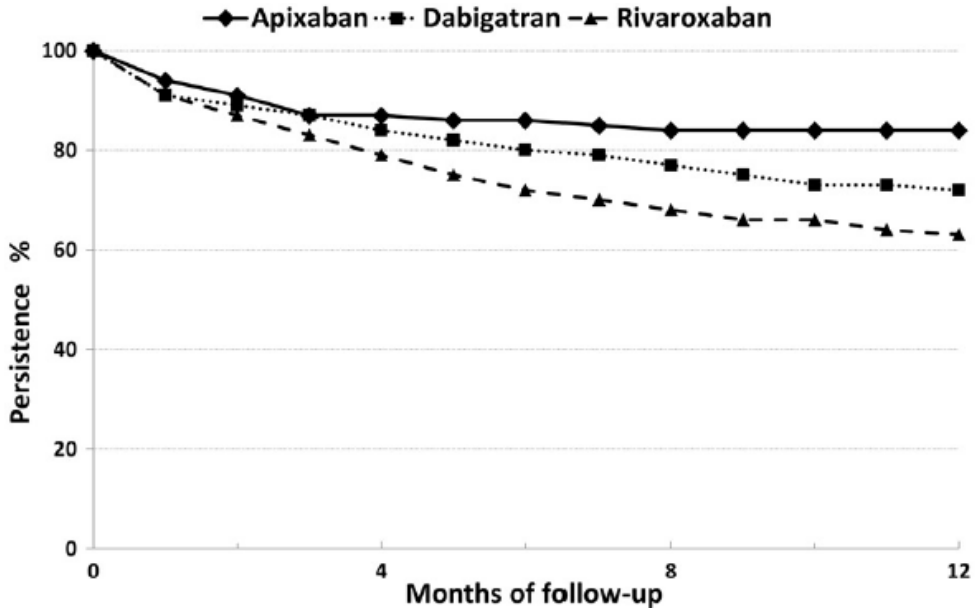
Populacja chorych	D150	R20	A5
Seniorzy / Mała masa ciała	-	-	≥80 lat oraz <60kg lub Krea ≥1,5kg → redukcja dawki do 2x2,5mg
Niewydolność wątroby	Child A i B: b/z	Child B i C: nie stosować	Child C: nie stosować

Curr Med Res Opin. 2016 Nov;32(11):1857-1861. Epub 2016 Aug 5.

Improved persistence with non-vitamin-K oral anticoagulants compared with warfarin in patients with atrial fibrillation: recent Australian experience.

Simons LA[1], Ortiz M[2,3], Freedman SB[4,5], Waterhouse BJ[6], Colquhoun D[7], Thomas G[8].

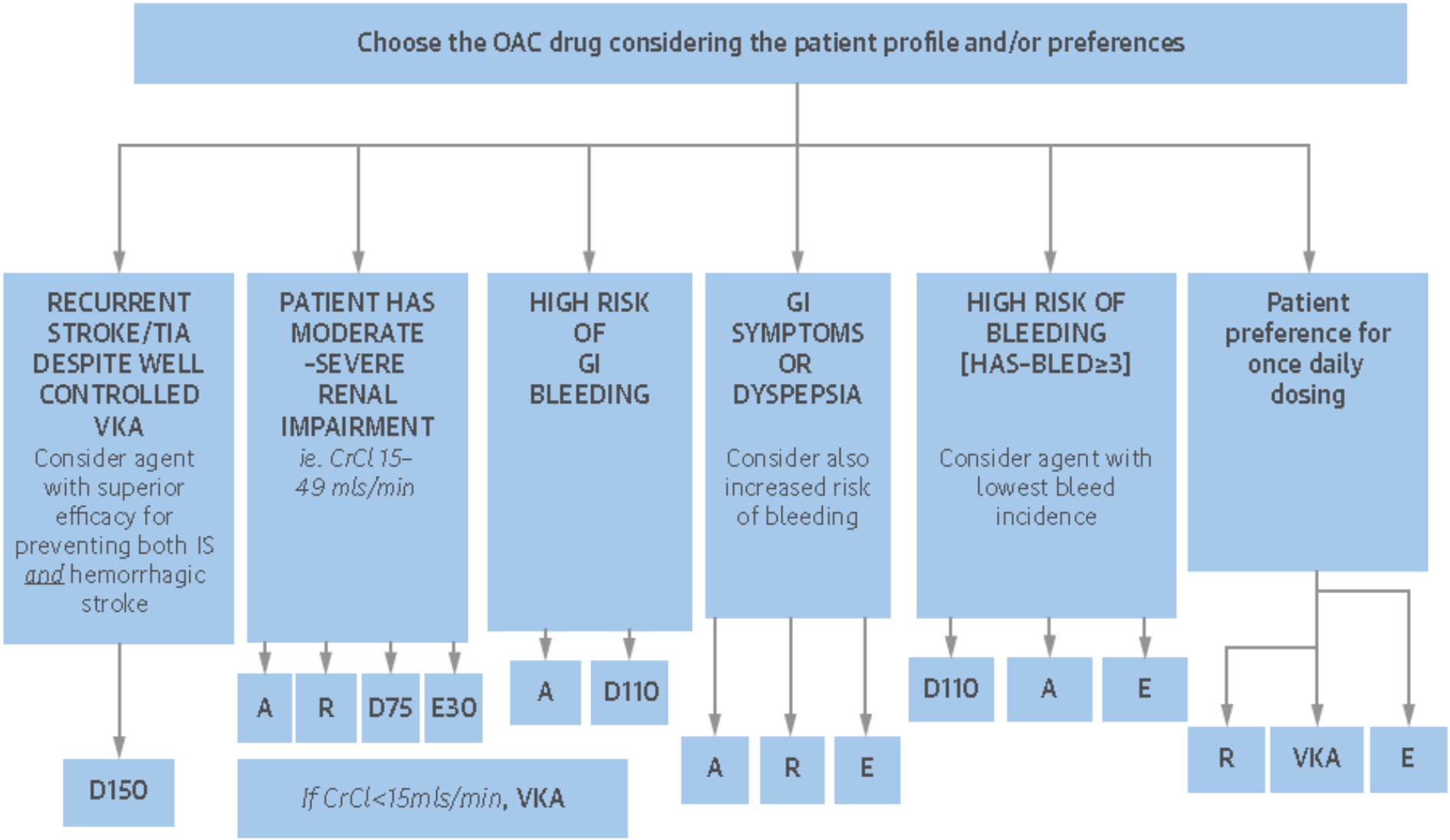




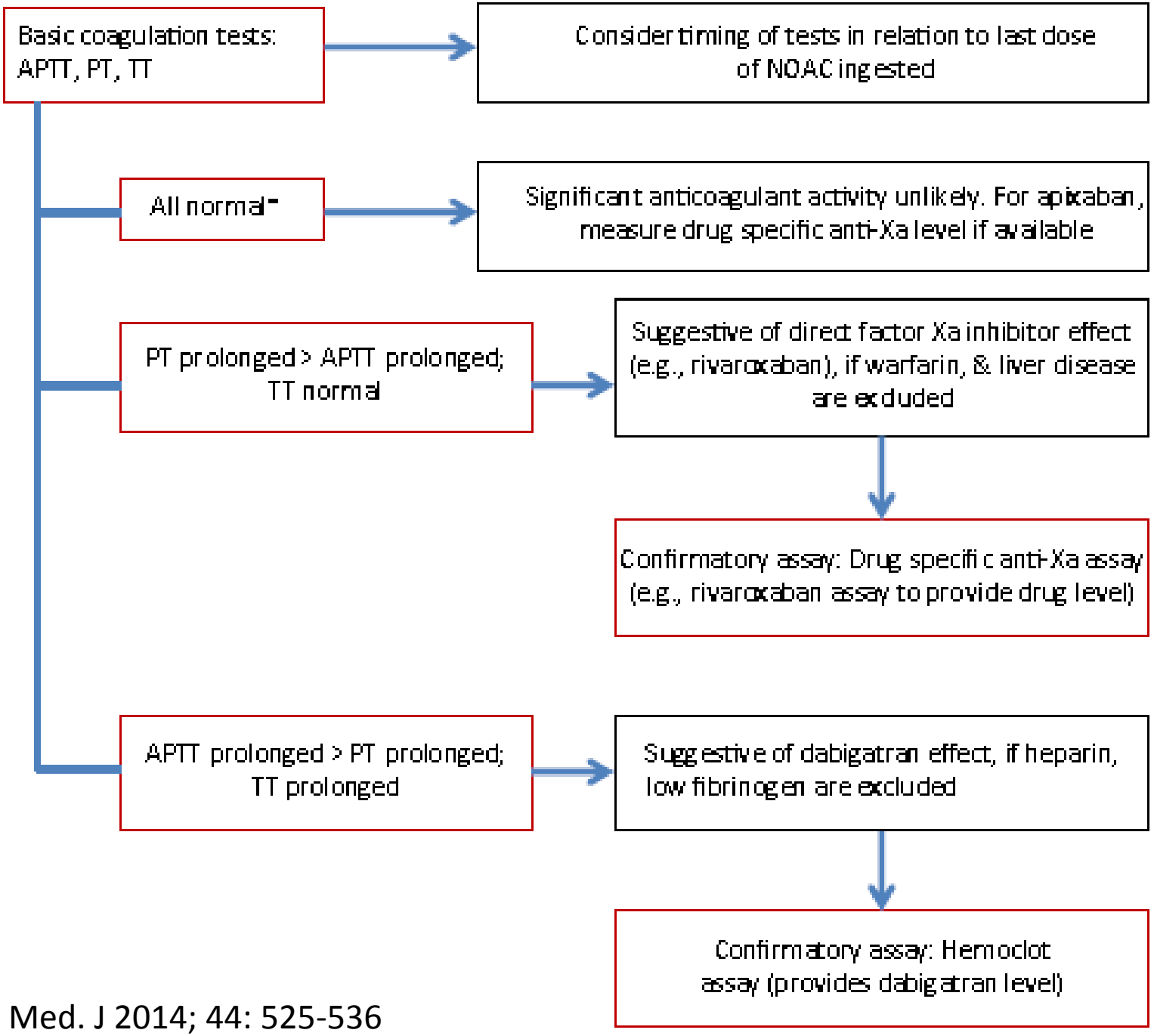
J Am Coll Cardiol. 2015 Dec 1;66(21):2282-4. doi: 10.1016/j.jacc.2015.07.086.

