What's New in Anticoagulant Treatment

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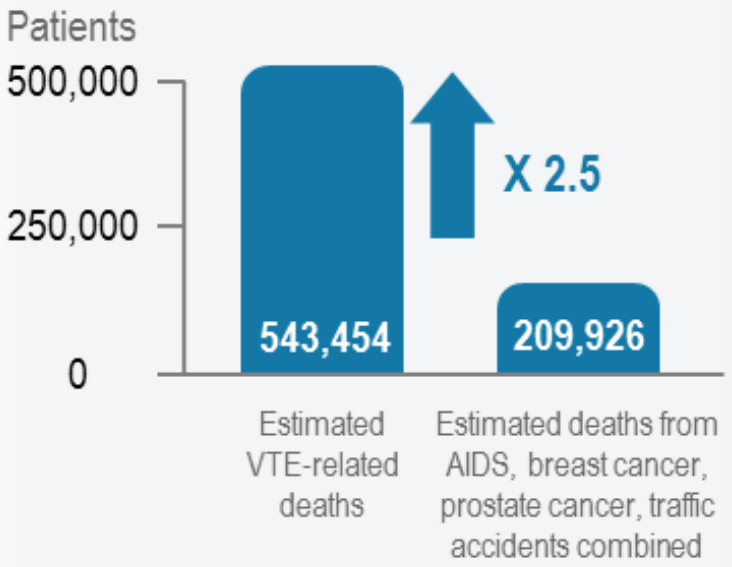
Rambam Health Care Campus, Haifa

VTE Acute Treatment

DVT and PE Represent a Major Health Problem



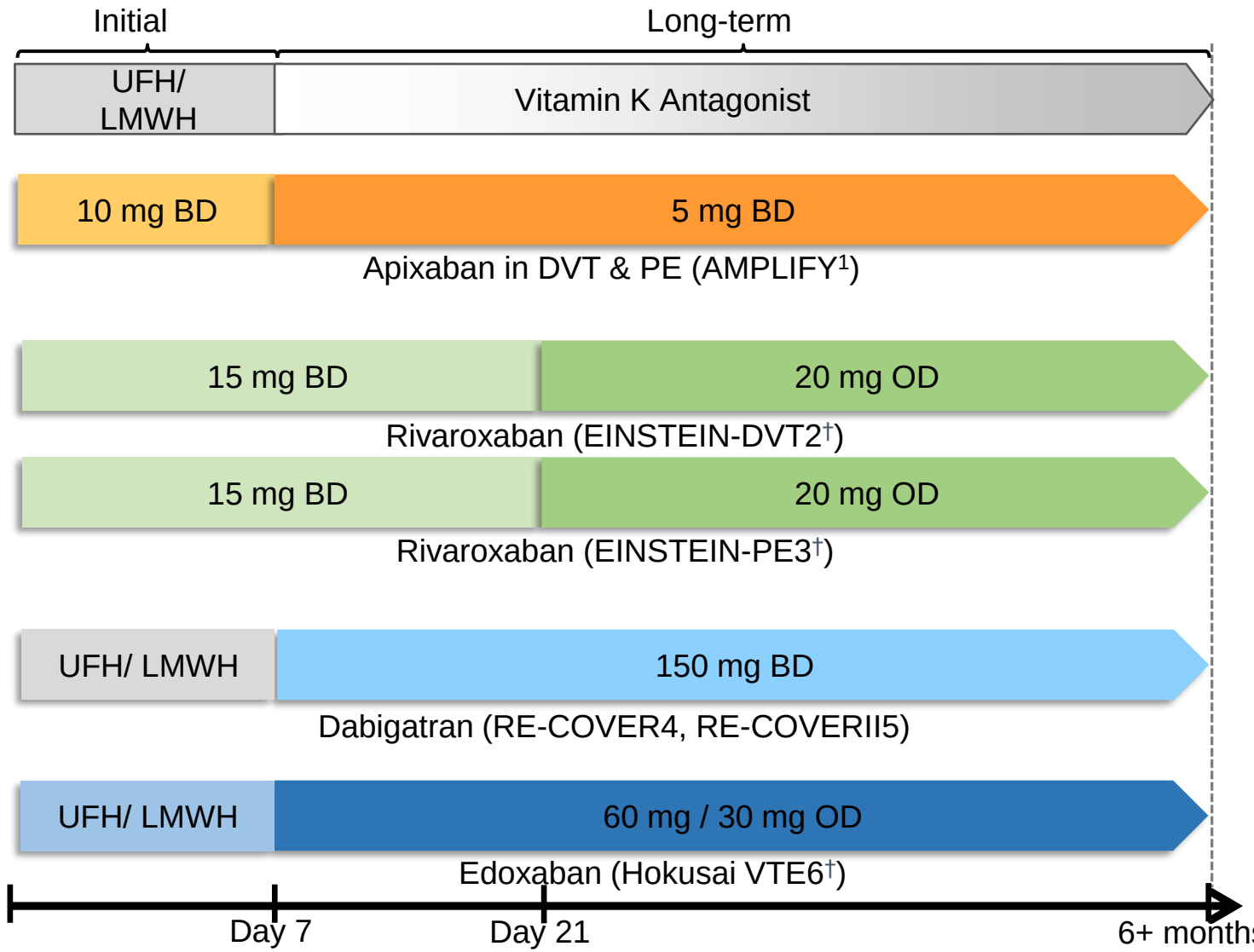
Annual VTE related death rates
in Europe are high[1]

Estimated
30% of DVT or PE patients
are at risk of a recurrence within 10 years[2]

Major bleeding occurs at a rate of
7.2 per 100 patient-years
in those receiving a coumarin derivative for VTE treatment[3]

1. Cohen AT. Thromb Haemost. 2007; 2. Heit JA . Arch Intern Med. 2000; 3. Linkins LA . Ann Intern Med 2003;

Acute VTE Treatment



VTE, venous thromboembolism; **UFH**, unfractionated heparin; **LMWH**, low molecular weight heparin; **BD**, twice daily; **OD**, once daily

† Duration of treatment was determined by the treating physician before randomisation: 3, 6, or 12 months in Einstein studies; 3 or 12 months in Hokusai VTE.

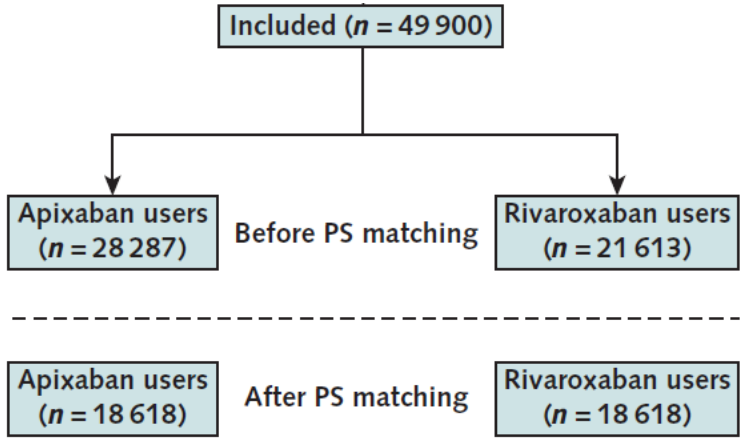
1. Agnelli. N Engl J Med 2013 2. Bauersachs. N Engl J Med 2010 3. Büller. N Engl J Med 2012 4. Schulman. N Engl J Med 2009 5. Schulman. Circulation 2014 6. The Hokusai-VTE Investigators. N Engl J Med 2013.

Annals of Internal Medicine ORIGINAL RESEARCH

Risk for Recurrent Venous Thromboembolism and Bleeding With Apixaban Compared With Rivaroxaban: An Analysis of Real-World Data

Ghadeer K. Dawwas, MSc, MBA, PhD; Charles E. Leonard, PharmD, MSCE; James D. Lewis, MD, MSCE; and Adam Cuker, MD, MS

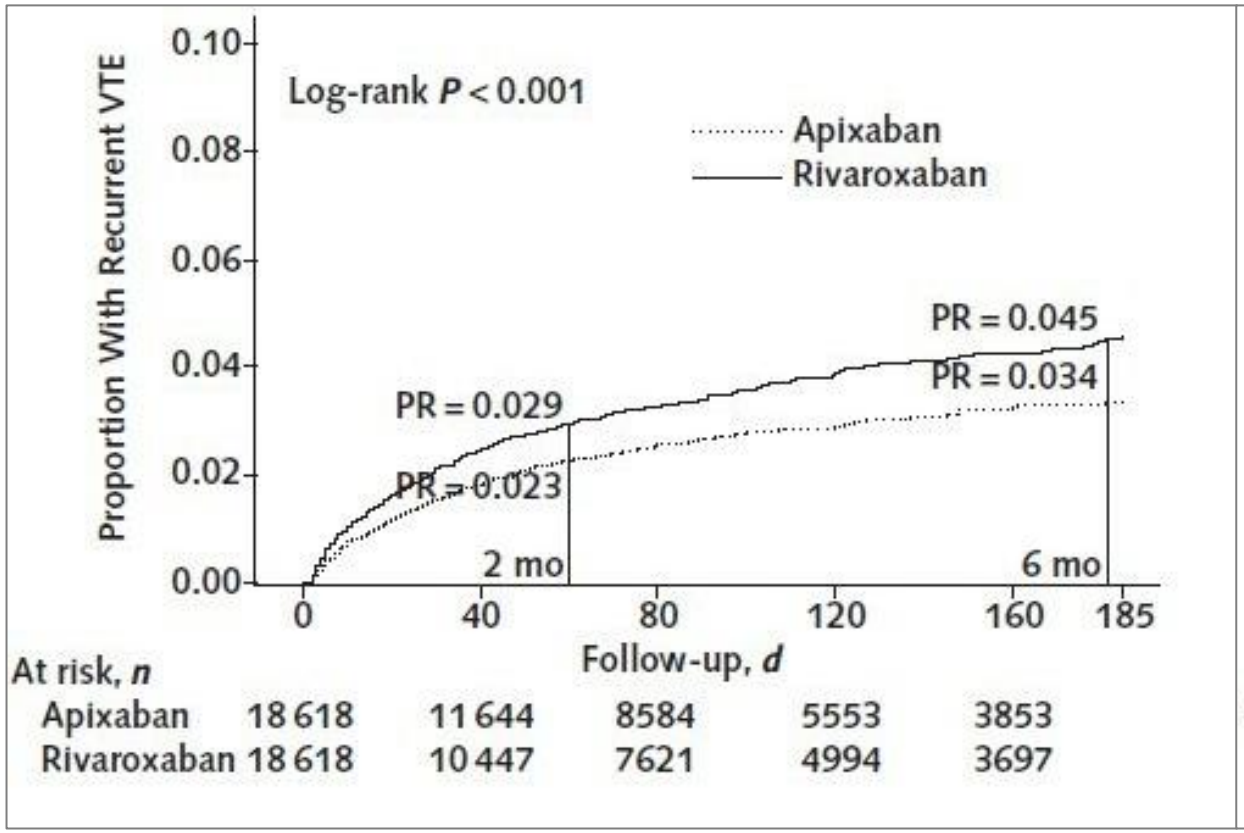
- Retrospective cohort study, Optum's Database, US, 2015-2020.
- VTE patients newly prescribed apixaban or rivaroxaban within 30 days of diagnosis:

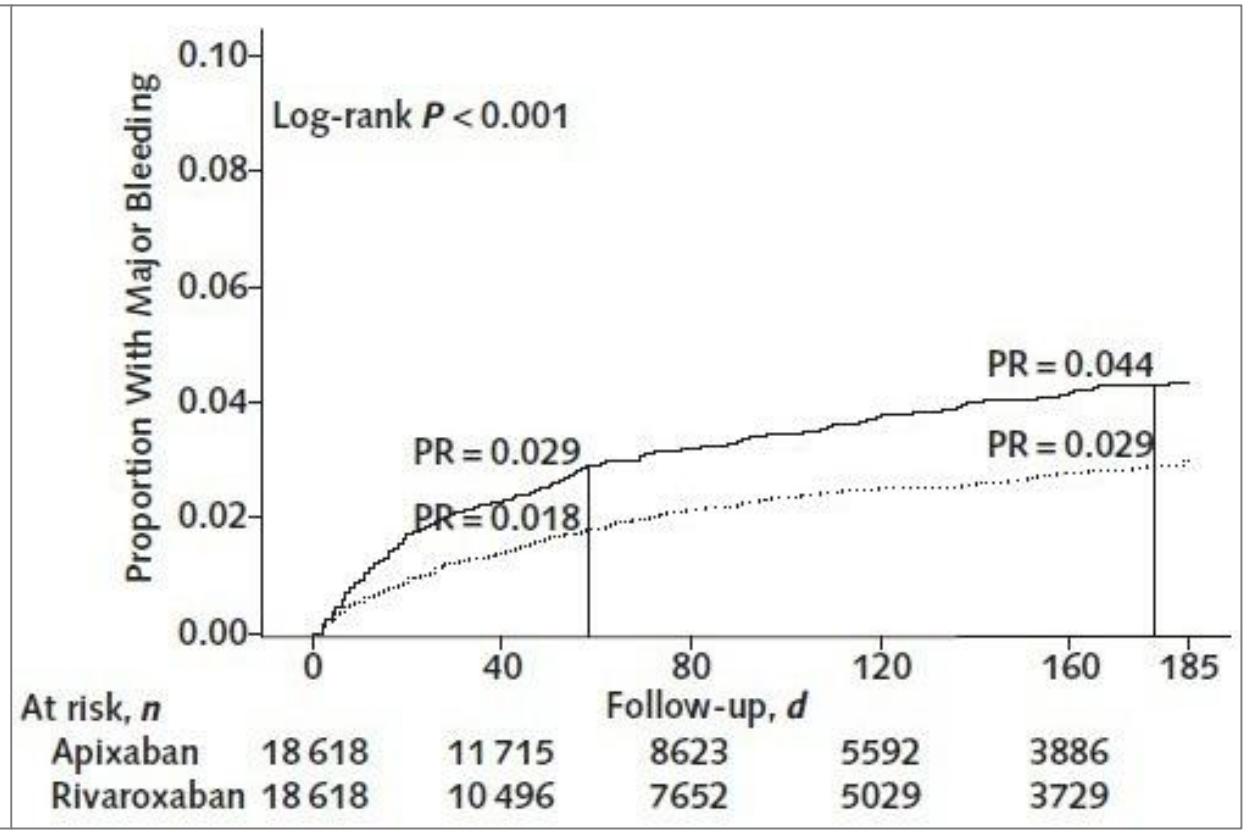


- 1:1 propensity score matching.
- Median follow-up: apixaban – 102 days, rivaroxaban – 105 days.

Dawwas GK. Ann Intern Med. 2022

Cumulative VTE and Bleeding Incidence Curves in Matched Cohorts of Patients With VTE Who Were New Users of Apixaban or Rivaroxaban





PR= probability; VTE= venous thromboembolism.

Dawwas GK. Ann Intern Med. 2022

Risk For Recurrent VTE and Bleeding Comparing Apixaban and Rivaroxaban in Patients With VTE*

Outcome	Apixaban				Rivaroxaban				Adjusted Marginal HR (95% CI)
	Patients, n	Events, *n*	PYs of Follow-up	Incidence Rate per 100 PYs	*Patients, n*	Events, *n*	PYs of Follow-up	Incidence Rate per 100 PYs	
Recurrent VTE	18 618	475	5314	8.9	18 618	595	5200	11.4	0.77 (0.69–0.87)
DVT	–	442	5322	8.3	–	501	5223	9.6	0.85 (0.74–0.97)
PE	–	33	5382	0.6	–	94	5276	1.8	0.59 (0.39–0.91)
Bleeding	18 618	386	5344	7.2	18 618	577	5239	11.0	0.60 (0.53–0.69)
GI	–	382	5344	7.0	–	566	5240	10.6	0.60 (0.53–0.69)
Intracranial	–	4	5389	0.2	–	11	5298	0.4	0.54 (0.14–1.20)

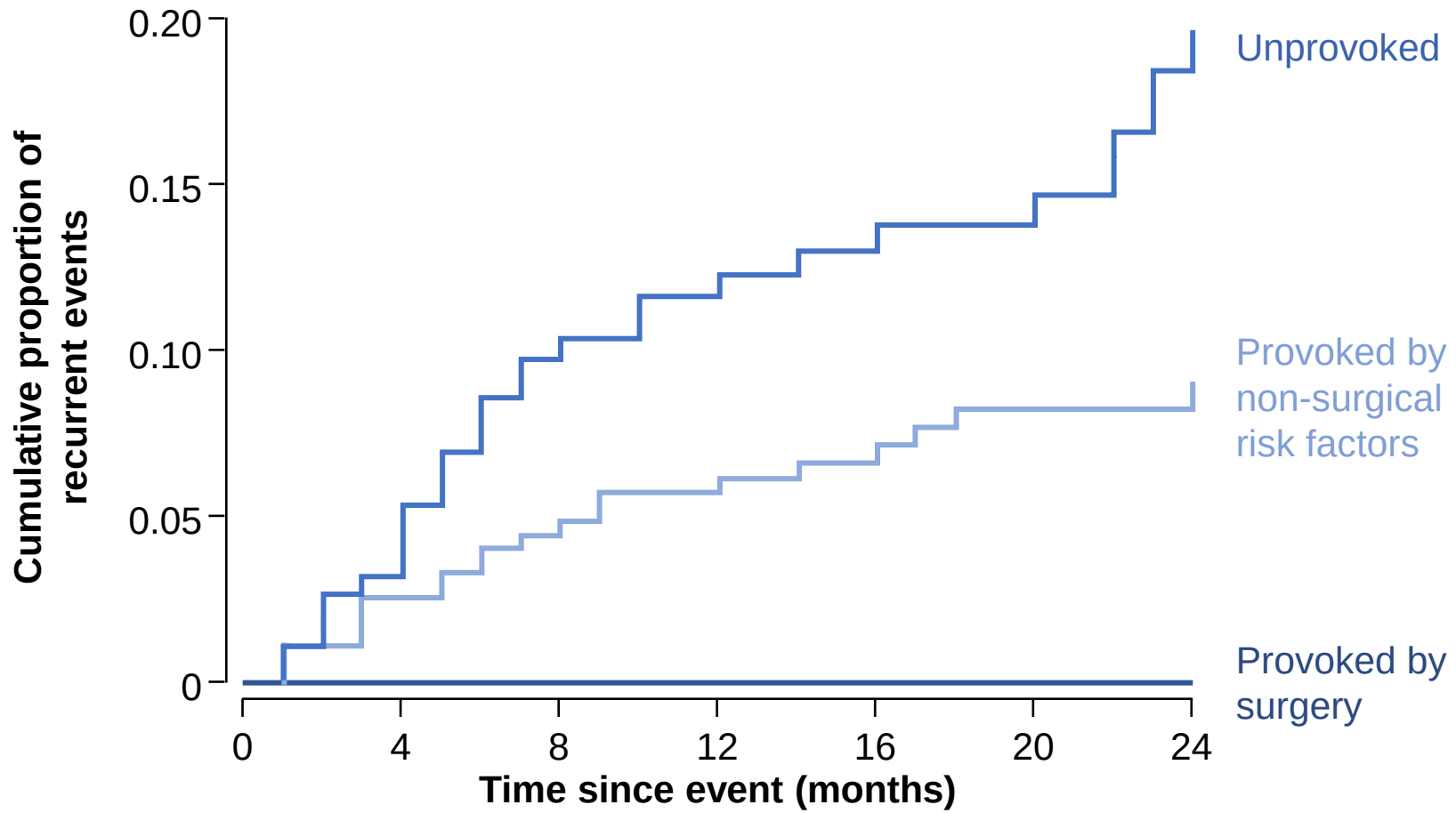
DVT = deep venous thrombosis; GI = gastrointestinal; HR = hazard ratio; PE = pulmonary embolism; PY = person-year; VTE = venous thromboembolism.
* Results from Cox proportional hazard models after propensity score 1:1 matching without replacement using a caliper of 0.1 of the SD of the logit of propensity score.