Matching the NOAC to the Patient: Remember the Modifiable Bleeding Risk Factors.

Lip GY[1], Lane DA[2].



Monitorowanie



Tran et al. Int Med. J 2014; 44: 525-536

Postępowanie w okresie okołooperacyjnym – zabiegi planowe

STOP

- Dabigatran:
  - Małe ryzyko krwawienia: 2 dni (opuść 2 dawki)
  - Duże ryzyko: 3 dni (opuść 4 dawki)
- Rivaroxaban:
  - Małe ryzyko: 2 dni (opuść 1 dawkę)
  - Duże ryzyko: 3 dni (opuść 2 dawki)
- Apixaban:
  - Małe ryzyko: 2 dni (opuść 2 dawki)
  - Duże ryzyko: 3 dni (opuść 4 dawki)

BEZ POMOSTOWANIA

START

- Dabigatran:
  - Małe ryzyko krwawienia: 1 dzień (24h / 2x150)
  - Duże ryzyko: 2-3 dni (48-72h / 2x150)
- Rivaroxaban:
  - Małe ryzyko: 1 dzień (24h / 1x20)
  - Duże ryzyko: 2-3 dni (48-72h / 1x20)
- Apixaban:
  - Małe ryzyko: 1 dzień (24h / 2x5)
  - Duże ryzyko: 2-3 dni (48-72h / 2x5)

J Atr Fibrillation. 2015 Dec 31;8(4):1230. eCollection 2015.

Periprocedural Management of Non-Vitamin K Oral Anticoagulants in Chronic Kidney Disease: A Review of Existing Heterogeneity and Contemporary Evidence.

Gunasekaran Md P[1], Parashara Md Facc Fscai DK[2].

Table 1: Discrepancies in the time of stoppage (in hours) of Dabigatran prior to elective surgeries*

Author	Creatinine Clearance (CrCl) (ml/min)							
	> 80		50-80		30-50		<30	
	Low-Risk	High Risk	Low-Risk	High Risk	Low-Risk	High Risk	Low-Risk	High Risk
Heidbuchel et al.	≥ 24	≥48	≥36`	≥72	≥48	≥96	-	-
Fawole et al.	-	-	24	48	48	96	96	144
Schulman et al.	24	48	24	48	48	96	96	144
Lai et al.	≥24	≥48	≥36	≥72	≥48	≥96	≥48	≥96
Hankey et al.	24	48-96	24	48-96	≥48	96	48-120	>120
Levy et al.	24	48-96	24	48-96	≥48	≥96	48-120	>120

*Package insert recommends discontinuing dabigatran 1-2 days (CrCl ≥ 50 mL/min) or 3 to 5 days (CrCl <50 mL/min) prior to elective surgical procedures. Longer but unspecified times are recommended for major surgery, spinal puncture, or placement of a spinal or epidural catheter or port.

J Atr Fibrillation. 2015 Dec 31;8(4):1230. eCollection 2015.

Periprocedural Management of Non-Vitamin K Oral Anticoagulants in Chronic Kidney Disease: A Review of Existing Heterogeneity and Contemporary Evidence.

Gunasekaran Md P[1], Parashara Md Facc Fscai DK[2].

Table 2: Recommended Timing of Pre-Procedural stoppage of Dabigatran in Relation to Creatinine Clearance Values Evaluated in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial

	Timing of Dabigatran Stoppage Before the Procedure	
Creatinine clearance (ml/min)	High Bleeding Risk	Standard Bleeding Risk
≥ 50 to <80	2-3 days	24 hours
≥ 30 to <50	4 days	2 days
< 30	> 5 days	2-4 days

Low bleeding risk procedures: coronary angiography or pacemaker implantation; High risk of bleeding: cardiac, abdominal, and neurosurgery or procedures requiring spinal anesthesia.

J Atr Fibrillation. 2015 Dec 31;8(4):1230. eCollection 2015.

Periprocedural Management of Non-Vitamin K Oral Anticoagulants in Chronic Kidney Disease: A Review of Existing Heterogeneity and Contemporary Evidence.

Gunasekaran Md P[1], Parashara Md Facc Fscai DK[2].

Table 3: Discrepancies in the time cut-off for stoppage (in hours) of Rivaroxaban prior to elective surgeries*

Author	Creatinine Clearance (ml/min)	Low-Risk	High Risk
Schulman et al./Fawole et al.	>30	24	48
	≤30	48	96
Heidbuchel et al.	≥30	≥24	≥48
	15-30	≥36	≥48
	<15	Not indicated	
Wysonkinski et al. (irrespective of surgical bleeding risk)	≥50	72	
	<50	120	

*Package insert recommends holding of rivaroxaban at least 24 hours prior to surgery irrespective of CrCl and magnitude of surgical bleeding risk.

J Atr Fibrillation. 2015 Dec 31;8(4):1230. eCollection 2015.

Periprocedural Management of Non-Vitamin K Oral Anticoagulants in Chronic Kidney Disease: A Review of Existing Heterogeneity and Contemporary Evidence.

Gunasekaran Md P[1], Parashara Md Facc Fscai DK[2].

Table 4: Discrepancies in the time cut-offs for holding (in hours) Apixaban prior to elective surgical interventions*

Author	Creatinine Clearance	Low-Risk	High Risk
Heidbuchel et al.	≥30	≥24	≥48
	15-30	≥36	≥48
	<15	No data	
Fawole et al.	>30	24	48
	≤30	48	96

*Package insert recommends holding of Apixaban at least 24 and 48 hours prior to low and high bleeding risk procedures respectively (irrespective of creatinine clearance)

J Atr Fibrillation. 2015 Dec 31;8(4):1230. eCollection 2015.

Periprocedural Management of Non-Vitamin K Oral Anticoagulants in Chronic Kidney Disease: A Review of Existing Heterogeneity and Contemporary Evidence.

Gunasekaran Md P[1], Parashara Md Facc Fscai DK[2].

Table 5: Unified Recommended Timing (in hours) for Discontinuation of Non-Vitamin K Oral Anticoagulants Prior to the Procedure

Agent	Bleeding Risk Associated With the Procedure	
	Low Risk	High Risk
Rivaroxaban*	≥72	≥96
Apixaban†	≥24	≥48
Edoxaban‡	≥24	unclear

Procedures with high risk of bleeding include cardiac surgery, vascular surgery (excluding endovascular procedures) and neurosurgery where bleeding could be deleterious. Most other procedures are considered low risk for bleeding.
*Data derived from ROCKET-AF trial. †Data derived from ARISTOTLE trial. ‡Data derived from ENGAGE TIMI-48 trial.

Masywne krwawienie

- Zabezpieczenie chirurgiczne
- Stabilizacja metaboliczna i krążeniowa
- Miejsce w OIT
- Podać antidotum (czy dostępne?)
- Podać węgiel aktywowany (złote 2 godz. po dabigatranie)
- Rozważyć hemodializę (dabigatran!)
- Podać PCC 4-czynnikowy (rivaroxaban, dabigatran) / aPCC (dabigatran)
- Podać antyfibrynolityk (kwas traneksamowy)
- Rozważyć desmopresynę

Siegel DM, Crowther MA. EHJ 2013; 34: 489-500

Antagoniści

- Leki omijające
- Antidota

J Clin Pharm Ther. 2016 Feb;41(1):92-3. doi: 10.1111/jcpt.12339. Epub 2015 Dec 18.

Prothrombin complex concentrate for the management of severe traumatic bleeding in a patient anticoagulated with apixaban.

Durie R[1,2], Kohute M[2,3], Fernandez C[4], Knight M[4].

Front Neurol Neurosci. 2015;37:93-106. doi: 10.1159/000437116. Epub 2015 Nov 12.

New Insights into Nonvitamin K Antagonist Oral Anticoagulants' Reversal of Intracerebral Hemorrhage.

Yasaka M[1].

Neurocrit Care. 2016 Jun;24(3):413-9. doi: 10.1007/s12028-015-0213-y.

The Role of FEIBA in Reversing Novel Oral Anticoagulants in Intracerebral Hemorrhage.

Dibu JR[1], Weimer JM[1], Ahrens C[1], Manno E[1], Frontera JA[2].

J Clin Pharm Ther. 2016 Feb;41(1):92-3. doi: 10.1111/jcpt.12339. Epub 2015 Dec 18.

Prothrombin complex concentrate for the management of severe traumatic bleeding in a patient anticoagulated with apixaban.

Durie R[1,2], Kohute M[2,3], Fernandez C[4], Knight M[4].

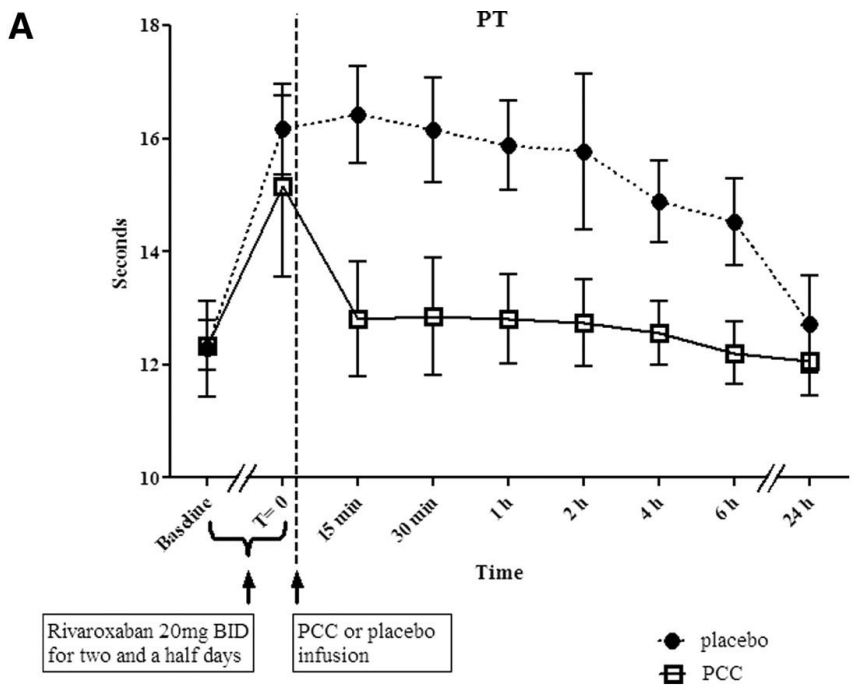
World Neurosurg. 2015 Dec;84(6):1956-61. doi: 10.1016/j.wneu.2015.08.042. Epub 2015 Sep 1.

Administration of 4-Factor Prothrombin Complex Concentrate as an Antidote for Intracranial Bleeding in Patients Taking Direct Factor Xa Inhibitors.

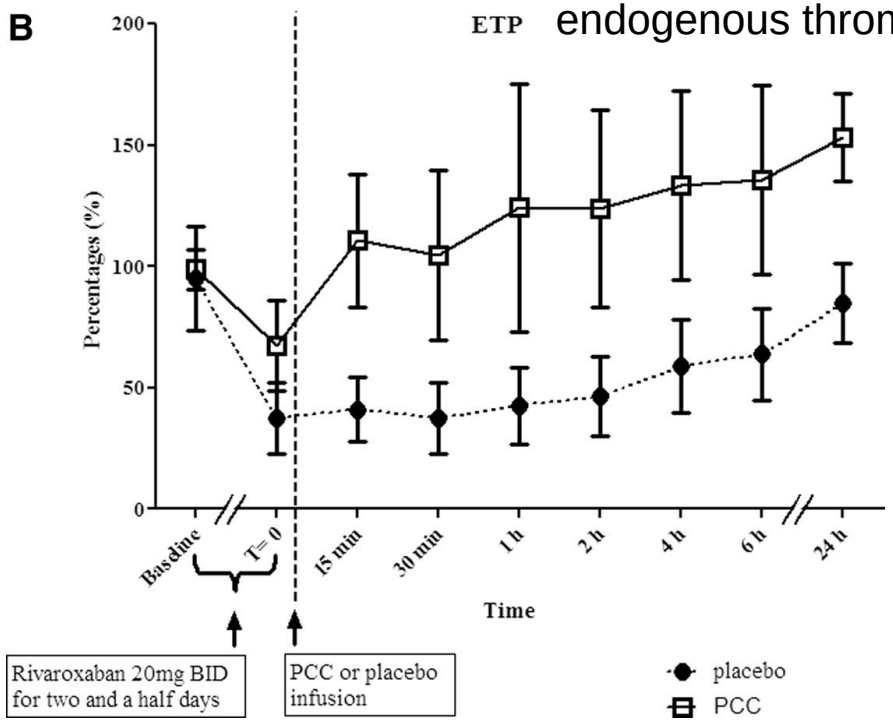
Grandhi R[1], Newman WC[2], Zhang X[3], Harrison G[4], Moran C[5], Okonkwo DO[2], Ducruet AF[2].

FEIBA
[anti-inhibitor coagulant complex]

Beriplex® P/N
Human Prothrombin Complex



Effect of rivaroxaban followed by prothrombin complex concentrate (PCC) or placebo on the prothrombin time (PT)



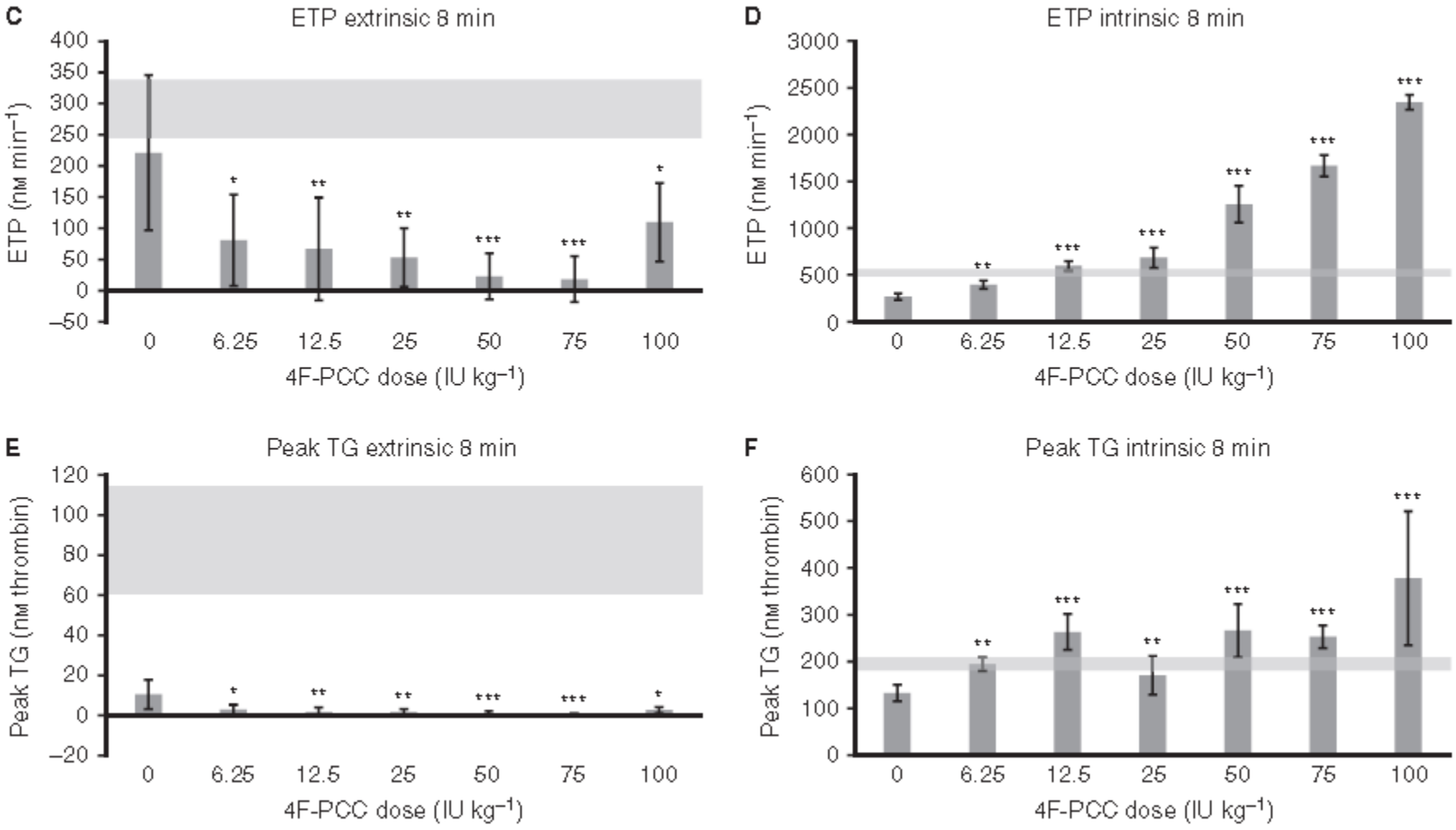
Eerenberg E et al. Circulation 2011;124:1573-1579

American Heart Association
Learn and Live

J Thromb Haemost. 2015 Dec;13(12):2220-6. doi: 10.1111/jth.13165. Epub 2015 Nov 24.

Four-factor prothrombin complex concentrate reverses apixaban-associated bleeding in a rabbit model of acute hemorrhage.