Dawwas GK. Ann Intern Med. 2022.

VTE Secondary Prevention

Patients with non-surgical provoked VTE are at risk of recurrence after stopping treatment

Cumulative proportions of recurrent VTE after cessation of anticoagulant therapy* (N=558)



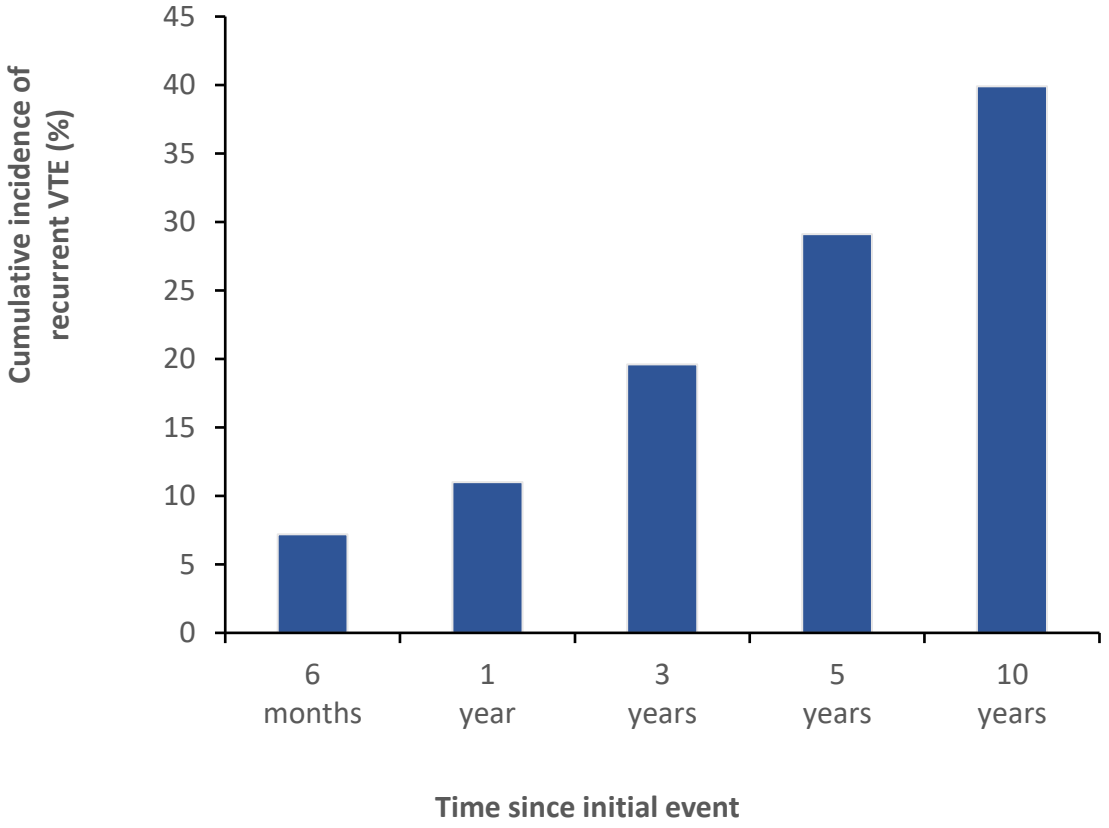
*Patients with malignant disease and antiphospholipid syndrome were excluded from the study.

Baglin T. *Lancet* 2003

High Risk of Recurrent VTE After Discontinuing Anticoagulation

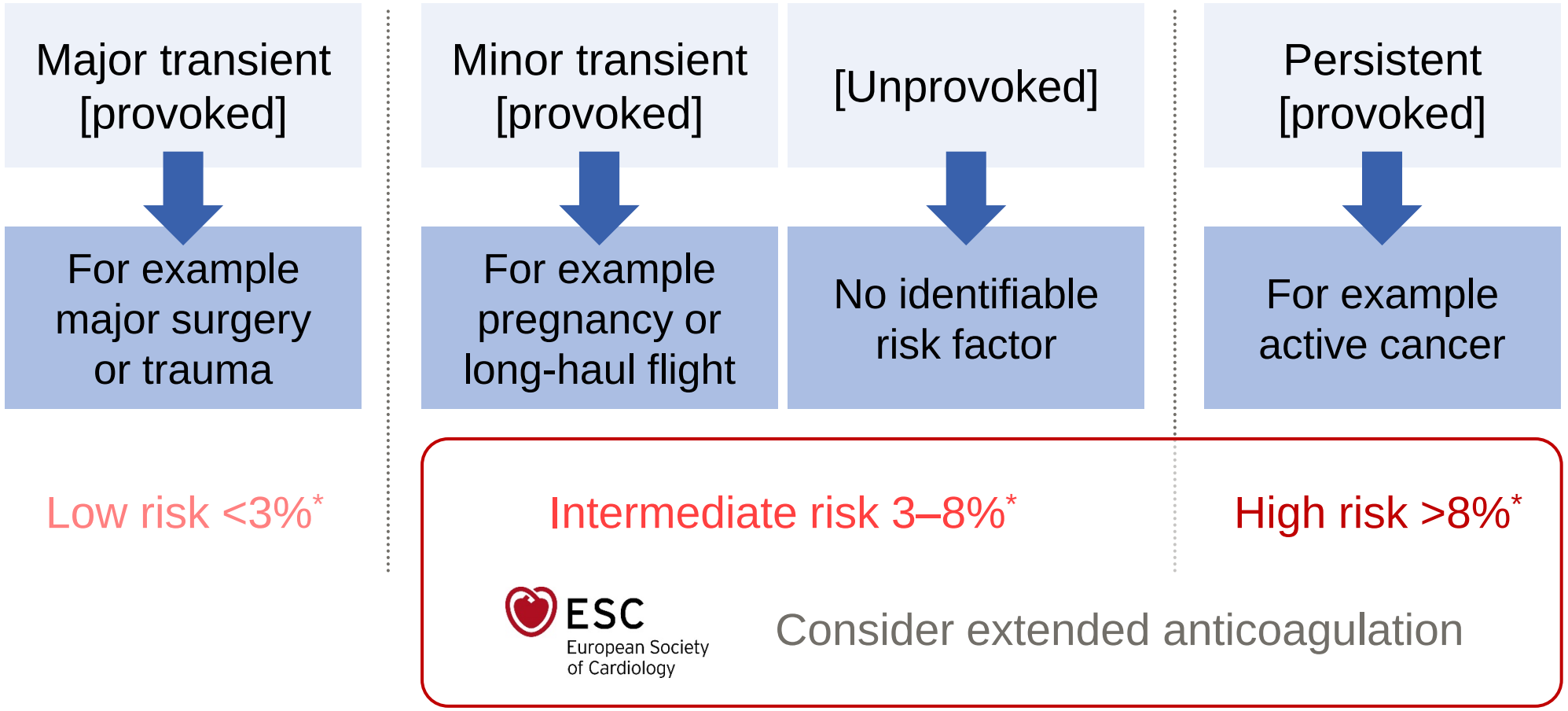
- Anticoagulation effectively resolves VTE, but stopping treatment increases the cumulative risk of VTE recurrence[1]
- The cumulative incidence of recurrent VTE is approximately 10% in the first year if anticoagulation is stopped[1]
- NOACs are well suited for extended treatment because:[2]
  - They do not require injections
  - No routine coagulation monitoring is required
  - They have very few known drug–drug and food–drug interactions

Cumulative incidence of VTE recurrence over time



1. Prandoni P. *Haematologica* 2007 2. Schulman S, *J Int Med* 2014

Simplified guidelines assist decision-making when considering extended treatment for patients



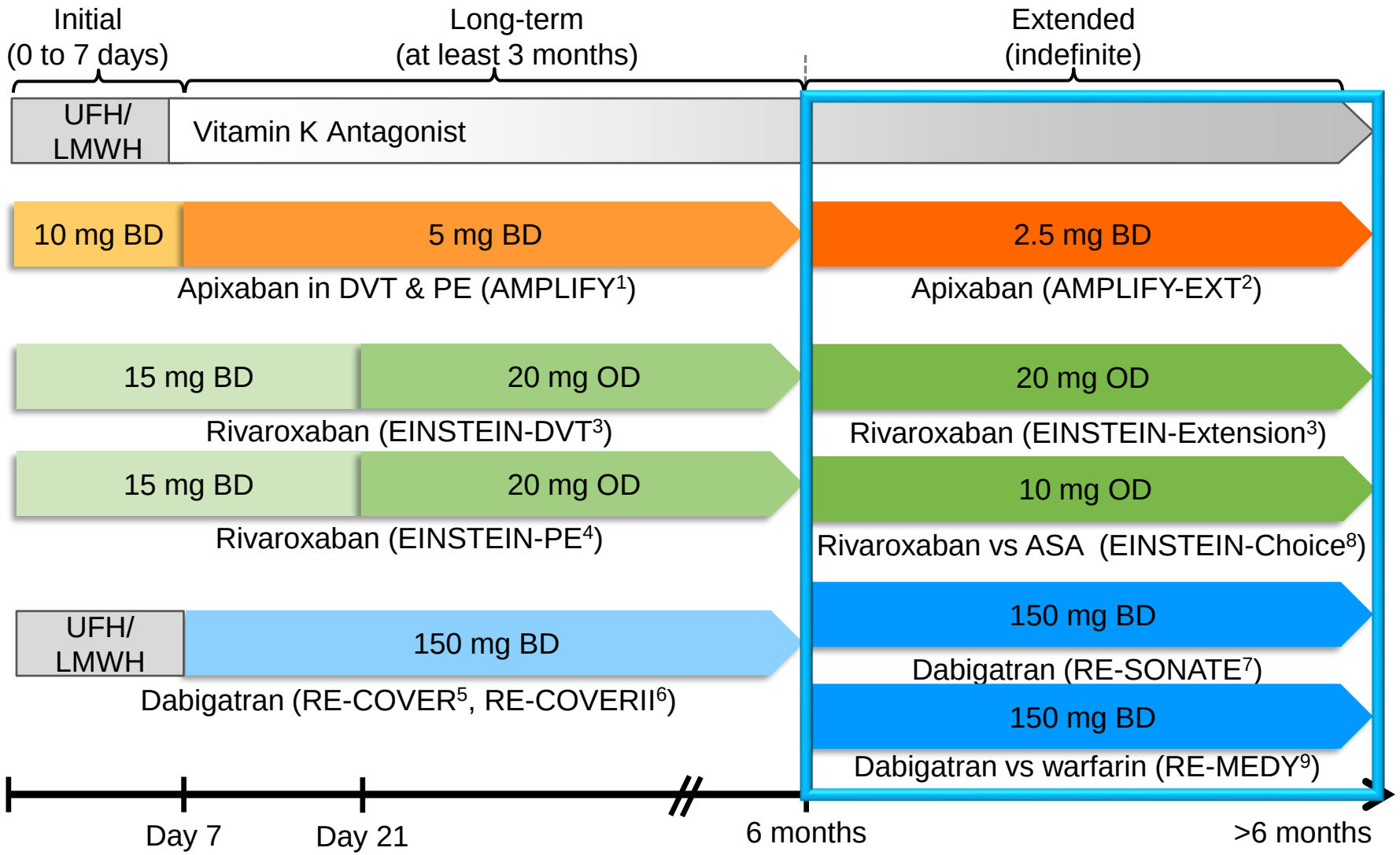
*Estimated annual risk for long-term recurrence.
Konstantinides SV. *Eur Heart J* 2019.

Recommendations for Extended Treatment: ESC PE 2019

Recommendations	Class	Level
Patients in whom extension of anticoagulation beyond 3 months is recommended		
Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with **recurrent VTE** (that is, with at least one previous episode of PE or DVT) **not related to a major transient or reversible risk factor**.	I	B
Oral anticoagulant treatment with a **VKA** for an indefinite period is recommended for patients with **antiphospholipid antibody syndrome**.	I	B
Extended oral anticoagulation of indefinite duration should be considered for patients with a **first episode of PE** and **no identifiable risk factor**.	IIa	A
Extended oral anticoagulation of indefinite duration should be considered for patients with a **first episode of PE** associated with a **persistent risk factor** other than antiphospholipid antibody syndrome.	IIa	C
Extended oral anticoagulation of indefinite duration should be considered for patients with a **first episode of PE** associated with a **minor transient or reversible risk factor**.	IIa	C

Konstantinidis. European Heart Journal 2020;

Extended VTE Treatment



UFH, unfractionated heparin; **LMWH**, low molecular weight heparin; **BD**, twice daily; **OD**, once daily

1. Agnelli . N Engl J Med 2013 2. Agnelli. N Engl J Med 2013 3. Bauersachs. N Engl J Med 2010 4. Büller. N Engl J Med 2012 5. Schulman. N Engl J Med 2009 6. Schulman. Circulation 2014 7. Schulman. N Engl J Med 2013 8. Weitz JI, N Engl J Med. 2017. 9. Schulman. Thromb Haemost. 2011

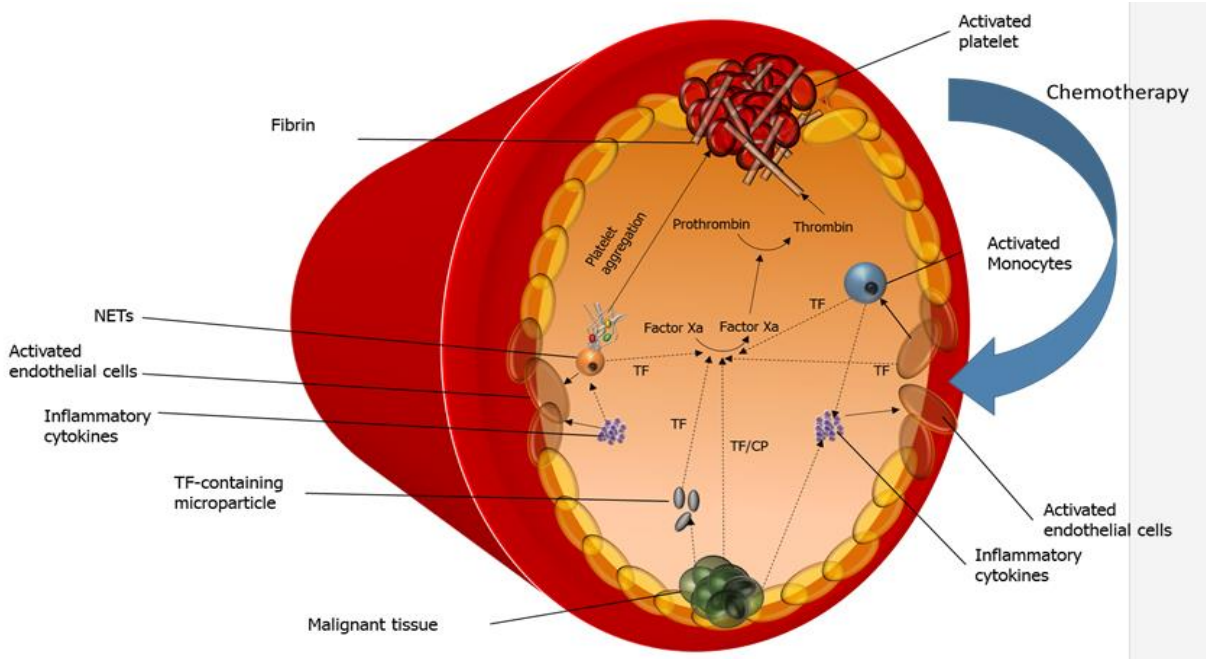
Extended VTE Treatment - Results

Drug	Trial	Dose	Recurrent VTE + VTE death	Major Bleeding	Major + CRNM Bleeding
			NOAC vs Comparator (%), *P*-value		
Apixa	**AMPLIFY-EXT** (**placebo** comparator)	2.5 mg BD	**Superiority** **81% RRR** 1.7 vs 8.8 *P*<0.001	**Not signif.** 0.2 vs 0.5 NR*	**Not signif.** 3.2 vs 2.7 NR*
		5 mg BD	**Superiority** **80% RRR** 1.7 vs 8.8 *P*<0.001	**Not signif.** 0.1 vs 0.5 NR*	**Not signif.** 4.3 vs 2.7 NR*
Riva	**EINSTEIN-Extension** (**placebo** comparator)	20 mg OD	**Superiority** **82% RRR** 1.3 vs 7.1 *P*<0.001	**Not signif.** 0.7 vs 0 *P*=0.11	**Significant increase** 6.0 vs 1.2 *P<0.001*
	EINSTEIN-Choice (**aspirin** comparator)	20 mg OD	**Superiority** **66% RRR** 1.5 vs 4.4 NR*	**Not signif.** 0.5 vs 0.3 *P*=0.32	**Not signif.** 3.3 vs 2.0 *P*=0.08
		10 mg OD	**Superiority** **74% RRR** 1.2 vs 4.4 NR*	**Not signif.** 0.4 vs 0.3 *P*=0.5	**Not signif.** 2.4 vs 2.0 *P*=0.60
Dabi	**RE-SONATE**[3] (**placebo** comparator)	150 mg BD	**Superiority** **92% RRR** 0.4 vs 5.6 *P*<0.001	**Not signif.** 0.3 vs 0 *P*=1.0	**Significant increase** 5.3 vs 1.8 *P=0.001*

The duration of follow-up differed between trials therefore event rates should not be compared or interpreted as an indicator of the risk of the population.
*Not significant based on 95% CI for relative risk. NR=not reported.