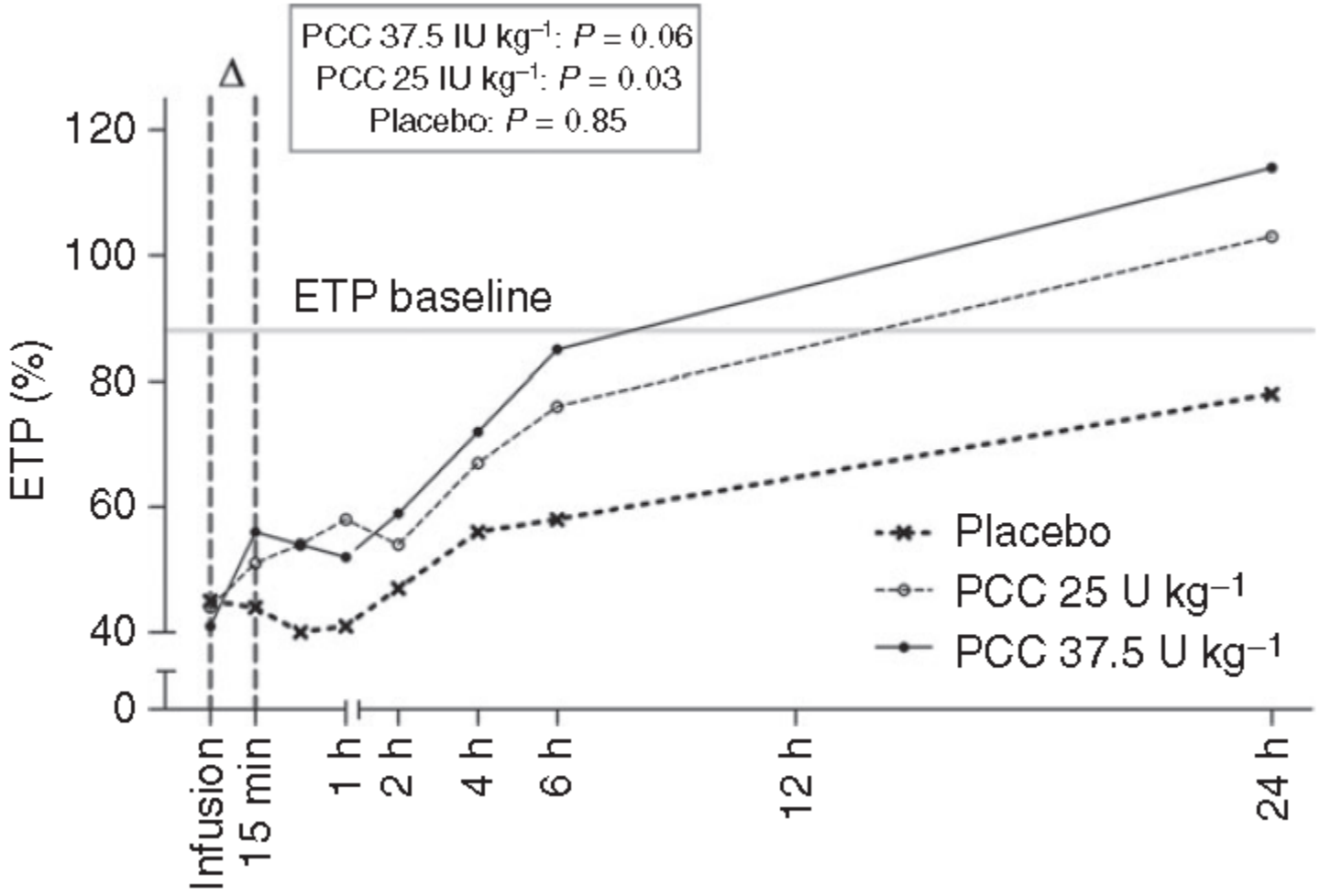
Herzog E[1], Kaspereit F[1], Krege W[1], Mueller-Cohrs J[1], Doerr B[1], Niebl P[1], Dickneite G[1].

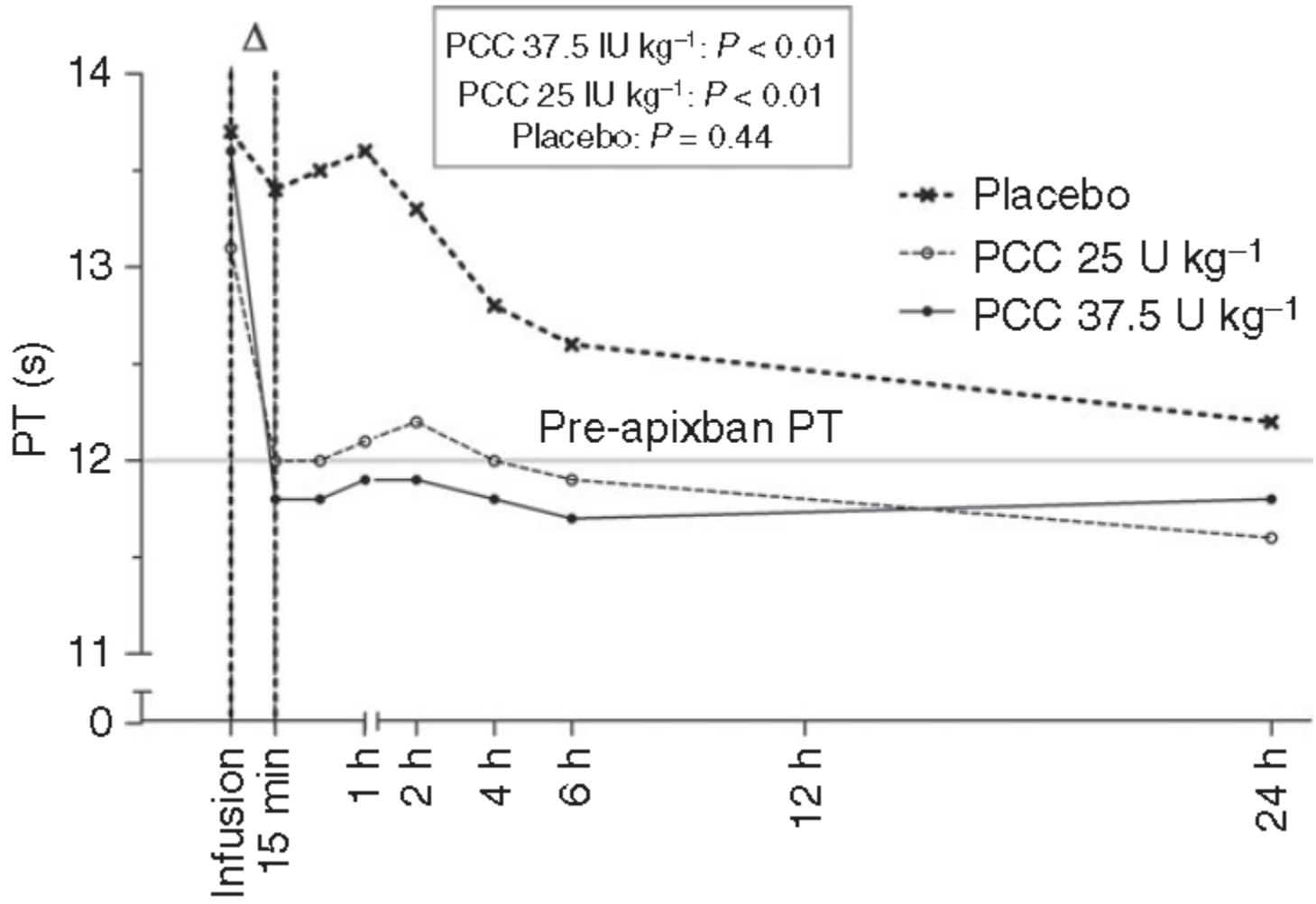


J Thromb Haemost. 2015 Oct;13(10):1799-805. doi: 10.1111/jth.13115. Epub 2015 Sep 21.

In vivo increase in thrombin generation by four-factor prothrombin complex concentrate in apixaban-treated healthy volunteers.

Cheung YW[1], Barco S[2], Hutten BA[3], Meijers JC[4,5], Middeldorp S[1], Coppens M[1].

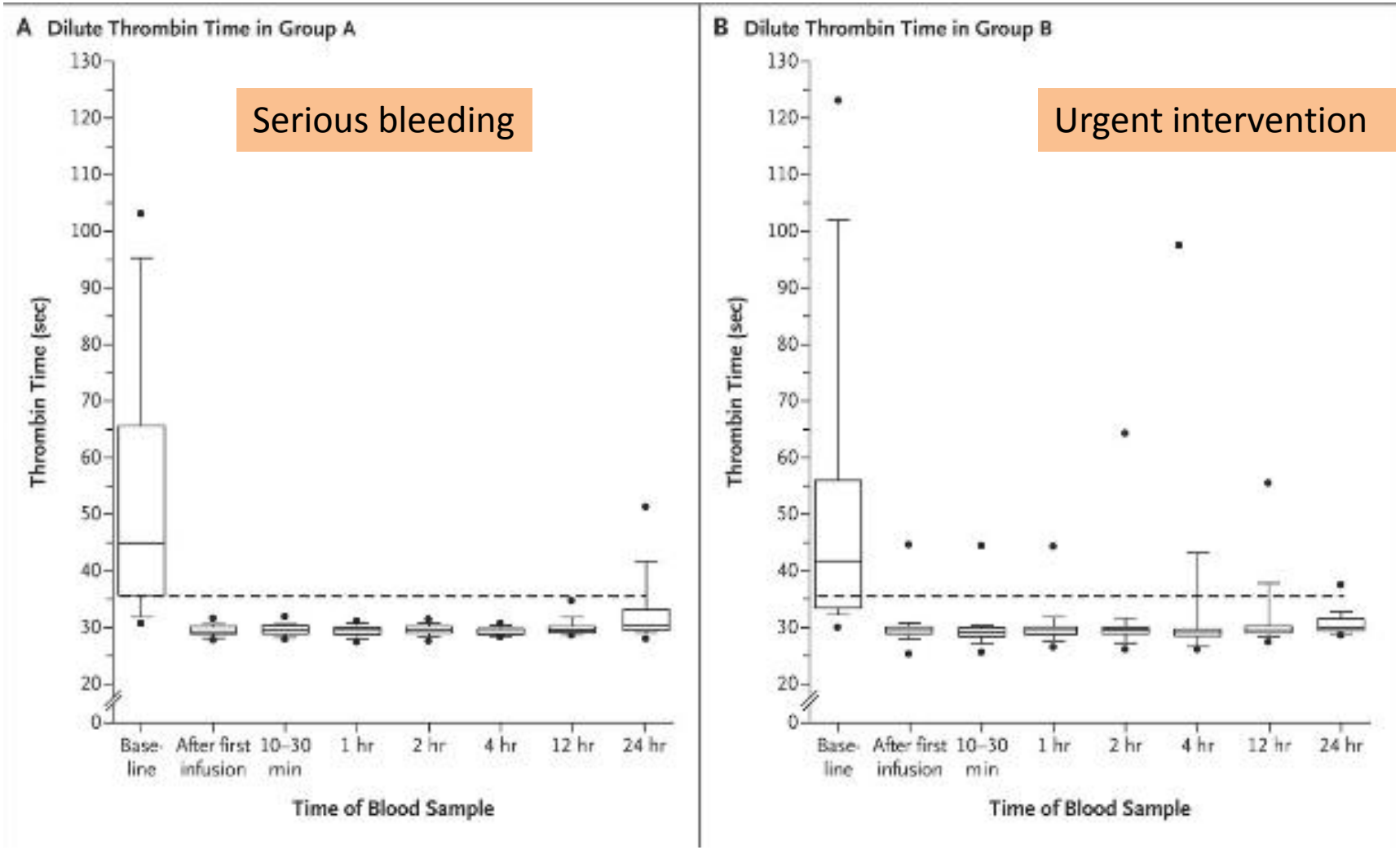



PCC 37.5 IU kg⁻¹: P < 0.01
PCC 25 IU kg⁻¹: P < 0.01
Placebo: P = 0.44
Δ
Placebo
PCC 25 U kg⁻¹
PCC 37.5 U kg⁻¹
Pre-apixban PT
PT (s)
14
13
12
11
0
Infusion
15 min
1 h
2 h
4 h
6 h
12 h
24 h

N Engl J Med. 2015 Aug 6;373(6):511-20. doi: 10.1056/NEJMoa1502000. Epub 2015 Jun 22.

Idarucizumab for Dabigatran Reversal.

Pollack CV Jr[1], Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T, Wang B, Kam CW, Weitz JI.



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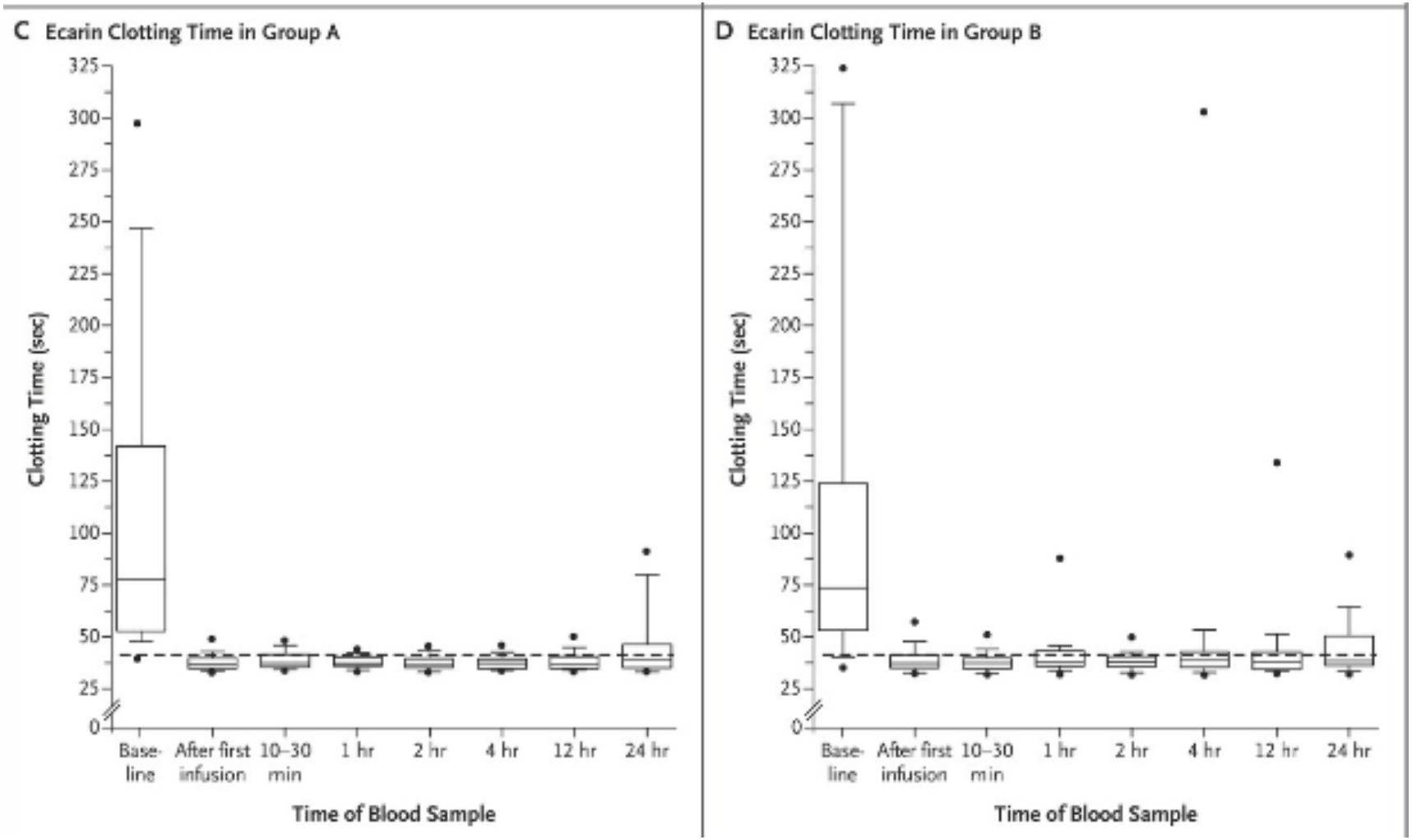

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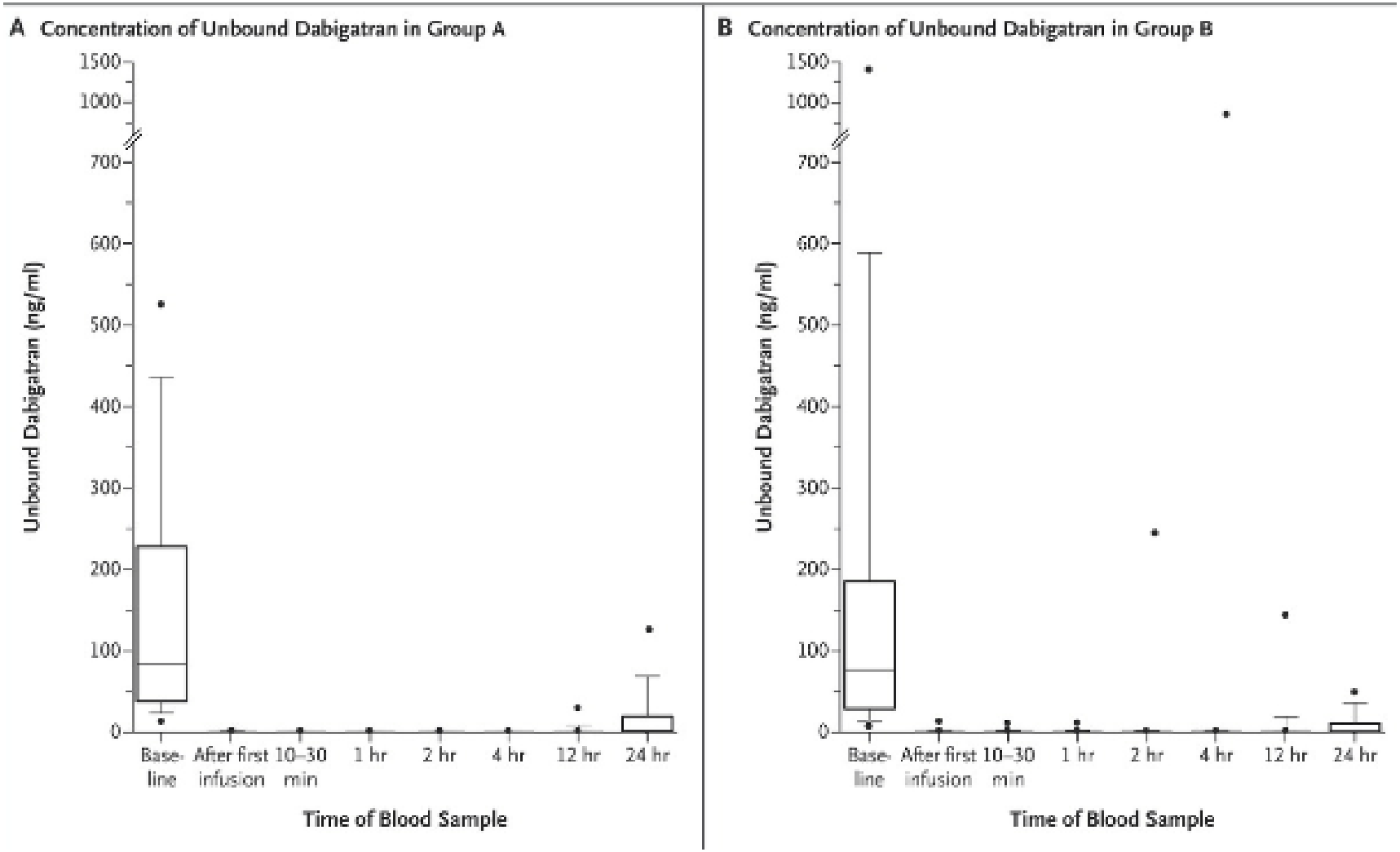

N Engl J Med. 2015 Aug 6;373(6):511-20. doi: 10.1056/NEJMoa1502000. Epub 2015 Jun 22.