CRNM – clinically relevant non-major

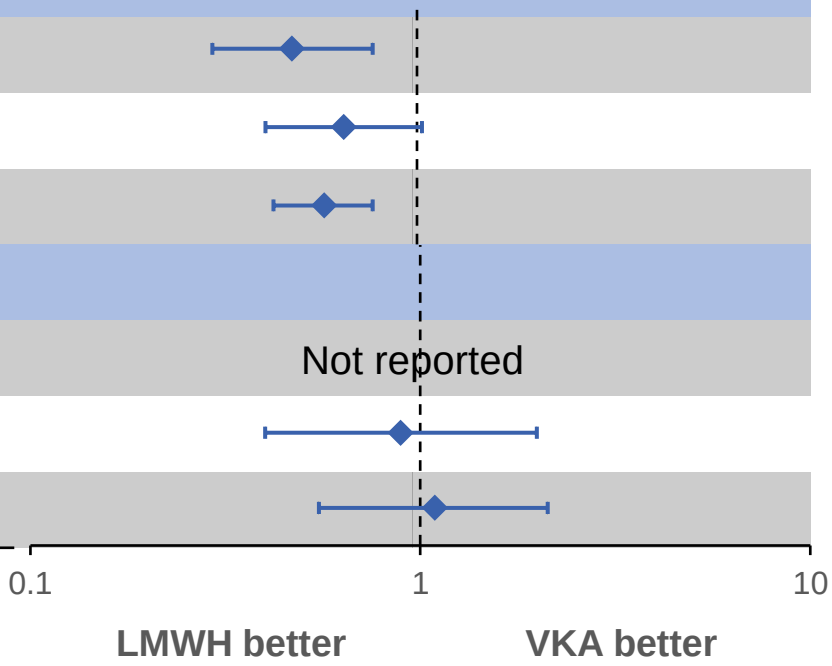
Venous Protection in patients with CAT



Ay C *et al*, *Thromb Haemost* 2017;117:219–230

LMWH Versus VKA in the Treatment of CAT

	LMWH monotherapy		LMWH overlapping with VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Recurrent VTE					
CLOT study*[1]	27/336	8.0	53/336	15.8	
CATCH study#[2]	31/449	6.9	45/451	10.0	
Meta-analysis‡[3a]	66/908	7.3	111/873	12.7	
Major bleeding					
CLOT study*[1]	19/338	5.6	12/335	3.6	Not reported
CATCH study#[2]	12/449	2.9	11/451	2.4	
Meta-analysis§[3a]	42/872	4.8	36/840	4.3	



*Dalteparin versus VKA; in the VKA arm the estimated time in therapeutic range was 46% (30% below and 24% above); #tinzaparin versus warfarin; in the warfarin arm the time in therapeutic range was 47% (26% below and 27% above); ‡meta-analysis included four other small studies in addition to the CLOT study; §meta-analysis included three other small studies in addition to the CLOT study, [a]Up to 6 months

1. Lee AYY, *New Engl J Med* 2003; 2. Lee AYY, *Blood* L2014:; 3. Kahale LA, Cochrane Database of Syst Reviews 2018,

VTE Treatment in Cancer Patients: NCCN 2021

DOACs (preferred for patients without gastric or gastroesophageal lesions)

- **Apixaban (category 1)** – monotherapy
- **Edoxaban (category 1)** – combination therapy with LMWH / UFH
- **Rivaroxaban (category 2A)** – monotherapy

LMWH (preferred for patients with gastric or gastroesophageal lesions)

- **Dalteparin (category 1)** – monotherapy
- **Enoxaparin (category 2A)** – monotherapy

DOACs (if above regimens not appropriate or unavailable)

- **Dabigatran (category 2A)** – combination therapy with LMWH / UFH

Fondaparinux (category 2A) – monotherapy

UFH (category 2B) – monotherapy

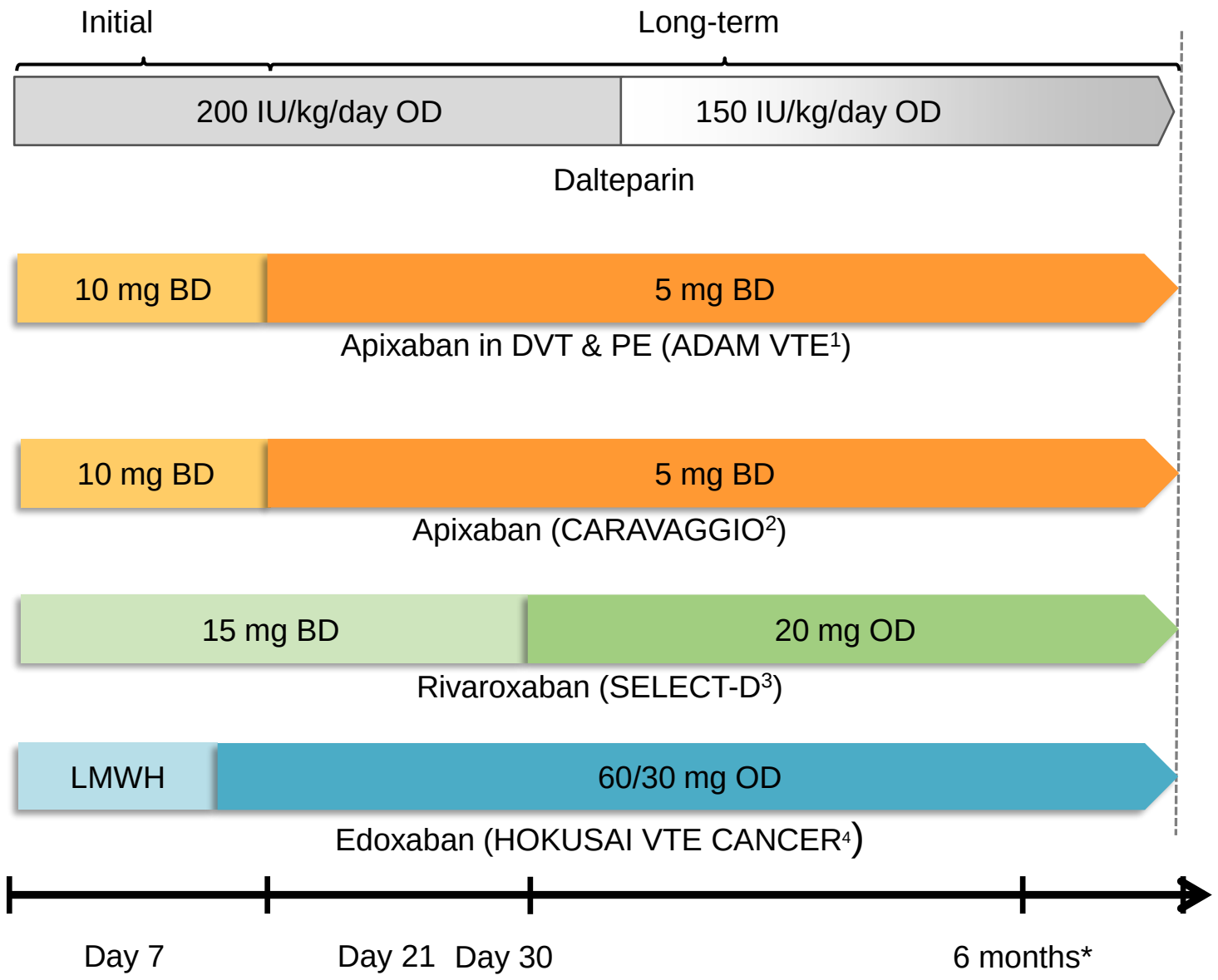
Warfarin (category 2A) – combination therapy with LMWH / Fondaparinux / UFH

NCCN, National Comprehensive Cancer Network; **VTE**, venous thromboembolism; **LMWH**, low molecular weight heparin; **UFH**, unfractionated heparin; **DOAC**, direct oral anticoagulant.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

www.NCCN.org.

VTE Treatment in Cancer Patients – Trials Design



***** Treatment with edoxaban or dalteparin was to be continued for ≥6 months and up to 12 months.
UFH, unfractionated heparin; **LMWH**, low molecular weight heparin; **BD**, twice daily; **OD**, once daily

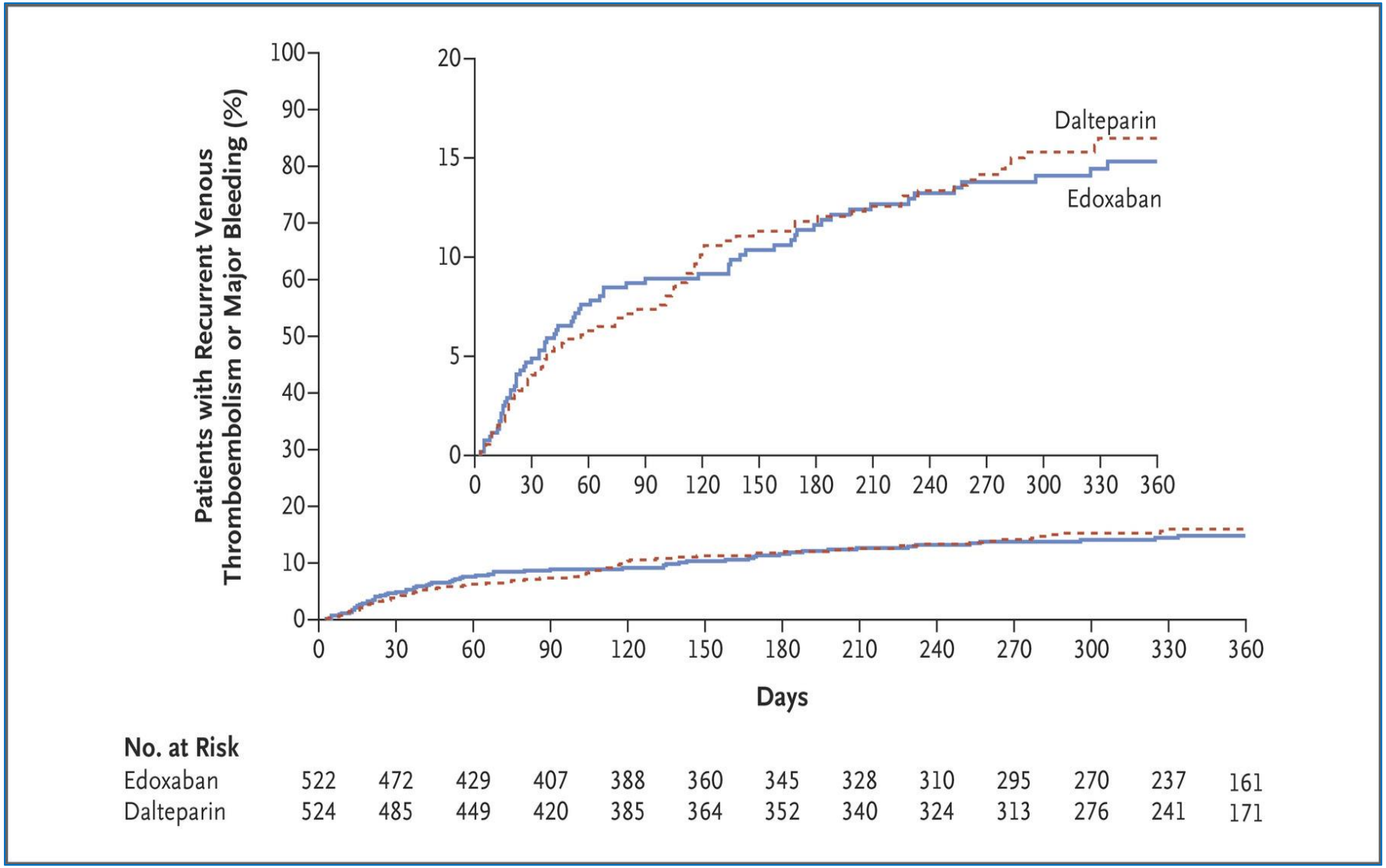
1. McBane RD, et al. J Thromb Haemost. 2020;
2. Agnelli G, et al. NEJM 2020;
3. Young AM, et al. J Clin Oncol. 2018;
4. Raskob GE, et al. NEJM 2018;

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

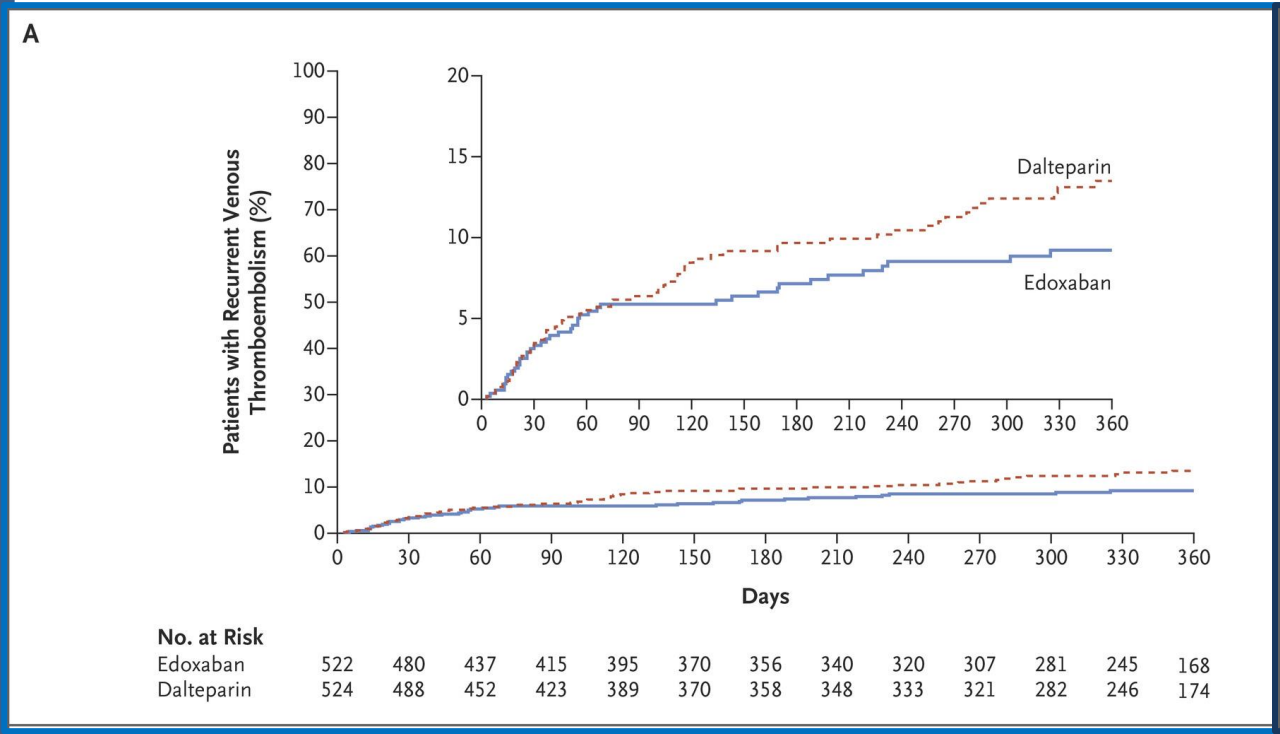
Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., et al., for the Hokusai VTE Cancer Investigators*

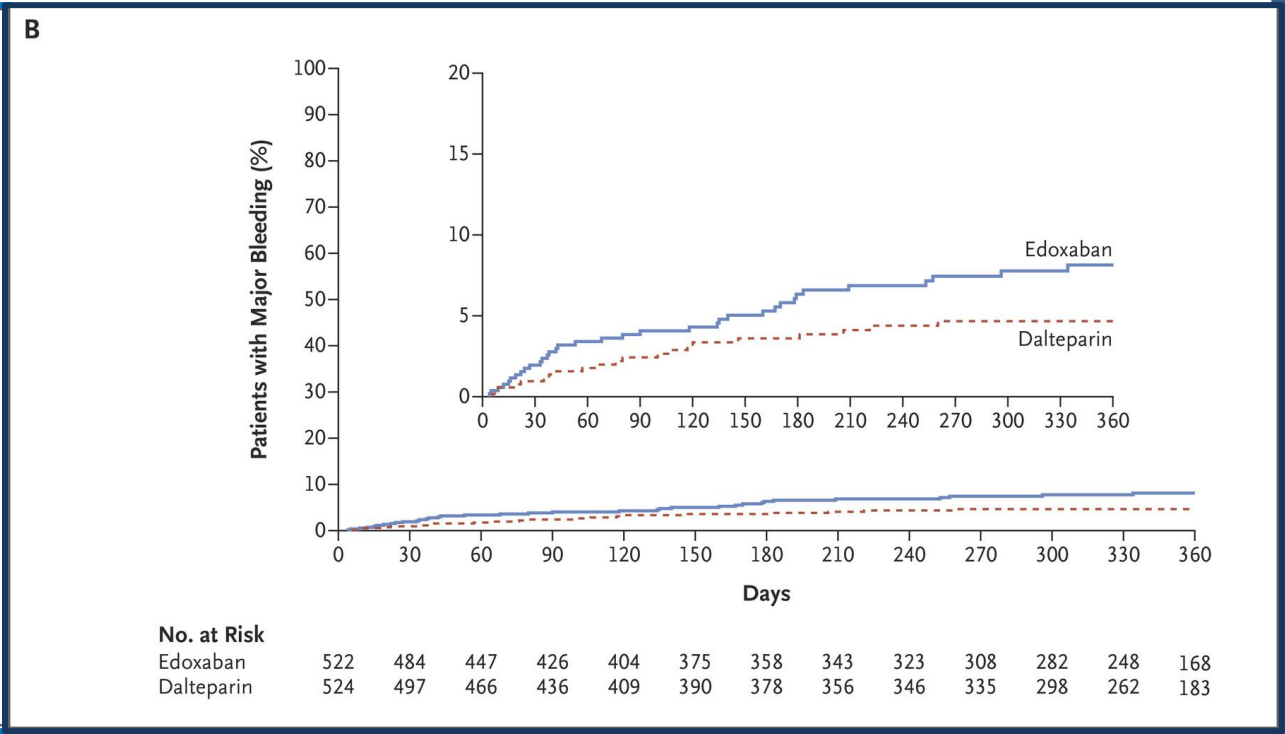
Raskob N Engl J Med 2018

Edoxaban was noninferior to dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding.



The rate of recurrent venous thromboembolism and the rate of major bleeding



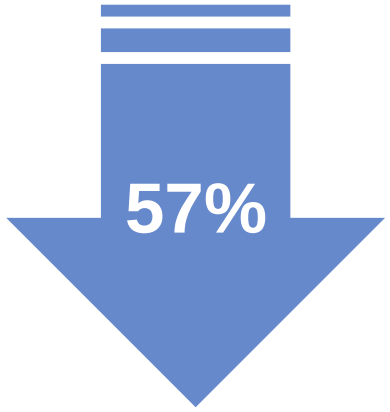


Raskob N Engl J Med 2018

SELECT-D

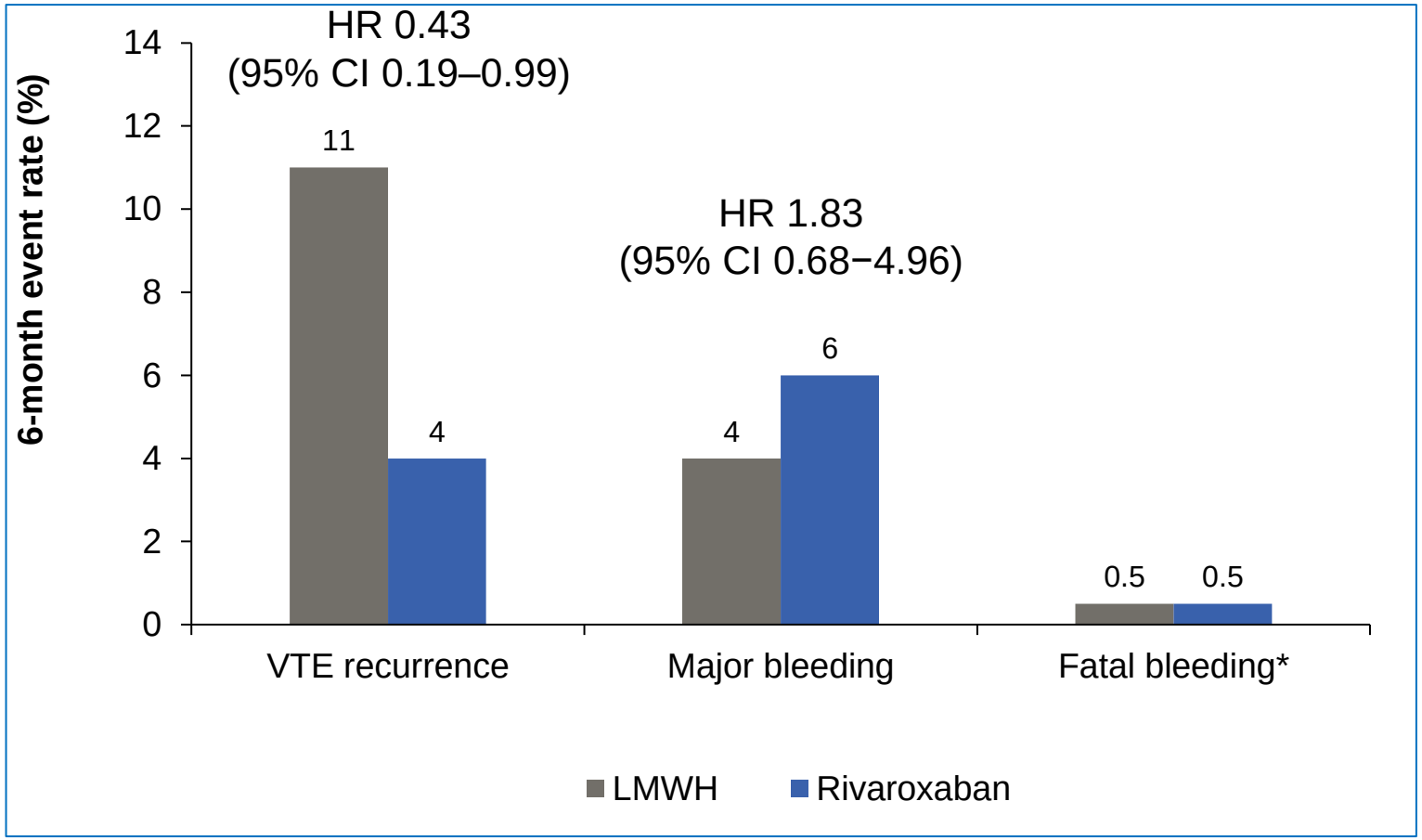
Young A et al, *J Clin Oncol. 2018;36:2017–2023*

Rivaroxaban provide protection against VTE recurrence without an excessive risk of bleeding



Decrease in VTE recurrence

SELECT-D, patients with CAT (N=406)



*One fatal bleeding event in each arm.

Young A et al. *J Clin Oncol* 2018;.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

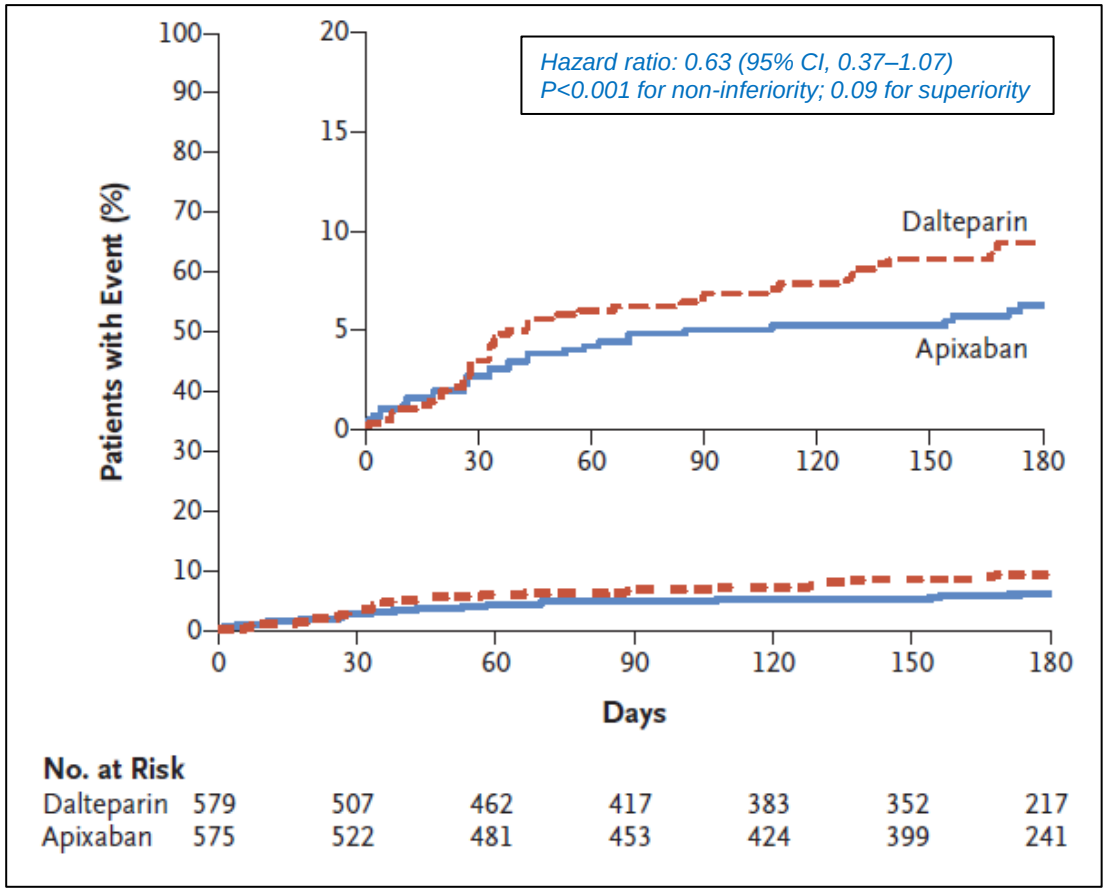
Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Guy Meyer, M.D., Andres Muñoz, M.D., Menno V. Huisman, M.D., Jean M. Connors, M.D., Alexander Cohen, M.D., Rupert Bauersachs, M.D., Benjamin Brenner, M.D., Adam Torbicki, M.D., Maria R. Sueiro, M.D., Catherine Lambert, M.D., Gualberto Gussoni, M.D., Mauro Campanini, M.D., Andrea Fontanella, M.D., Giorgio Vescovo, M.D., and Melina Verso, M.D., for the Caravaggio Investigators*

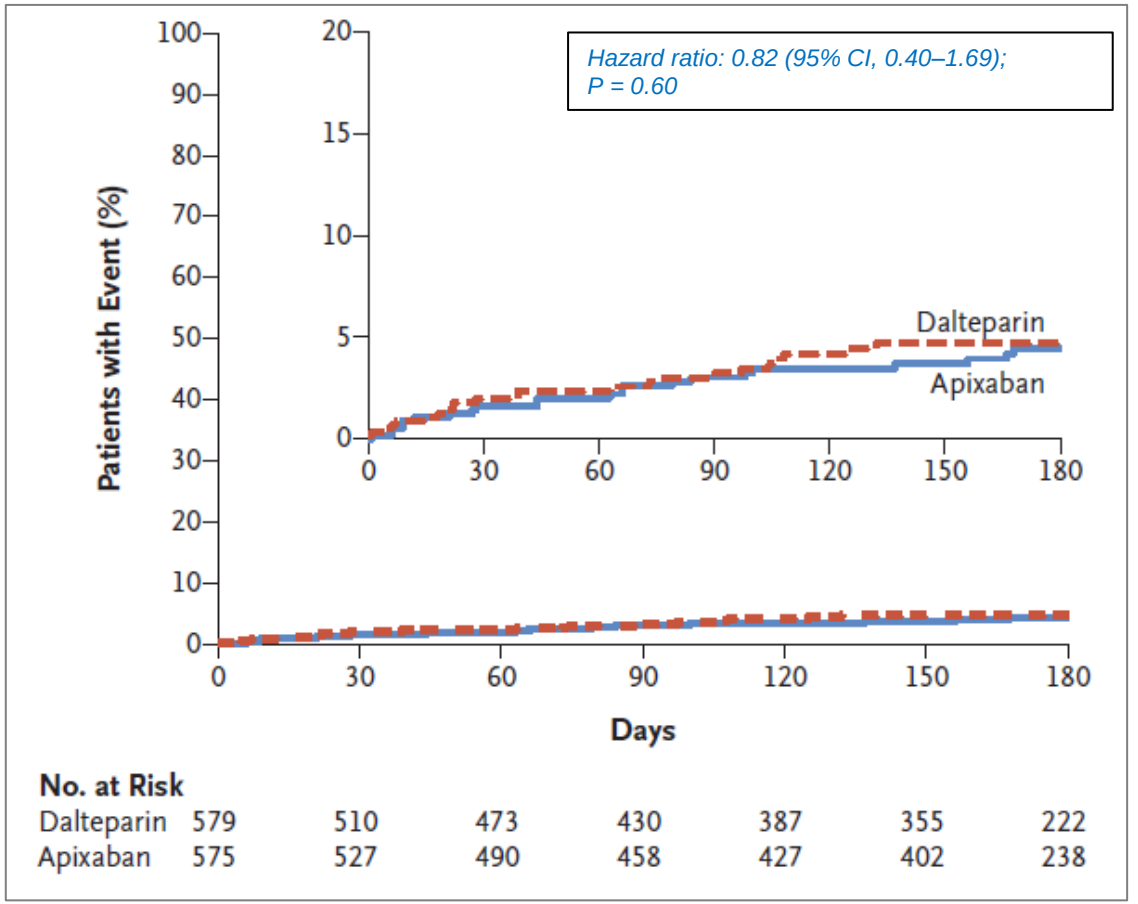
Agnelli G, N Engl J Med. 2020.

Caravaggio Trial

Recurrent VTE



Major Bleeding



Agnelli G. N Engl J Med. 2020.

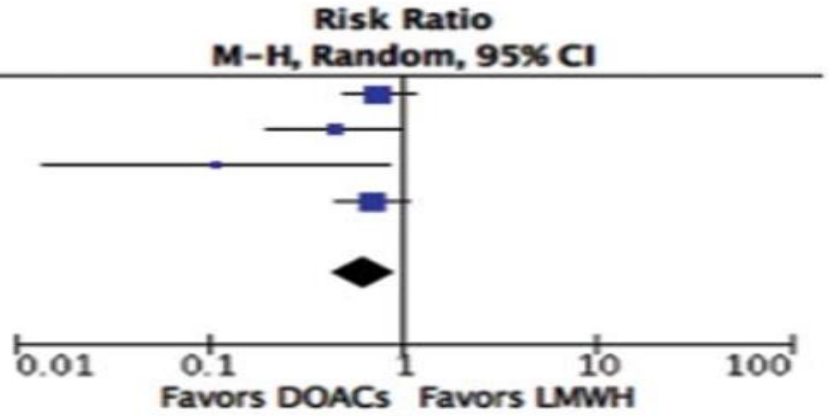
Direct Oral Anticoagulants for the Treatment of Acute Venous Thromboembolism Associated with Cancer: A Systematic Review and Meta-Analysis

Recurrent VTE

Study or Subgroup	DOACs Events	DOACs Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob, 2018	34	522	46	524	40.3%	0.74 [0.48, 1.14]
Young, 2018	8	203	18	203	17.1%	0.44 [0.20, 1.00]
McBane, 2019	1	145	9	142	3.2%	0.11 [0.01, 0.85]
Agnelli, 2020	32	576	46	579	39.4%	0.70 [0.45, 1.08]
Total (95% CI)		**1446**		**1448**	**100.0%**	**0.62 [0.43, 0.91]**
Total events	75		119			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.30$, df = 3 (P = 0.23); $I^2 = 30\%$

Test for overall effect: Z = 2.46 (P = 0.01)

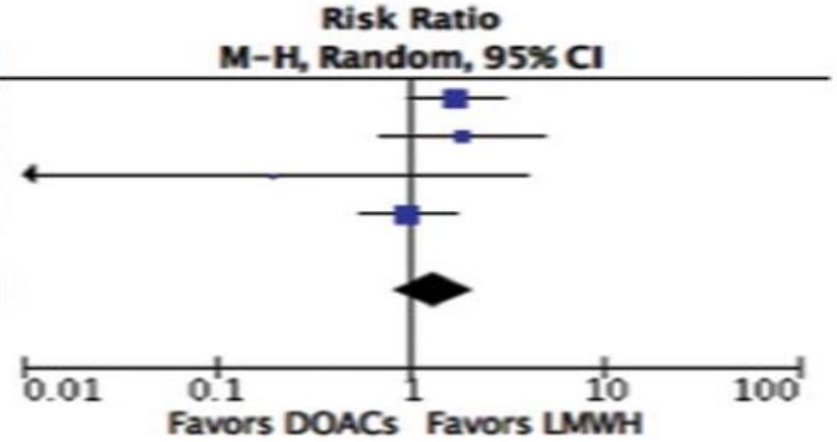


Major bleeding

Study or Subgroup	DOACs Events	DOACs Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob, 2018	29	522	17	524	39.1%	1.71 [0.95, 3.08]
Young, 2018	11	203	6	203	18.4%	1.83 [0.69, 4.86]
McBane, 2019	0	145	2	142	2.3%	0.20 [0.01, 4.04]
Agnelli, 2020	22	576	23	579	40.2%	0.96 [0.54, 1.71]
Total (95% CI)		**1446**		**1448**	**100.0%**	**1.31 [0.83, 2.08]**
Total events	62		48			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 3.89$, df = 3 (P = 0.27); $I^2 = 23\%$