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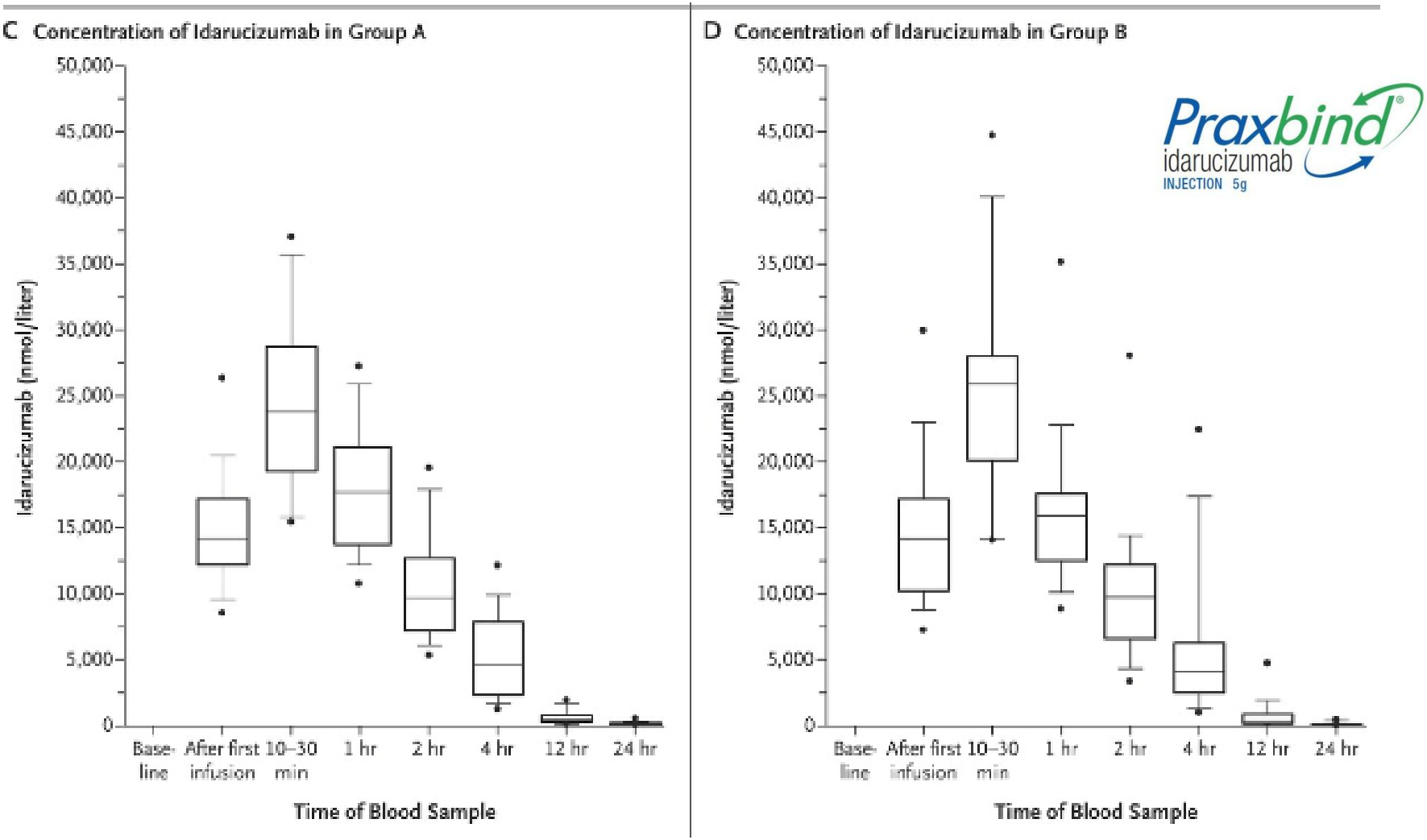
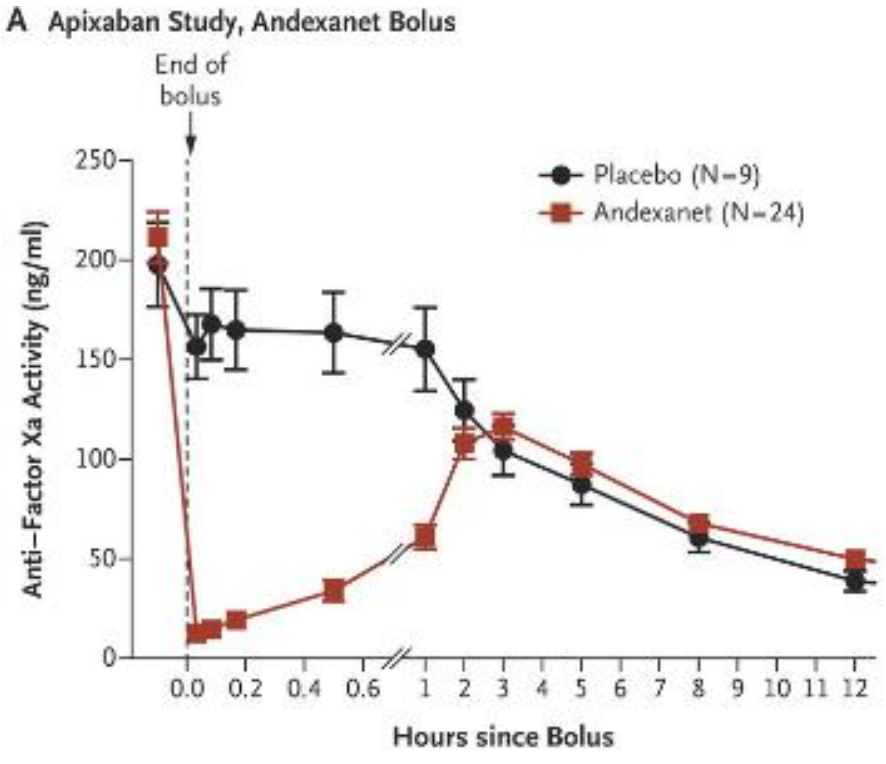
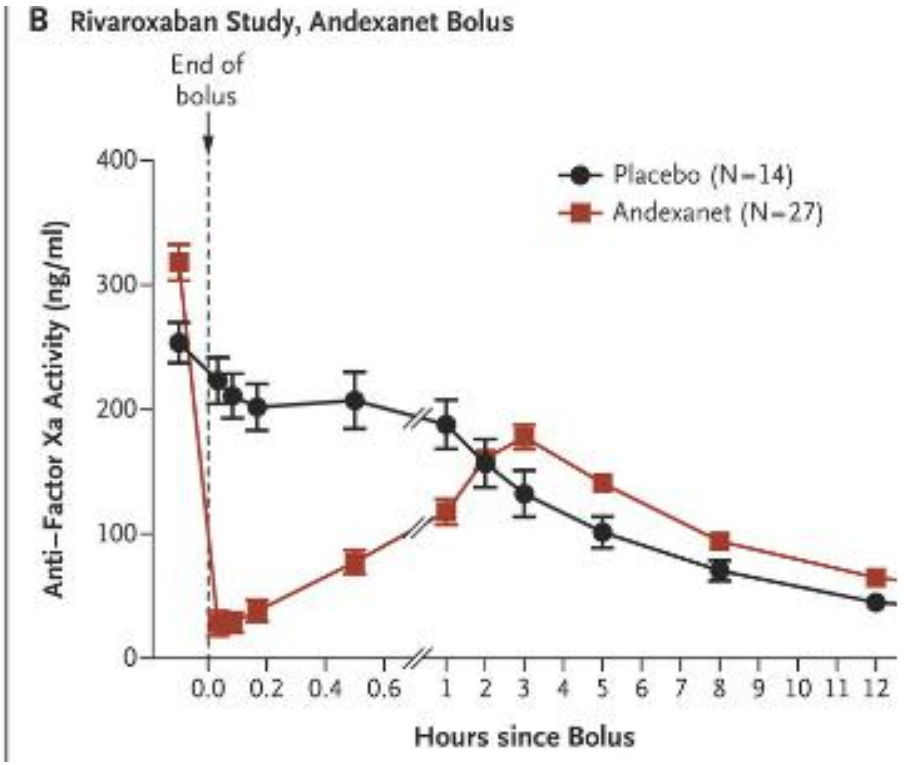


N Engl J Med. 2015 Dec 17;373(25):2413-24. doi: 10.1056/NEJMoa1510991. Epub 2015 Nov 11.

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity.

Siegal DM[1], Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA.





N Engl J Med. 2015 Dec 17;373(25):2413-24. doi: 10.1056/NEJMoa1510991. Epub 2015 Nov 11.

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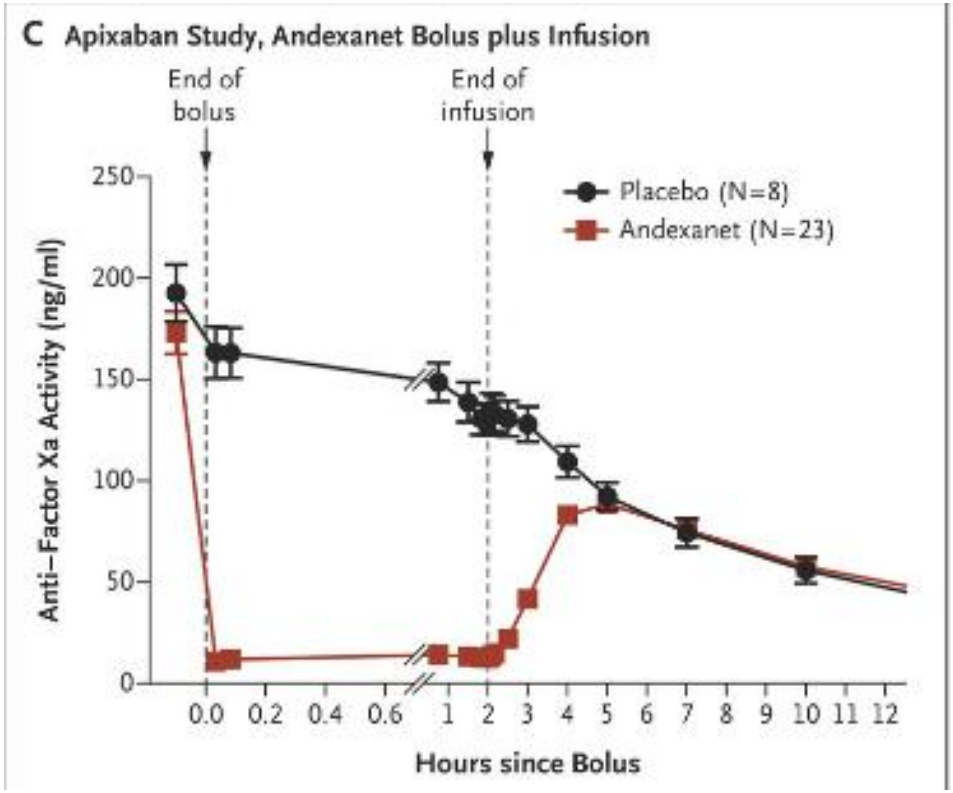

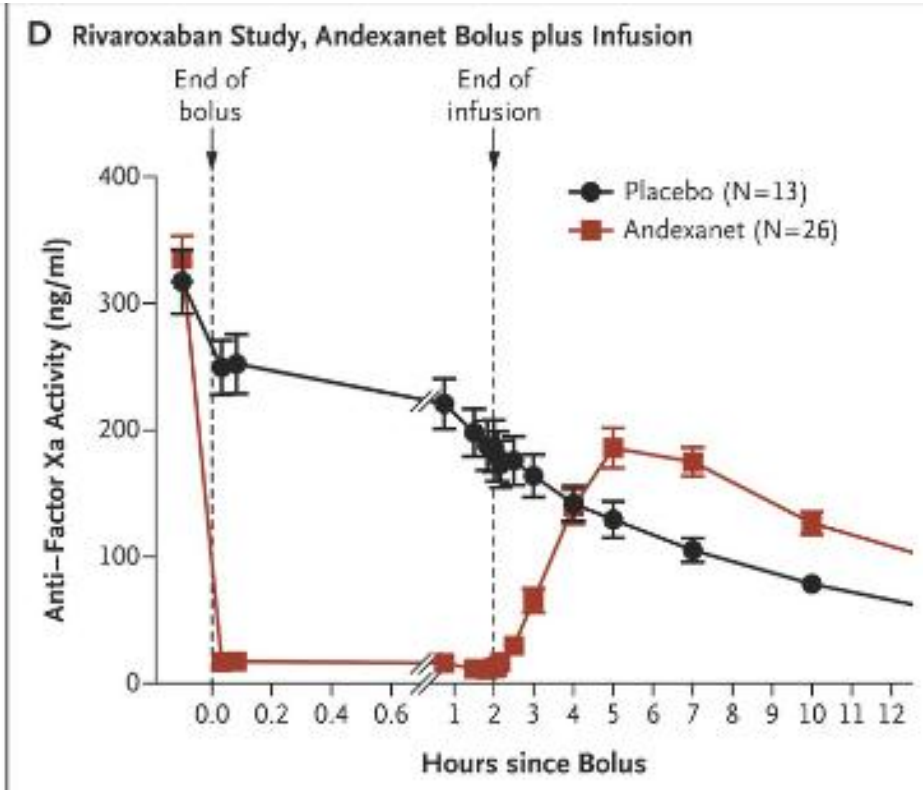

N Engl J Med. 2015 Dec 17;373(25):2413-24. doi: 10.1056/NEJMoa1510991. Epub 2015 Nov 11.

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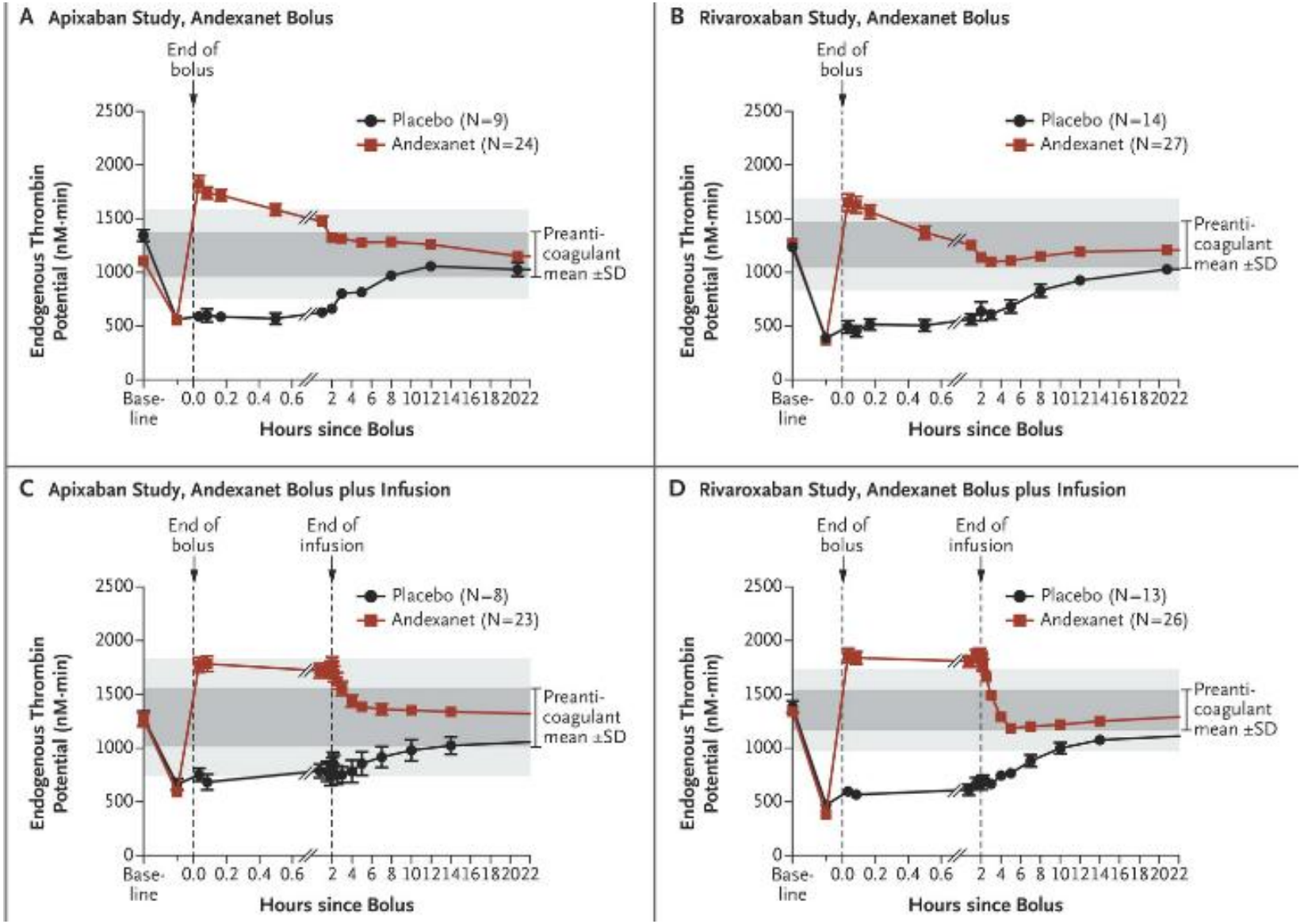
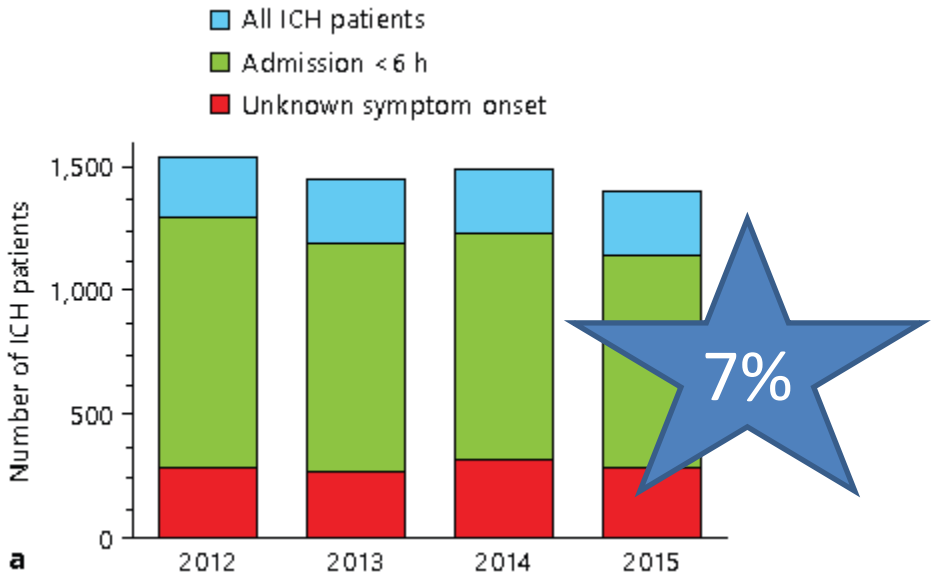
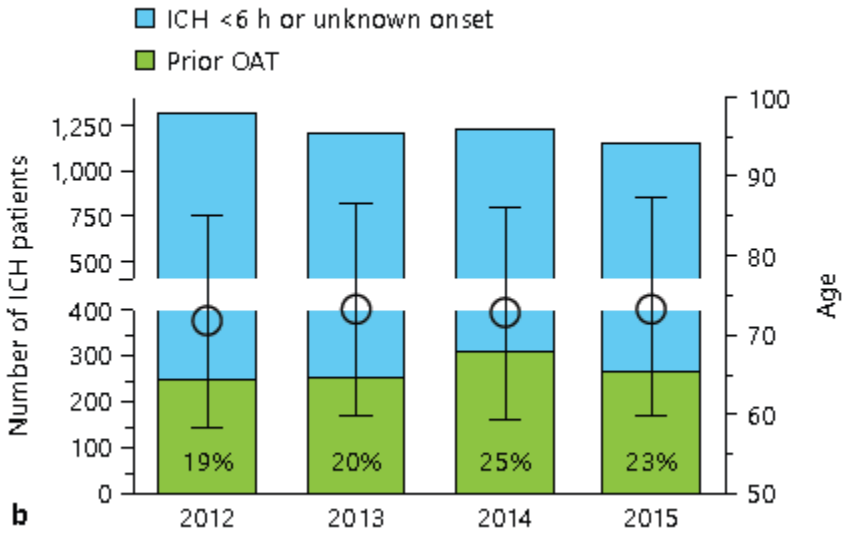


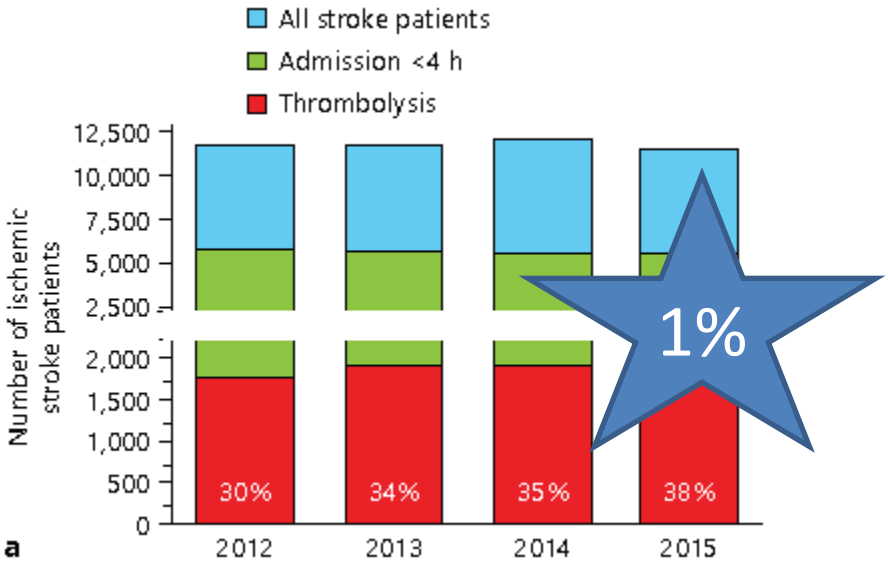
Cerebrovasc Dis. 2016;42(5-6):415-420. Epub 2016 Jul 21.