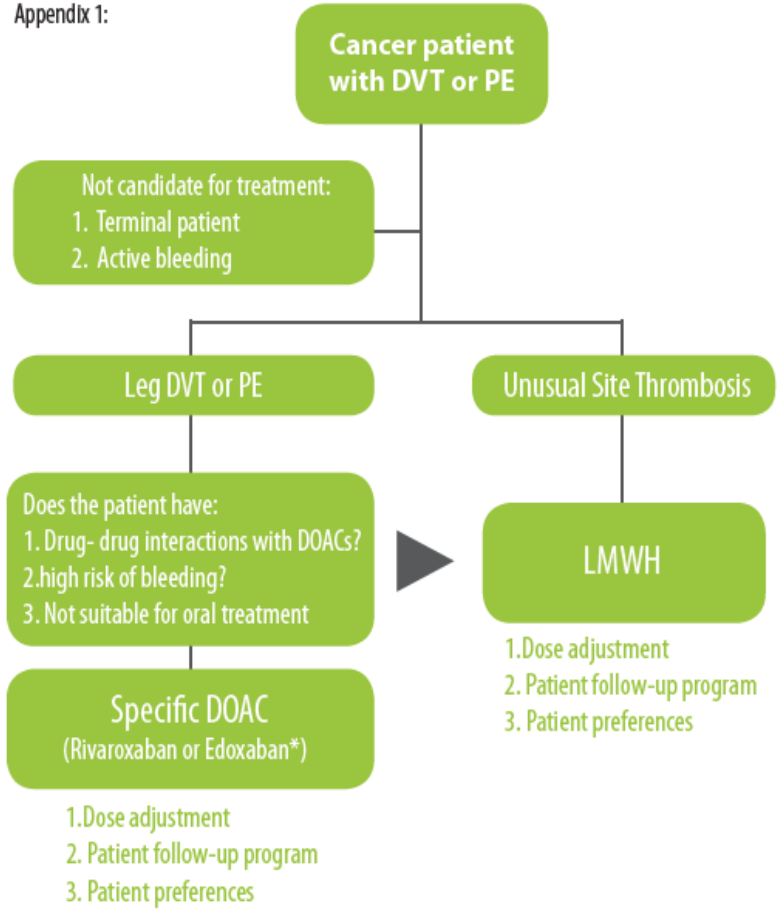
Test for overall effect: Z = 1.14 (P = 0.25)



Giustozzi M, Thrombos Hemostas 2020

Cancer Associated Thrombosis (CAT) פרוטוקול טיפול בחולי

Appendix 1:



האיגוד הישראלי לרפואה פנימית
ISRAEL SOCIETY OF INTERNAL MEDICINE

1. DOACs הם אופציה לגיטימית לטיפול ב-CAT, גם בחולים תסמיניים וגם בחולים עם פקקת שנמצאה אקראית.
2. ההתייחסות היא אל תכשירים ספציפיים, (rivaroxaban או edoxaban*) נכון לפרסום מסמך זה פורסמו מאמרים על rivaroxaban שזמין בישראל, ועל edoxaban* שלא זמין בישראל. מחקר על apixaban הוצג בכנס ASH 2018 וטרם פורסם בעיתונות הרפואית (מאמר 3).
3. ככלל, DOACs יכולים להוות אופציה ראשונה בטיפול, למעט מספר מצבים בהם הם מהווים אופציה חלופית לטיפול.
4. קיים קושי לתרגם את המידע מהמחקרים לכל המקרים בהם אנו נתקלים בחיי היום יום, יש לשקול כל מקרה לגופו. כעיקרון נדרש טיפול מותאם אישית לחולה, הרופא המטפל במחלקה או במיון יכול לבחור לטפל DOAC או ב- LMWH לבחירתו ולהעדפת המחלקה. יש להפנות את החולה ליעוץ מסודר במסגרת מרפאת קרישה על האופציה הטיפולית העדיפה לטיפול ממושך.
5. חולים בהם הטיפול הראשון המועדף הוא LMWH:
   A. חולים במשקל ק"ג ומטה או משקל מעל 120 ק"ג.
   B. חולים עם בעיות במערכת העיכול:
      - חולים עם ממאירות במערכת העיכול.
      - חולים עם כיבים, קוליטיס, IBD, סטומות וכו'.
      - חולים עם בעיה קיימת או צפויה בנטילה פומית (כגון טיפול לסרטן בעל פוטנציאל בינוני-גבוה להקאות, קושי בבליעה, בעיות ספיגה).
   C. חולים עם פקקת באתרים שאינם רגליים או ריאות, כגון – sinus vein thrombosis, טרומבוזיס בורידי הבטן, חולים עם פקקת סביב קטטר מרכזי.
   D. חולים עם גידולי מוח ראשוני או שניוני.
   E. חולים עם אירועים תרומבואמבוליים חוזרים.
   F. טיפול בחולים בהם הסיכון לדמם מוגדר מלכתחילה כמוגבר.

   להלן דוגמאות לקבוצות סיכון:

   a) חולים הנוטלים תרופות נוספות שמעלות סיכון לדימום, כגון נוגדי טסיות (שאינן אספירין בלבד), bevacizumab (אווסטין).
   b) חולים הנוטלים תרופות עם אינטראקציה ידועה ל DOACs-(ראו appendix 2).
   c) חולים המיועדים לקבל טיפולים כימיים עם שכיחות גבוהה של מוקוזיטיס או קוליטיס.
   d) חולים תרומבוציטופניים (מתחת ל- 50,000/µL<).
   e) חולים עם מחלות דמם תורשתיות.

   G. חולים שלא נכללו במחקרי DOACs.
6. משך הטיפול בנוגד קרישה - לפי הקווים המנחים הקיימים, כלומר כל עוד קיימת מחלה פעילה, מטופלת או גרורתית.
7. מומלץ שחולים אלה יופנו באופן מסודר ליעוץ של רופאי קרישה לגבי סוג ומשך הטיפול.

Cancer Associated Thrombosis (CAT) פרוטוקול טיפול בחולי

Table 1: Cancer-therapy–specific inhibitors and inducers of CYP3A4 and P-glycoprotein[5]

Cancer-related therapies	Cytochrome p450 CYP3A4	P-glycoprotein
Anthracyclines		
Doxorubicin	↓	↑
Idarubicin	↓	
Antimycotic agents		
Vinblastine	↓	↑
Vincristine	↓	
Vinorelbine		
Paclitaxel		
Topoisomerase inhibitors		
Topotecan		
Etoposide		
Alkylating agents		
Cyclophosphamide		
Ifosfamide		
Lomustine		
Tyrosine kinase inhibitors		
Afatinib		
Alectinib		↓
Ceritinib	↓	
Crizotinib	↓	↓
Dasatinib	↓	
Ibrutinib		↓
Idelalisib	↓	↓
Imatinib	↓	↓
Lapatinib	↓	↓
Nilotinib	↓	↓
Osimertinib	↓	
Vemurafenib	↑	↓
Lenvatinib	↑	↑
Sunitinib		↓
Vandetanib		↓

Cancer-related therapies	Cytochrome p450 CYP3A4	P-glycoprotein
Immune-modulating agents		
Cyclosporine	↓	↓
Sirolimus	↓	
Temsirolimus	↓	
Tacrolimus	↓	↓
Methylprednisolone	↑	
Dexamethasone	↑	↑
		↓
		↓
		↓
Fentanyl	↓	
Methadone	↓	
Acetaminophen	↓	
Other		
Bortezomib	↓	
Bexarotene	↑	
Venetoclax		↓

פרמקולוג קליני

Cancer-treatment specific inducers (↑) and inhibitors (↓) of cytochrome p450 CYP3A4 and P-glycoprotein are shown. **DOACs are substrates to CYP3A4 and P-glycoprotein enzymes. Inducers of these enzymes may potentially increase metabolization of DOACs thereby leading to lower plasma concentrations, and inhibitors may decrease metabolization leading to higher plasma concentrations.** Edoxaban and rivaroxaban, are reported to have major interactions with the P-glycoprotein pathway. Rivaroxaban is reported to have major interactions with the CYP3A4 pathway whereas edoxaban has been reported to have minor interactions. **The extent to which plasma concentrations of DOACs are influenced by inducers or inhibitors of CYP3A4 and P-glycoprotein is unknown.**

References: 1. Annie M. Young, Andrea Marshall, Jenny Thirlwall, et al. Rivaroxaban: Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin In Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol 36:2017-2023. 2. Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med 2018; 378:615-624. 3. Robert D. McBane, Waldemar E. Wysokinski, Jennifer Le-Rademacher et al. Apixaban, Dalteparin, in Active Cancer Associated Venous Thromboembolism, Abstract421 . ASH 2018. Blood 2018 132:421. 4. A. A. Khorana, S. Noble, A. Y. Y. Lee, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018; 16: 1891–4. 5. No˙emie Kraaijpoel and Marc Carrier. How I treat cancer-associated venous thromboembolism. Blood. 2019;133(4):291-298

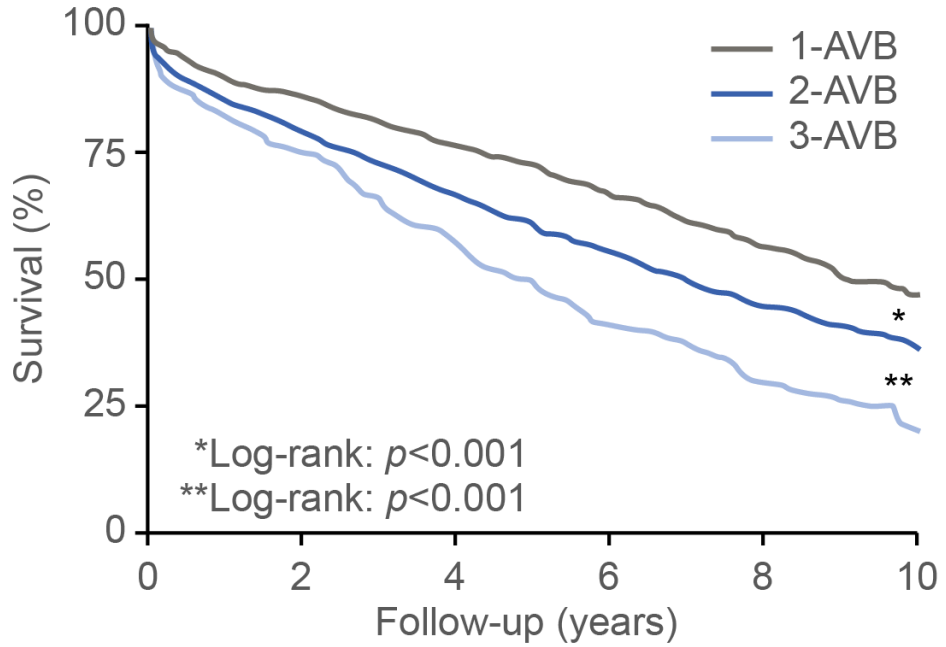
* Edoxaban is not approved by Israeli MoH.

CAD and PAD treatment

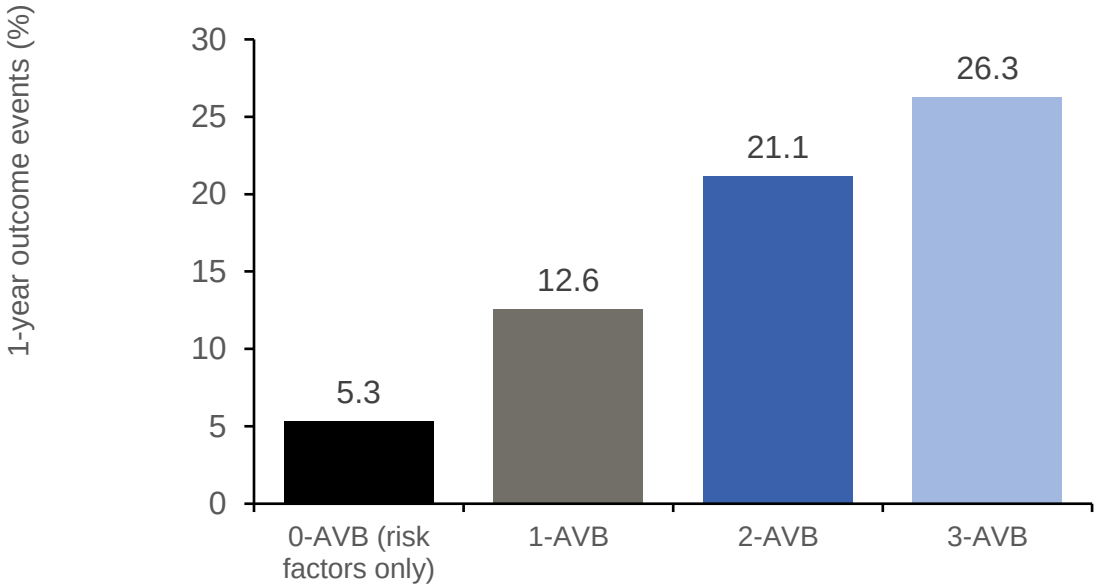
Patients with Polyvascular Disease Have Even Higher Risk of Morbidity and Mortality

- Patients with PAD or CAD often have polyvascular disease[1,2,4]
- Polyvascular disease is associated with an increased risk of morbidity and mortality[2–4]

Long-term all cause mortality in patients with PAD stratified according to number of affected vascular beds (AVB)[2]



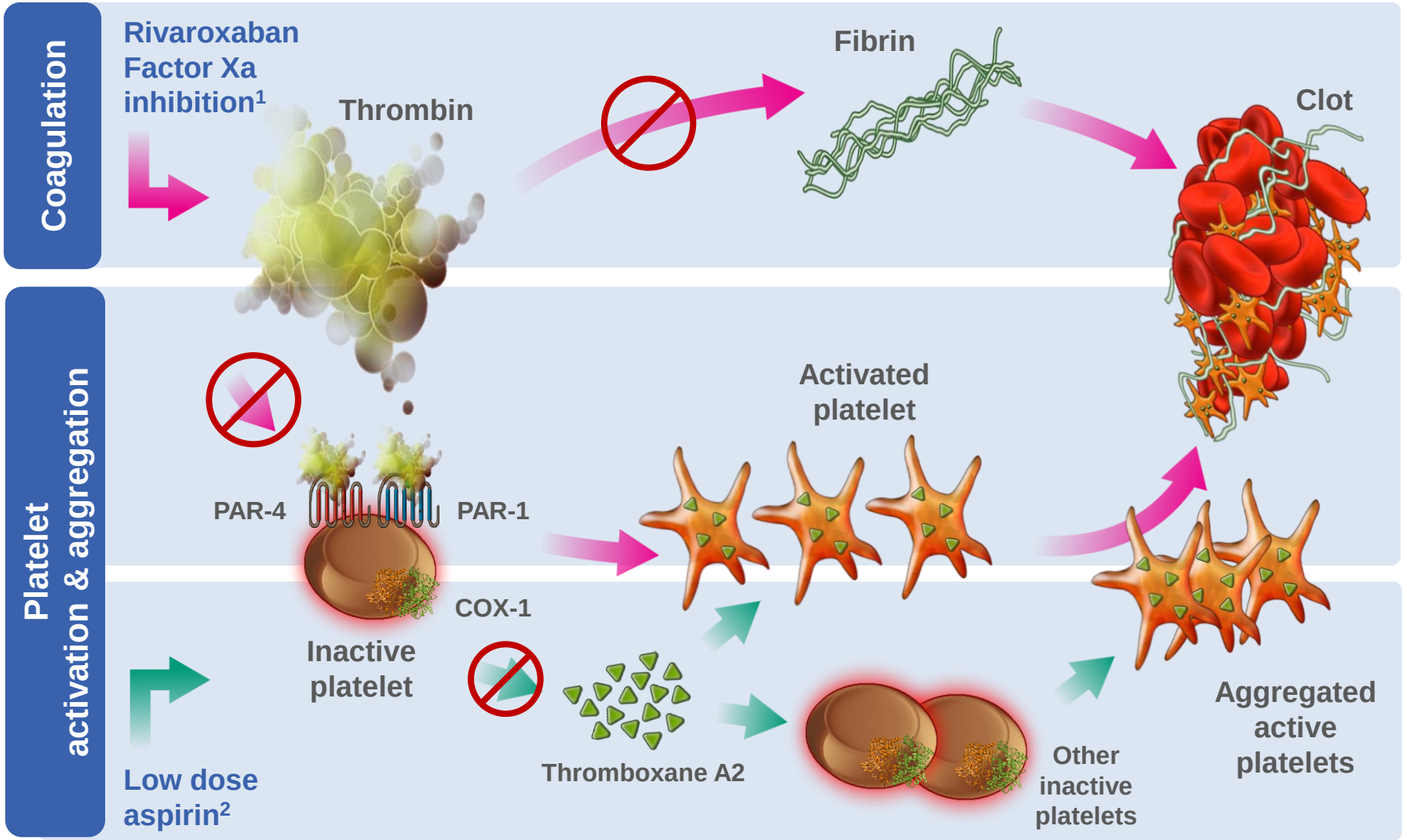
CV death, MI, stroke or hospitalization for atherothrombotic events according to number of affected vascular beds (AVB)[4]