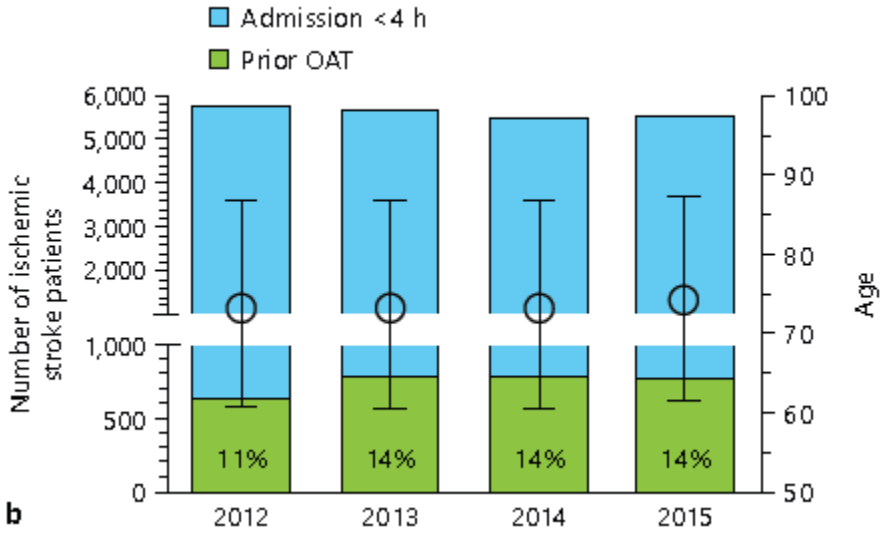
Estimating the Quantitative Demand of NOAC Antidote Doses on Stroke Units.

Pfeilschifter W[1], Farahmand D, Niemann D, Ikenberg B, Hohmann C, Abruscato M, Thonke S, Strzelczyk A, Hedtmann G, Neumann-Haefelin T, Kollmar R, Singer OC, Ferbert A, Steiner T, Steinmetz H, Reihs A, Misselwitz B, Foerch C.









Take home message

- ✓ Populacja chorych stosujących NOAC rośnie w siłę (ale też są nowe wskazania, nowe leki, nowe refundacje)
- ✓ Co dla pacjenta jest zbawieniem, dla anestezjologa staje się problemem (ale nic na to nie poradzimy)
- ✓ Monitorowanie terapii jest trudne (ale też niepotrzebne)
- ✓ Przygotowanie chorych do zabiegów planowych jest proste i oparte o sprawdzone algorytmy (ale trzeba się ich nauczyć)
- ✓ W sytuacjach nagłych zastosowanie znajdują leki omijające i bezpośredni antagoniści NOAC (ale to rozwiązania drogie)

Dodatkowe informacje, czyli o czym nie powiedziałem

Med Klin Intensivmed Notfmed. 2017 Jan 10. doi: 10.1007/s00063-016-0247-8. [Epub ahead of print]

[Neuraxial anaesthesia and NOACs].

[Article in German]

Standl T[1].

⊕ **Author information**

Abstract

BACKGROUND: Cardiovascular comorbidities in surgical patients are frequent and have a substantial impact on the postoperative outcome. Neuraxial blockades are able to reduce perioperative morbidity and mortality. The increasing use of new oral anticoagulants (NOAC) requires a high level of attention, especially in patients undergoing neuraxial blockades or requiring postoperative analgesia.

OBJECTIVE: The goal of this article is to present the benefit of neuraxial anaesthesia and analgesia in patients with cardiovascular risks and perioperative management of NOAC in this setting.

MATERIALS AND METHODS: Review of the respective literature in PubMed during the last 25 years as well as presentation of the S1 guideline "Neuraxial anaesthesia and thrombo-embolic prophylaxis/antithrombotic medication" of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI).

RESULTS: Thoracic epidural anaesthesia and analgesia contribute to an improved outcome in surgical patients with high cardiovascular risk. In order to avoid severe complications in patients on NOACs undergoing neuraxial blockades the S1 guideline of the DGAI must be respected and close interdisciplinary consultations between anaesthetist, cardiologist and surgeon are mandatory.

CONCLUSION: In consideration of the respective guideline neuraxial blockades can be performed in cardiovascular risk patients on NOACs, since these techniques contribute to an improved postoperative outcome.

NOAC a anestezja regionalna

Reg Anesth Pain Med. 2015 May-Jun;40(3):182-212. doi: 10.1097/AAP.0000000000000223.

Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain.

Narouze S[1], Benzon HT, Provenzano DA, Buvanendran A, De Andres J, Deer TR, Rauck R, Huntoon MA.

Czas	Dabigatran (150/220)	Rivaroxaban (10)	Apixaban (5)
Ostatnia dawka NOAC vs założenie lub usunięcie cewnika	4-5d (min 2x half time!) (6 dni*)	3d	3-5d
Nowa dawka NOAC po usunięciu cewnika	24h (12h**)	24h (12h**)	24h (12h**)
Nowa dawka NOAC po założeniu cewnika	?	22-26h	26-30h

* Uwaga na CrCl

** Duże ryzyko DVT

Lancet Haematol. 2016 Oct;3(10):e480-e488. doi: 10.1016/S2352-3026(16)30111-9.

Management and outcomes of vaginal bleeding and heavy menstrual bleeding in women of reproductive age on direct oral anti-factor Xa inhibitor therapy: a case series.

Beyer-Westendorf J[1], Michalski F[2], Tittl L[2], Hauswald-Dörschel S[2], Marten S[2].

Author information

Abstract

BACKGROUND: Observational data and results from post-hoc analyses in clinical trials suggest that direct oral factor Xa inhibitors might increase menstrual bleeding intensity in women of reproductive age, but the extent of this effect is unknown. We aimed to investigate the management and outcomes of vaginal bleeding complications during therapy with direct oral factor Xa inhibitors in a case series of women of reproductive age.

METHODS: To identify individuals for inclusion in this case series, we searched two sources of prospectively collected data from women of reproductive age treated with direct oral factor Xa inhibitors: the non-interventional Dresden NOAC Registry (NCT01588119), which is based in the administrative district of Dresden (Saxony, Germany), and all locally archived data from phase 3 trials of direct oral factor Xa inhibitors done at University Hospital Carl Gustav Carus Dresden. Vaginal bleeding events were defined as any vaginal bleeding complications as reported by the patient. We collected data on type and dosage of anticoagulation; suspected or confirmed bleeding events, hospital admissions, and mortality; and pattern and management of vaginal bleeding events. For all cases of bleeding identified, we reviewed all available source data to identify examination results suggesting potential underlying anatomical causes of bleeding.

FINDINGS: We identified 178 women of reproductive age who received direct oral factor Xa inhibitor therapy, of whom 57 had vaginal bleeding events, including 50 who received rivaroxaban, six who received apixaban, and one who received edoxaban. These 57 women had 72 vaginal bleeding events, including 59 cases of heavy menstrual bleeding and 13 bleeding events unrelated to the menstrual cycle. 51 (86%) of these heavy menstrual bleeding events (two major bleeding events, 17 clinically relevant non-major bleeding events, 32 minor bleeding events) were treated conservatively (eg, change of oral hormone therapy or reduction, temporary interruption, or discontinuation of direct oral factor Xa inhibitor) and the remaining eight (14%) events (three major bleeding events and five clinically relevant non-major bleeding events) required elective surgical or interventional treatment (hysterectomy, curettage, ovary excision, or excision of ovarian cysts). Of the 57 women, 13 (23%) had a second bleeding event and two (4%) had a third event. Nine patients had underlying anatomical abnormalities; compared with patients without abnormalities, these patients had more intense bleeding, more had recurrent bleeding (five [56%] of nine patients with abnormalities vs eight [17%] of 48 patients without abnormalities), and more needed surgical treatment for bleeding (eight [89%] of nine vs zero of 48).

INTERPRETATION: Vaginal bleeding, particularly heavy menstrual bleeding, is a common complication in women of reproductive age on direct oral factor Xa inhibitor therapy. Most cases can be treated conservatively, but patients with severe or recurrent vaginal bleeding complications should be assessed for underlying anatomical abnormalities, which might require surgical or interventional treatment. Further data are needed to provide guidance on prevention and treatment of vaginal bleeding complications in this patient population.

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journal homepage: http://www.elsevier.com/locate/pjnns

Case report

Fatal consequences of climbing a ladder under apixaban and drunken

Claudia Stöllberger *, Josef Finsterer

Krankenanstalt Rudolfstiftung, Wien, Austria