1. Bhatt DL , *JAMA* 2006; 2. van Kuijk P. *Eur Heart J* 2010; 3. Alberts MJ, *Eur Heart J* 2009;3; 4. Steg P *et al*, *JAMA* 2007;

Rivaroxaban and Aspirin Synergistically Target Essential Components of Atherothrombosis

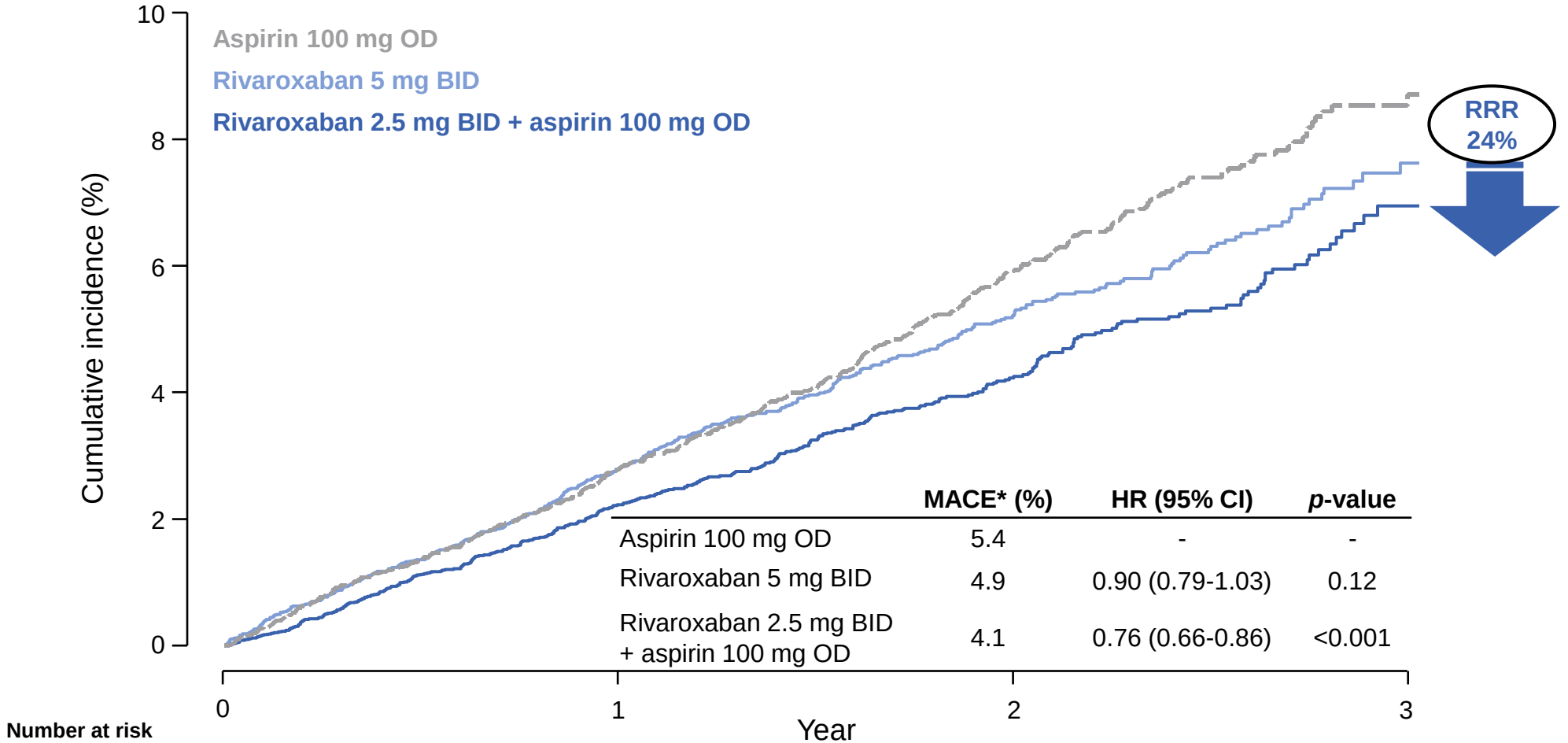
Rationale for Rivaroxaban



Rivaroxaban impacts not only fibrin formation, but also platelet activation

1. Angiolillo DJ. *Eur Heart J* 2010 2.Mitchell JRA. *BMJ*

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg BID + Aspirin Reduced Stroke, CV Death and MI in COMPASS trial



	MACE* (%)	HR (95% CI)	*p*-value
Aspirin 100 mg OD	5.4	-	-
Rivaroxaban 5 mg BID	4.9	0.90 (0.79-1.03)	0.12
Rivaroxaban 2.5 mg BID + aspirin 100 mg OD	4.1	0.76 (0.66-0.86)	<0.001

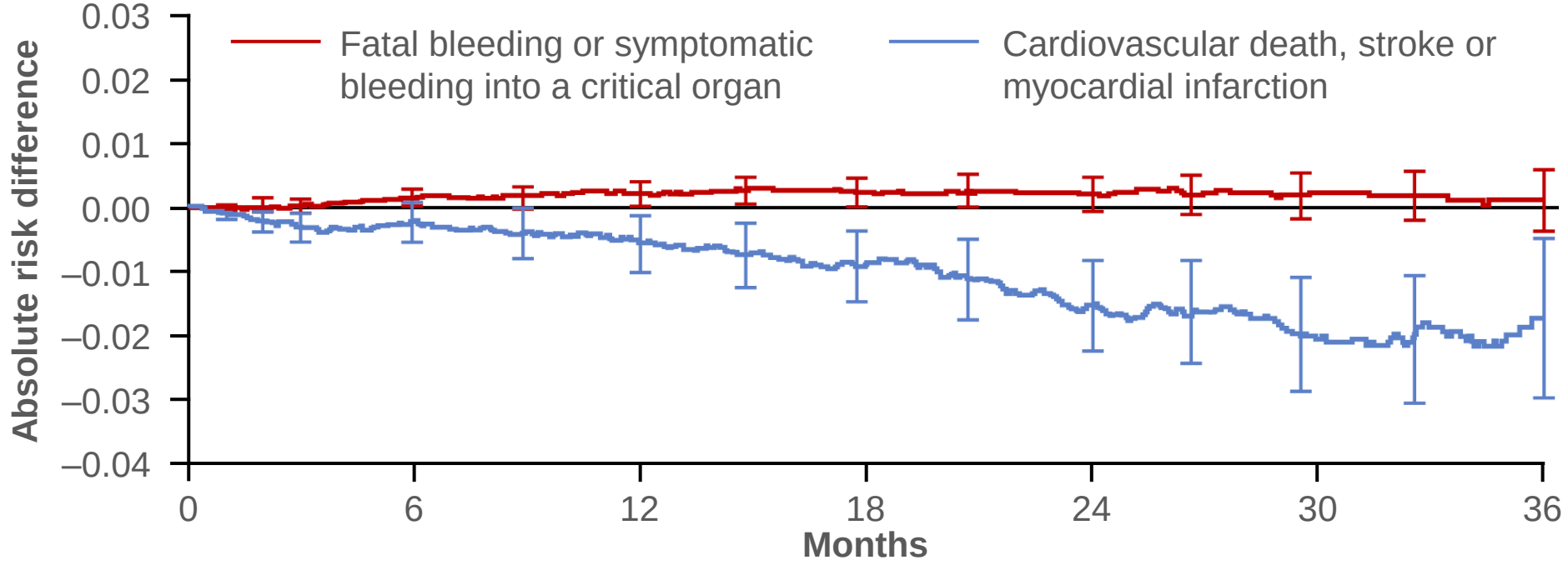
Number at risk				
Aspirin 100 mg OD	9,126	7,808	3,860	669
Riva 5 mg BID	9,117	7,824	3,862	670
Riva 2.5 mg BID + aspirin 100 mg OD	9,152	7,904	3,912	658

*Rates as at mean follow up of 23 months

Eikelboom JW . *N Engl J Med* 2017

The Balance Between The Increase in Bleeding Events and Reduction in MACE Suggests a Net Clinical Benefit Over Time

Absolute risk differences over time for severe bleeding and MACE



- The increase in major bleeding and GI bleeding with rivaroxaban 2.5 mg bid plus aspirin was confined to the first year after randomization, with no significant excess bleeding thereafter
- In contrast, the benefits of rivaroxaban 2.5 mg bid plus aspirin in preventing CV death, stroke or MI, and mortality were consistent over time

Eikelboom JW, *J Am Coll Cardiol* 2019;

2020 ESC NSTE-ACS guidelines likewise emphasise the need for long-term vascular protection of patients with chronic CAD

Recommendations	Class	Evidence level
ESC Adding a **second antithrombotic agent** to aspirin for extended long-term secondary prevention should be considered in patients with a **high risk of ischemic events** and without increased risk of major or life-threatening bleeding	IIa	A
ESC Adding a **second antithrombotic agent** to aspirin for extended long-term secondary prevention may be considered in patients with **moderately increased risk of ischamic events** and without increased risk of major or life-threatening bleeding	IIb	A

High ischaemic risk defined as:

- Complex CAD* with ≥1 of the following:

Risk enhancers

- Diabetes mellitus requiring medication
- Recurrent MI
- PAD
- CKD with eGFR 15–59 mL/min/1.73 m^2
- Any multivessel CAD
- Premature or accelerated CAD†
- Systemic inflammatory disease‡

Technical aspects

- ≥3 stents implanted
- ≥3 lesions treated
- Total stent length >60 mm
- History of complex revascularisation
- History of stent thrombosis on antiplatelet treatment

Moderate ischaemic risk defined as:

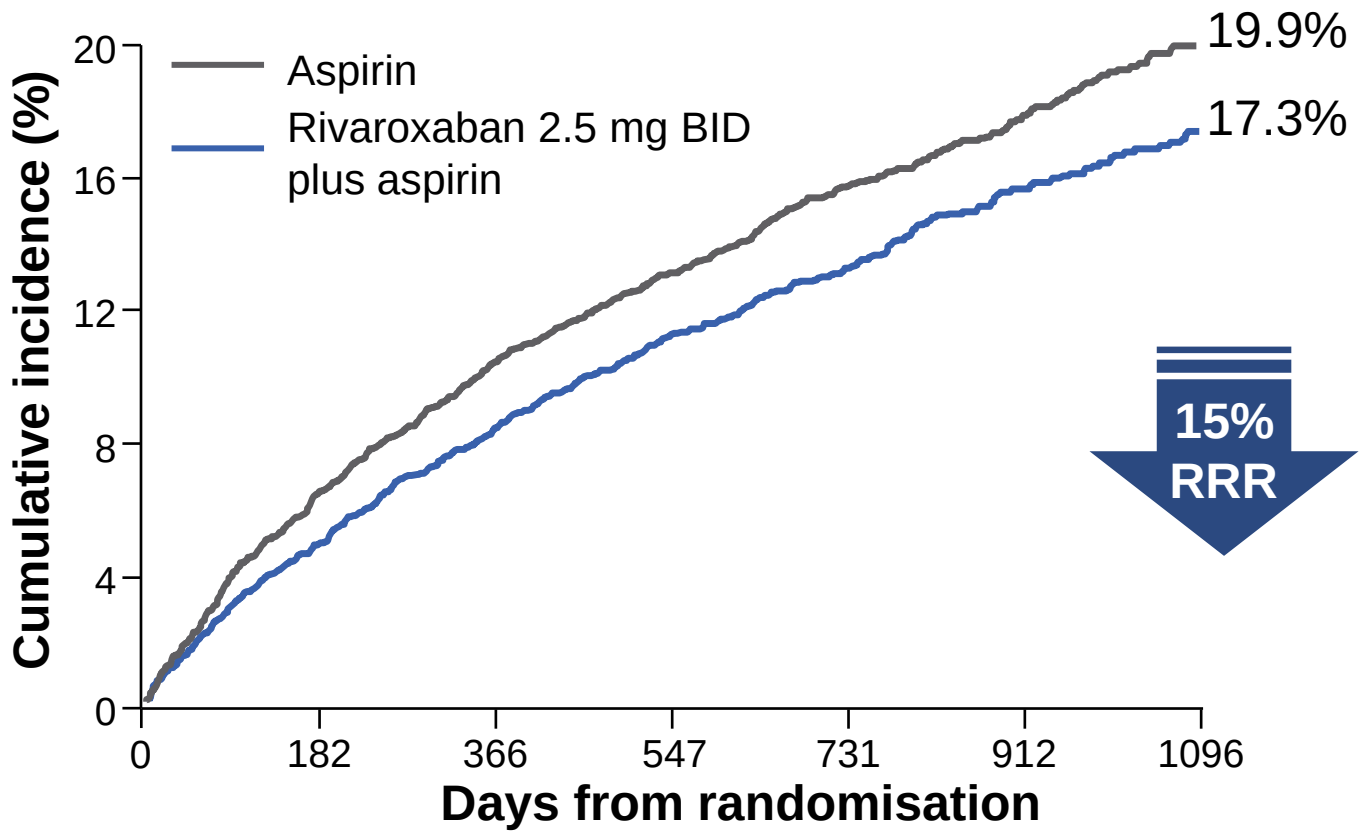
- Non-complex CAD* with ≥1 of the following:
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - CKD with eGFR 15–59 mL/min/1.73 m^2

*Stratification of patients towards complex vs non-complex CAD is based on individual clinical judgement with knowledge of patients' CV history and/or coronary anatomy; †CAD at <45 years or new lesion within a 2-year timeframe; ‡E.g. HIV, systemic lupus erythematosus, chronic arthritis.

Collet JP et al. *Eur Heart J* 2020; .

Enhance vascular protection after revascularization based on VOYAGER PAD

Cumulative incidence of ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death in VOYAGER PAD



HR 0.85
(95% CI 0.76–0.96)
p=0.009
NNT over 3 years: 39

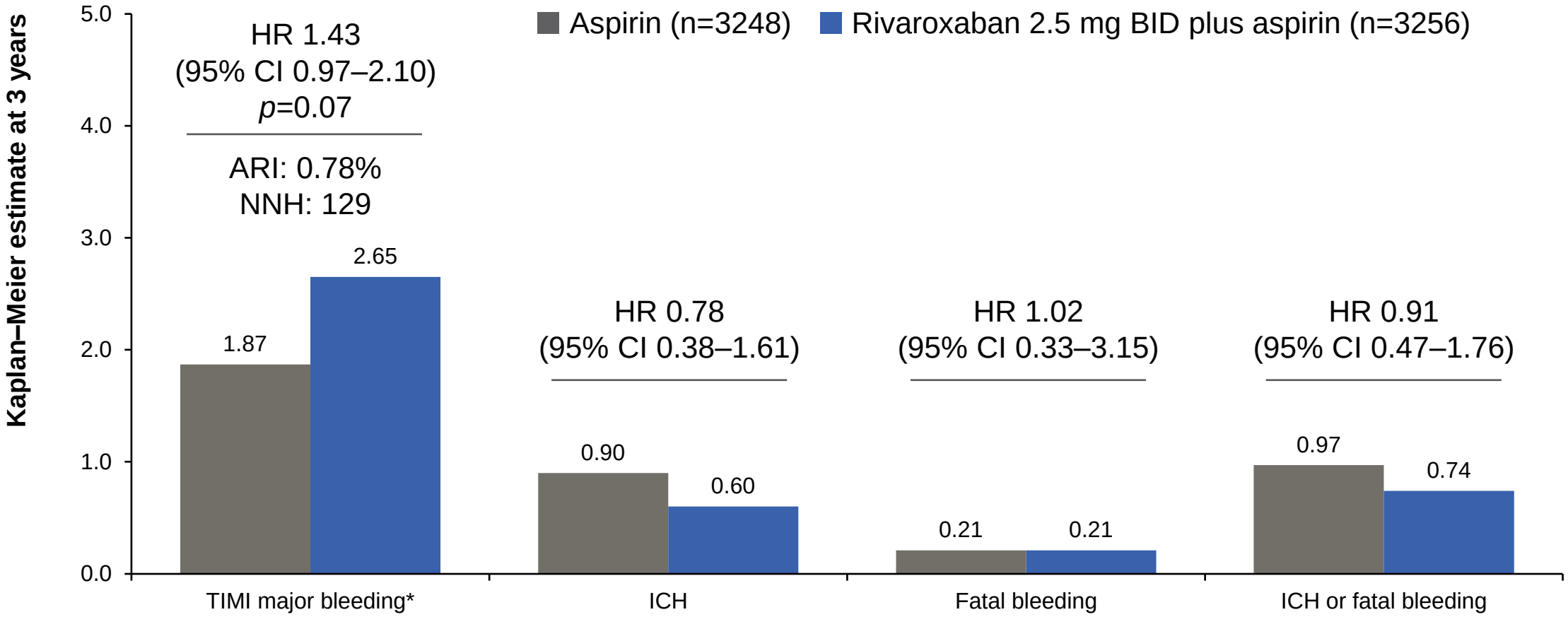
Number at risk

Rivaroxaban plus aspirin	3286	3082	2938	2834	2219	1415	684
Aspirin	3278	3030	2881	2773	2151	1351	642

Bonaca MP et al. *N Engl J Med* 2020

Patients could have enhanced protection without an increase in the most serious bleeds

Safety outcomes in VOYAGER PAD



*The incidence of Thrombolysis in Myocardial Infarction TIMI major bleeding did not differ significantly between the groups (primary end point).
The incidence of ISTH major bleeding (secondary endpoint) was significantly higher with rivaroxaban and aspirin than with aspirin alone.

Bonaca MP . *N Engl J Med* 2020.

קסרלטו במינון הווסקולרי של 2.5 מ"ג פעמיים ביום בשילוב עם אספירין 75-100 מ"ג פעם ביום כעת בסל הבריאות

טיפול למניעת שבץ, אוטם שריר הלב, מוות קרדיווסקולרי, איסכמיה חריפה בגפיים ותמותה עבור חולים במחלת לב איסכמית ידועה

- Ischemic heart disease (IHD) או
Coronary artery disease (CAD)

ביחד עם מחלת כלי דם פריפרית

Peripheral arterial disease (PAD) *

<u>לעניין זה יוגדרו:</u>

1. מחלת לב איסכמית ידועה (IHD או CAD) מצב לאחר אוטם או רה-וסקולריזציה בעבר או היצרויות כליליות ידועות.

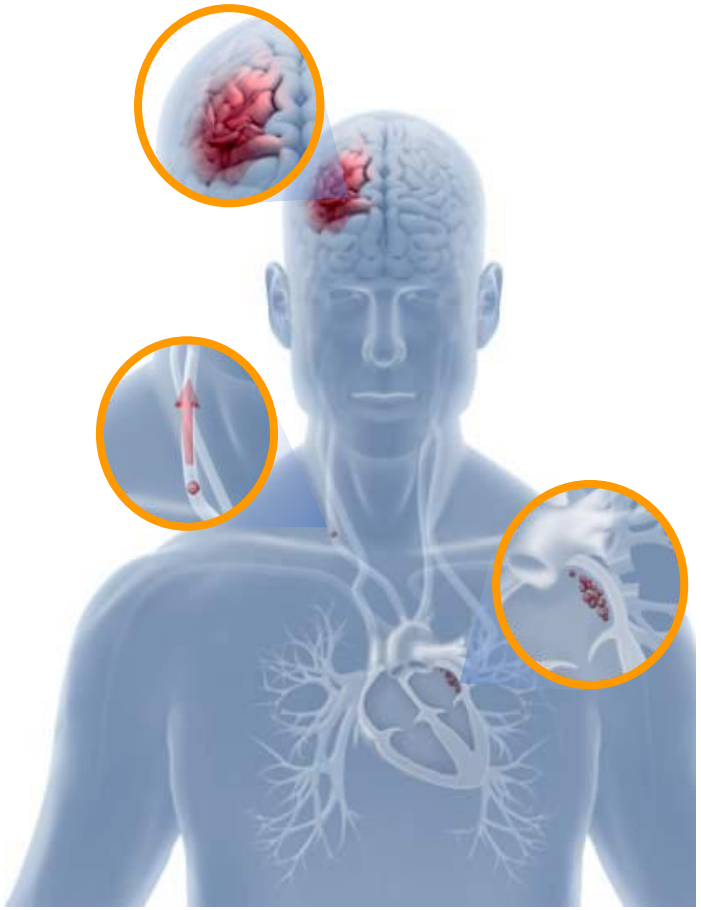
2. מחלת כלי דם פריפרית (PAD) -
   א. מצב לאחר רה וסקולריזציה או ניתוח כלי דם או קטיעה בעבר, או קיום צליעה לסירוגין עם ABI מתחת ל- 0.9 או היצרות כלי דם ידועה גדול מ- 50%
   ב. מחלה בעורקי התרדמה (קרוטיד) מצב לאחר רה-וסקולריזציה או היצרות ידועה גדול מ- 50%

* מתוך חוזר מנהל רפואה, ינואר 2019

Implementation of Oral Anticoagulant Therapy in AF related thrombosis

Atrial fibrillation (AF) increases thromboembolic risk, notably in the brain

- AF increases risk of stroke by 5-fold[1]
- Approximately 20% of all strokes are caused by AF[2]
  - AF-related strokes are more severe and fatal[3]
- AF is often asymptomatic[4]
  - The absence of symptoms (e.g. palpitations) does not imply a lower risk of thromboembolism[4]



1. Wolf . Stroke 1991
2. Friedmanl. Circulation 1968
3. Lin . Stroke 1996
4. Flaker . Am Heart J 2005

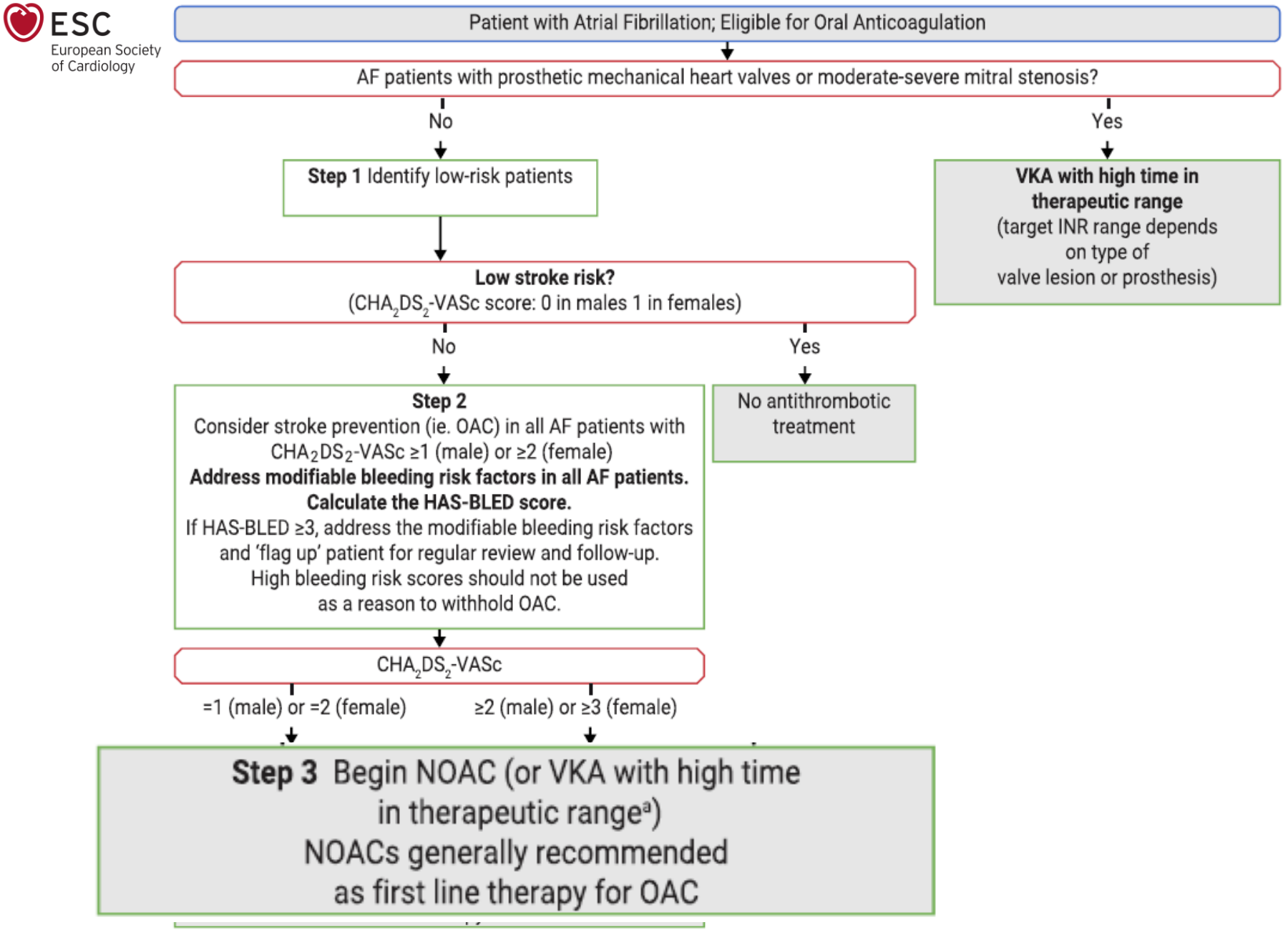
AF Risk-Management Decision

$CHADS_2$ criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 yrs	1
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	2

Old risk score

New risk score
Health Care Basket>=2
Since 2019

CHA_2DS_2-VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction, HCM	1
Hypertension	1
Age ≥75 yrs	2
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	2
Vascular disease (angiographically significant CAD, previous MI, PAD, or aortic plaque)	1
Age 65–74 yrs	1
Sex category (female gender – added to other criteria)	1



Hindricks G. European Heart Journal 2020,.

Dose adjustment for NOACs

	Dabigatran (PRADAXA™)	Apixaban (ELIQUIS™)	Rivaroxaban (XARELTO™)
Dose	**150 mg twice daily** or **110 mg twice daily**	**5 mg twice daily**	**20 mg once daily**
Dose reduction criteria	**110 mg twice daily** if: age ≥80 years CrCl 30–49 ml/min (ESC guidelines)	**2.5 mg twice daily**, if at least 2 of: **A**ge ≥80 years **B**ody weight ≤60 kg **C**reatinine ≥1.5 mg/dl or if: CrCl 15–29 ml/min	**15 mg once daily** if : CrCl 15–49 ml/min
Not recommended if:	CrCl <30 mL/min	CrCl <15 mL/min	CrCl <15 mL/min

Kirchhof. Eur Heart J. 2016.

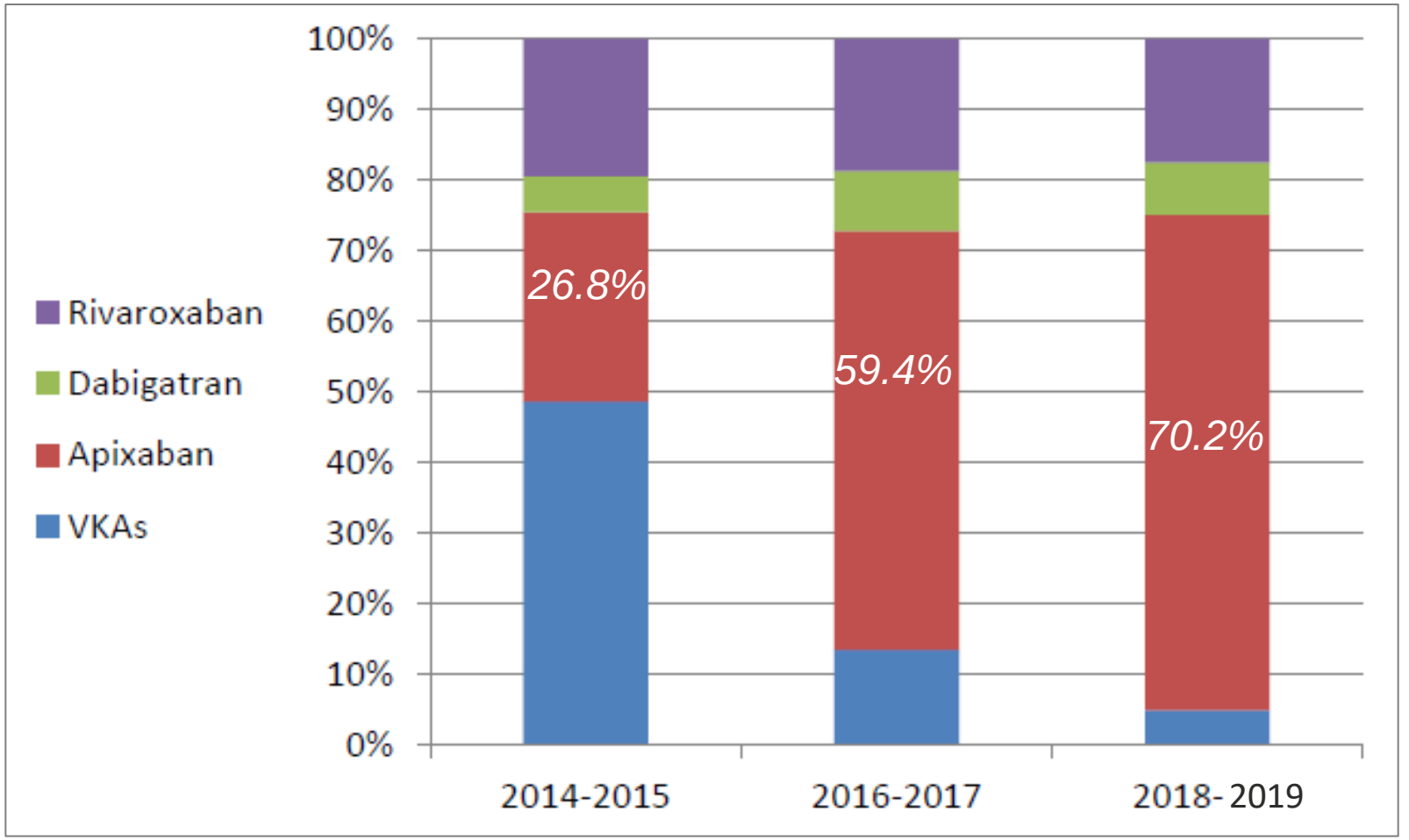
NOAC Treatment Patterns in Clinical Practice

BJCP British Journal of Clinical Pharmacology

ORIGINAL ARTICLE | Full Access

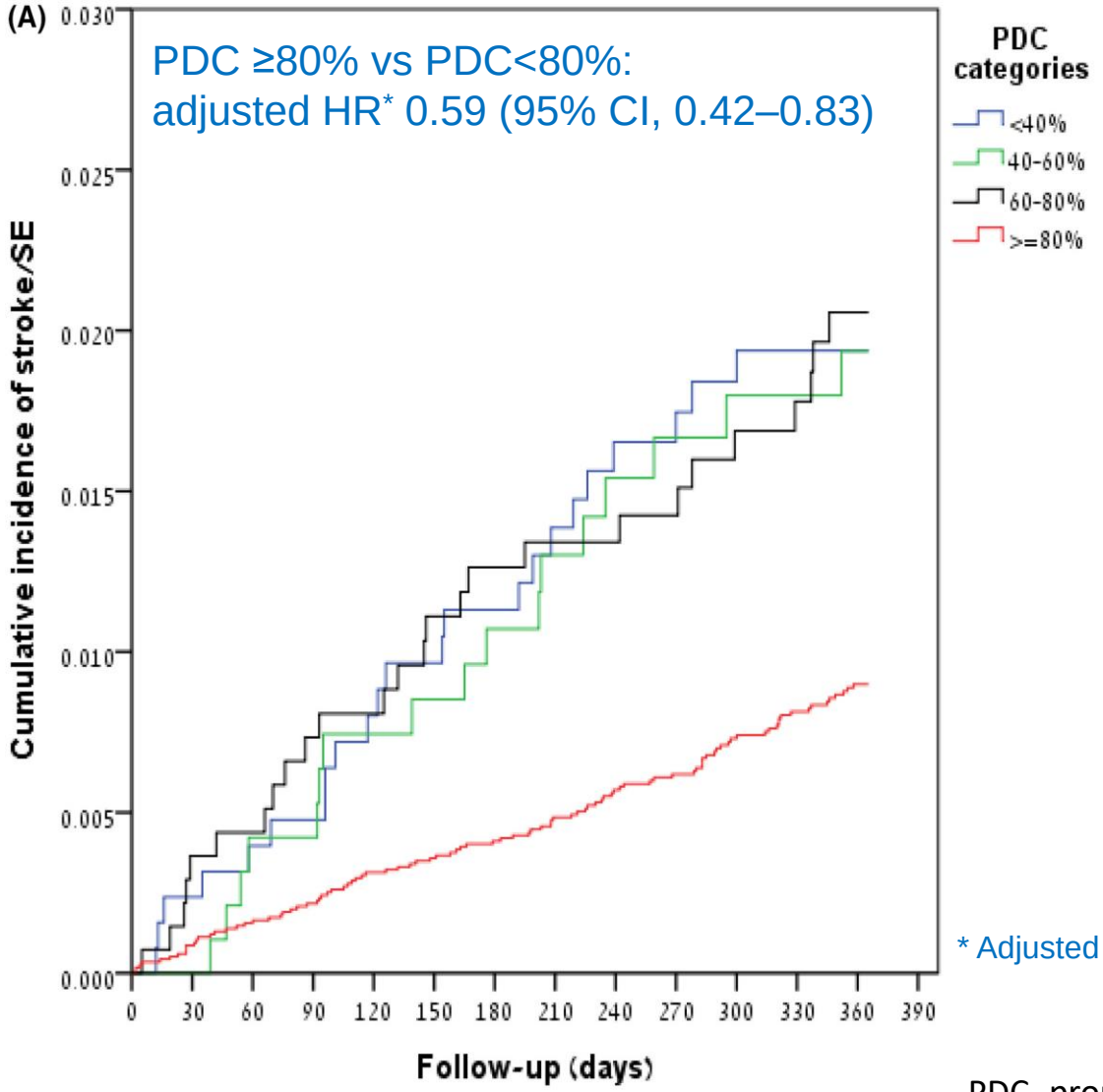
Implementation of Oral Anticoagulation Treatment Guidelines in Patients with Newly Diagnosed Atrial Fibrillation

- 46,531 AF patients with CHA_2DS_2-VASc score ≥2 from Clalit.



Arbel A. Br J Clin Pharmacol. 2021

High adherence lowers risk of stroke and SE

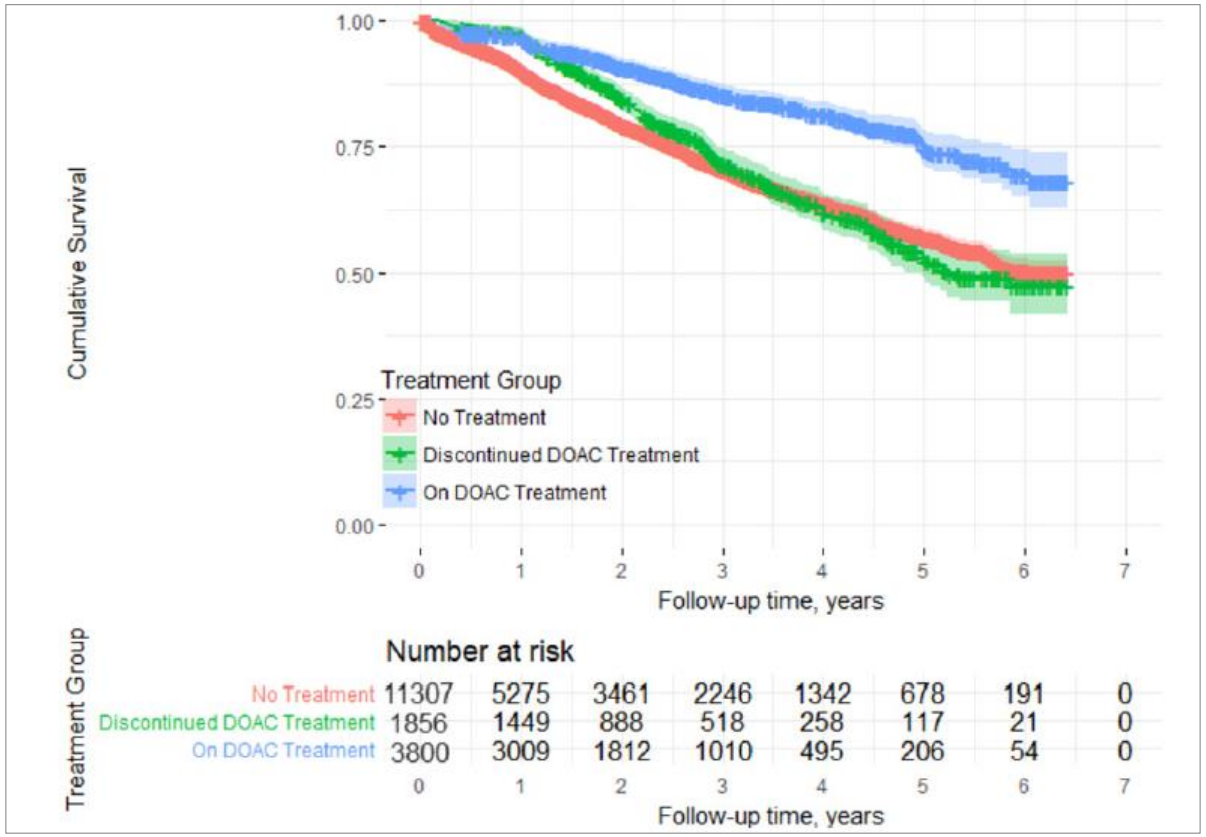


* Adjusted for CHA2DS2-VASc score.

PDC -proportion of days covered during the year

Arbel A. Journal of Arrhythmia. 2021.

Anticoagulant treatment discontinuation has similar survival to no anticoagulant treatment

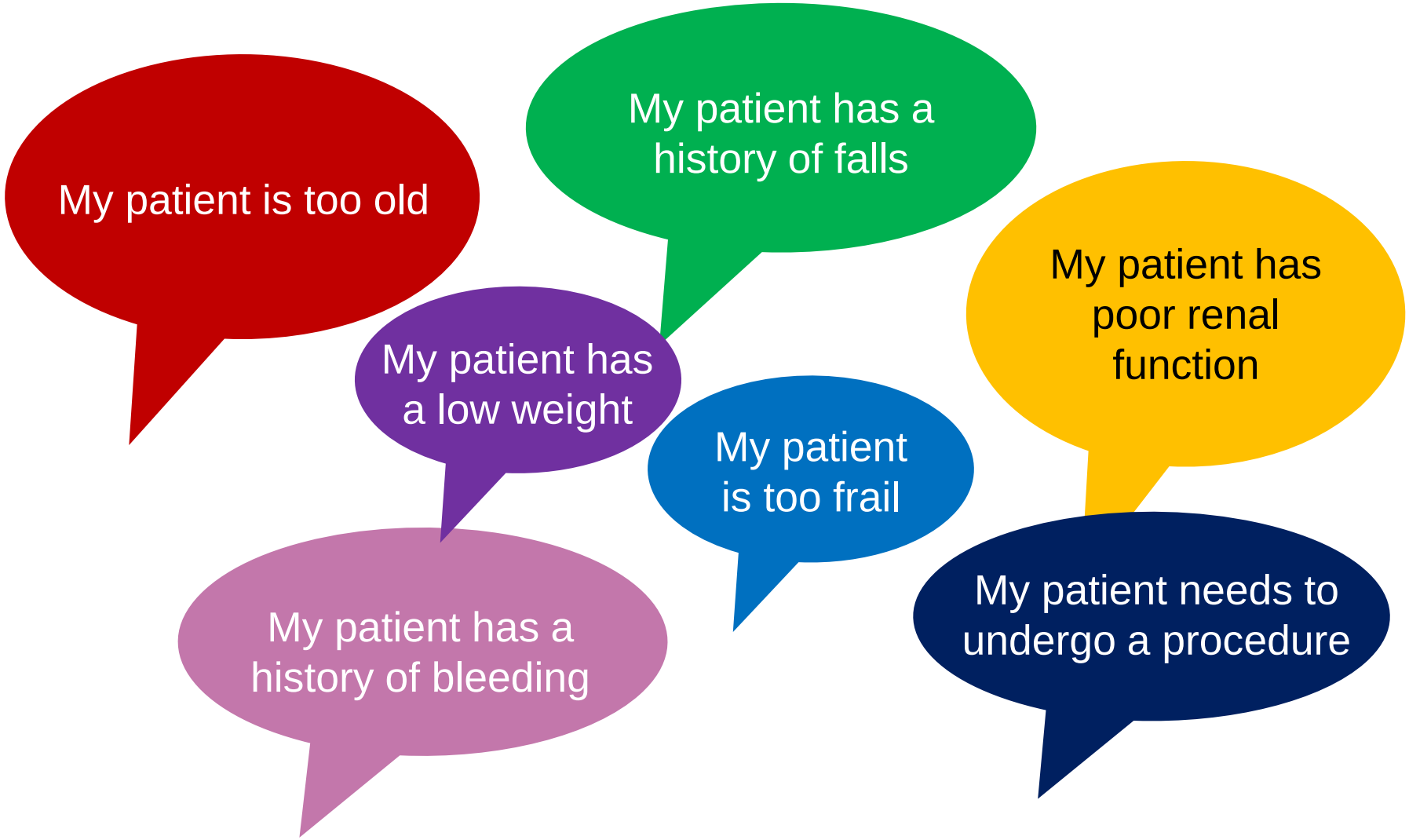


	DOAC			No anticoagulant				
Population	Patients (n)	Deaths (n)	Deaths/100 patient-years	Patients (n)	Deaths (n)	Deaths/100 patient-years	Adjusted HR (95% CI)	P value
All patients	5657	715	7.6	5657	2075	11.1	0.69 (0.63 to 075)	<0.001
Continuous treatment	3801	336	5.3	5657	2075	11.1	0.47* (0.42 to 0.53)	<0.001
Discontinued treatment	1856	379	12.1	5657	2075	11.1	0.95† (0.85 to 1.07)	0.60

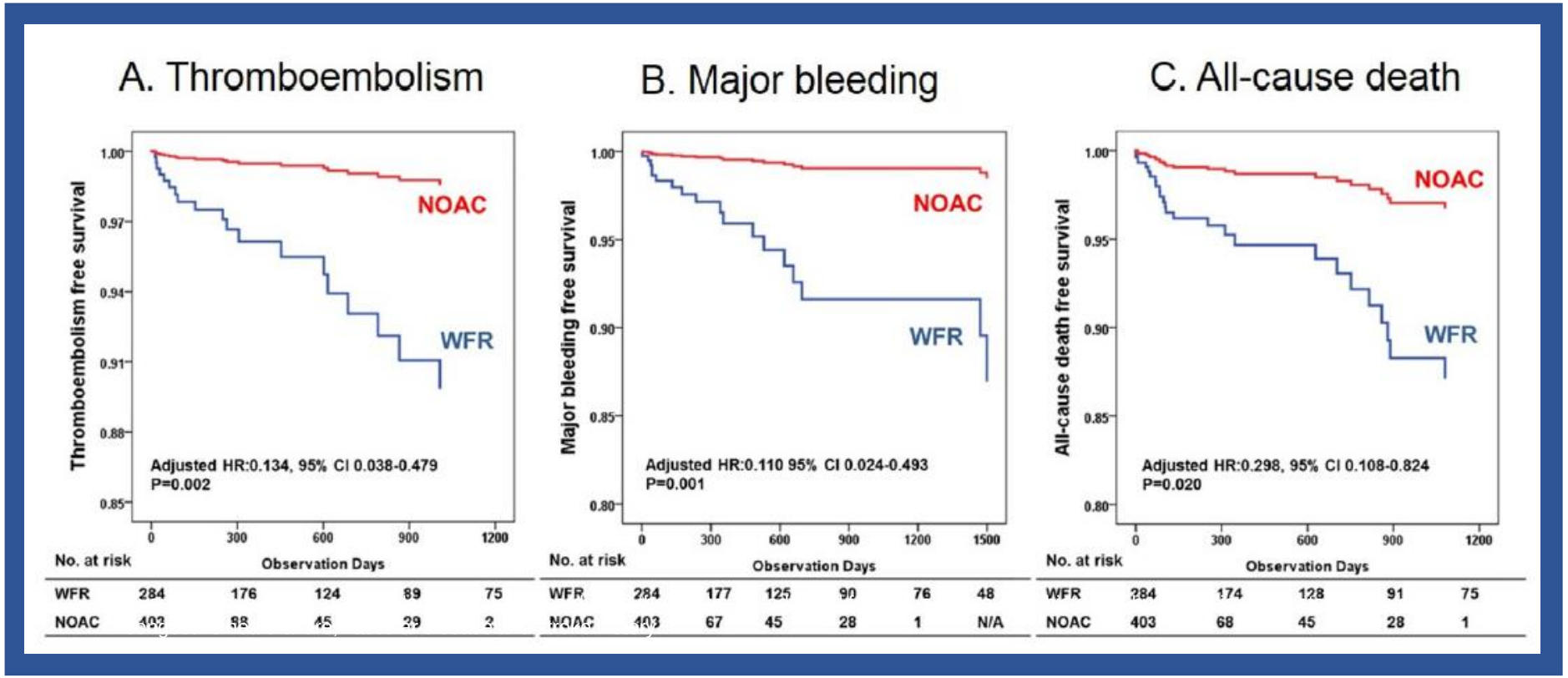
Arbel R. Heart. 2019;

Barriers to NOAC Prescription

“High risk of bleeding?”



Retrospective study - Korea, 2012-2016: 687 AF patients, age 83.4±3.1 years, receiving OACs



Kim HM. PLoS One. 2019.

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2021) 7, f20–f29
doi:10.1093/ehjcvp/pvz073
ORIGINAL ARTICLE
Atrial fibrillation

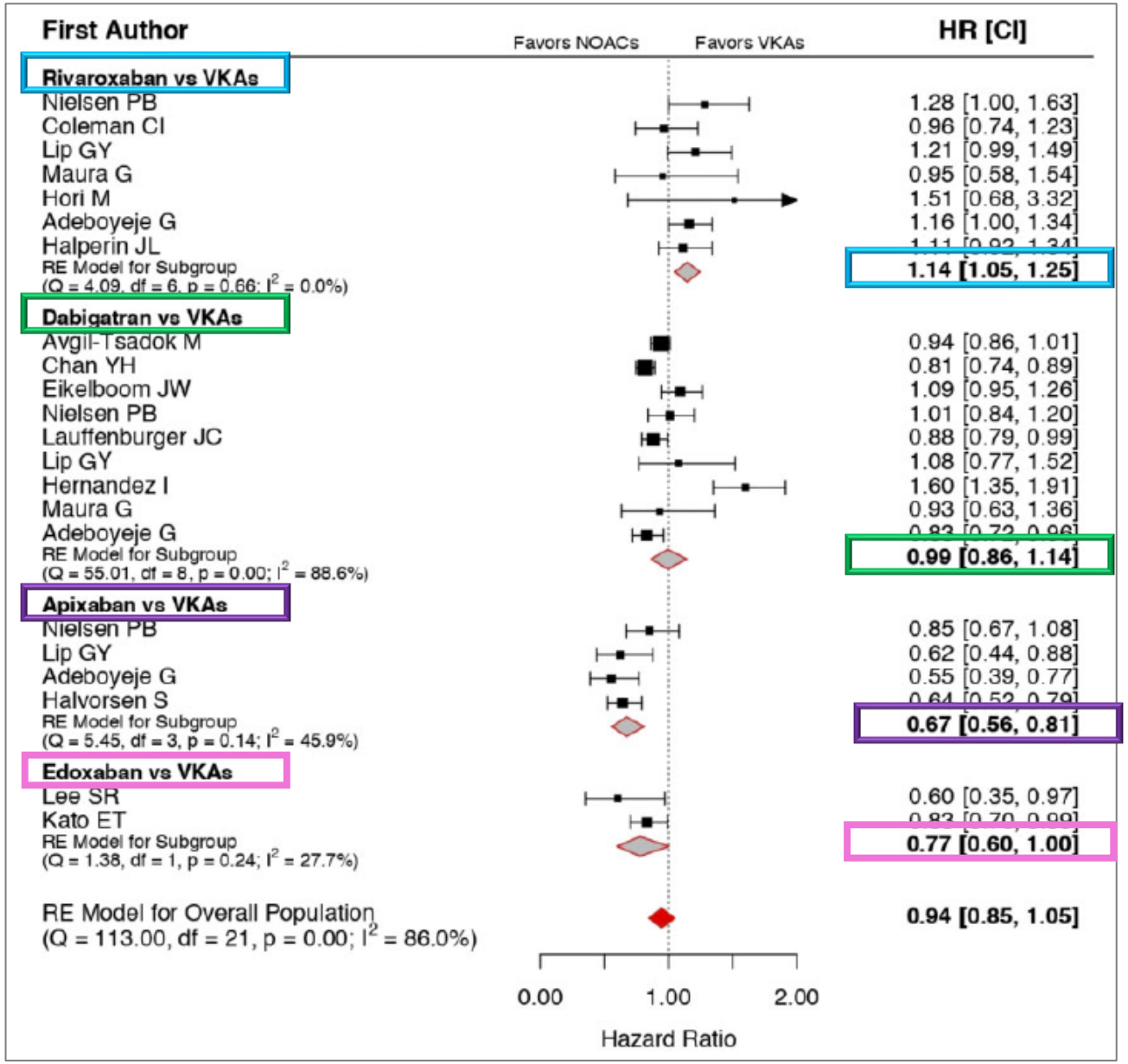
Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients

Angelo Silverio[1], Marco Di Maio[2], Costantina Prota[1], Elena De Angelis[1], Ilaria Radano[1], Rodolfo Citro[1], Albino Carrizzo[3], Michele Ciccarelli[1], Carmine Vecchione [1,3], Davide Capodanno[4], and Gennaro Galasso[1]*

- **Design:** meta-analysis of 22 studies (5 RCTs and 17 observational studies), published 2011-2018.
- **Study population:** 440,281 AF patients ≥75 years taking OACs.

Silverio A. Eur Heart J Cardiovasc Pharmacother. 2021

Major Bleeding - NOACs Vs. VKAs



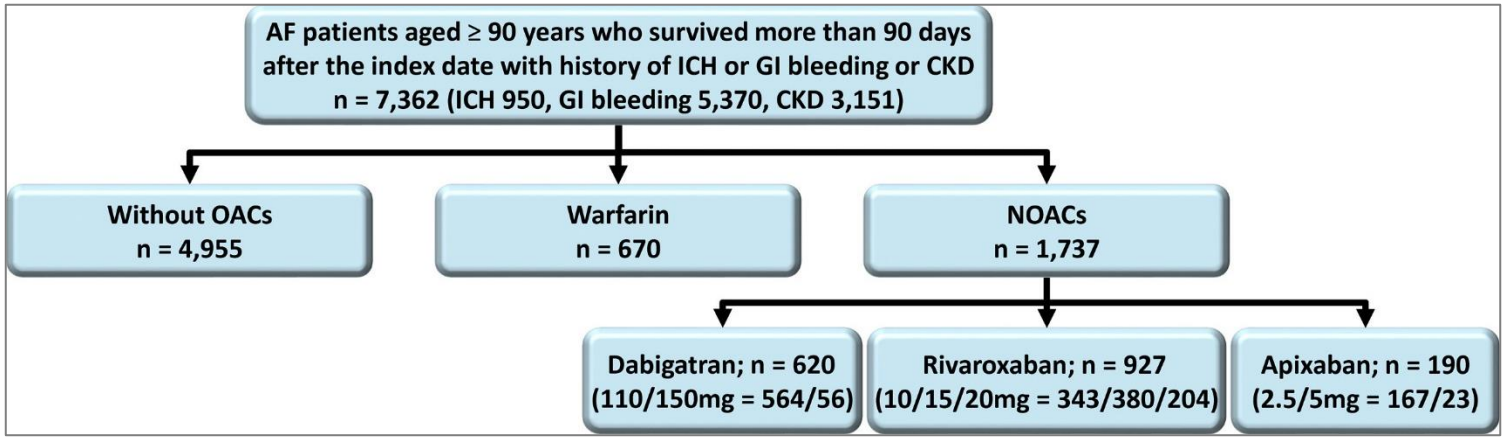
Silverio A. Eur Heart J Cardiovasc Pharmacother. 2021

Journal Pre-proof

Oral Anticoagulants in Extremely High Risk Very Elderly (>90 years) Patients with Atrial Fibrillation

Tze-Fan Chao, M.D., Chern-En Chiang, M.D., Yi-Hsin Chan, MD, Jo-Nan Liao, M.D., Tzeng-Ji Chen, M.D., Gregory Y.H. Lip, M.D., Shih-Ann Chen, M.D.

- **Design:** retrospective study, Taiwan, 2012-2016.

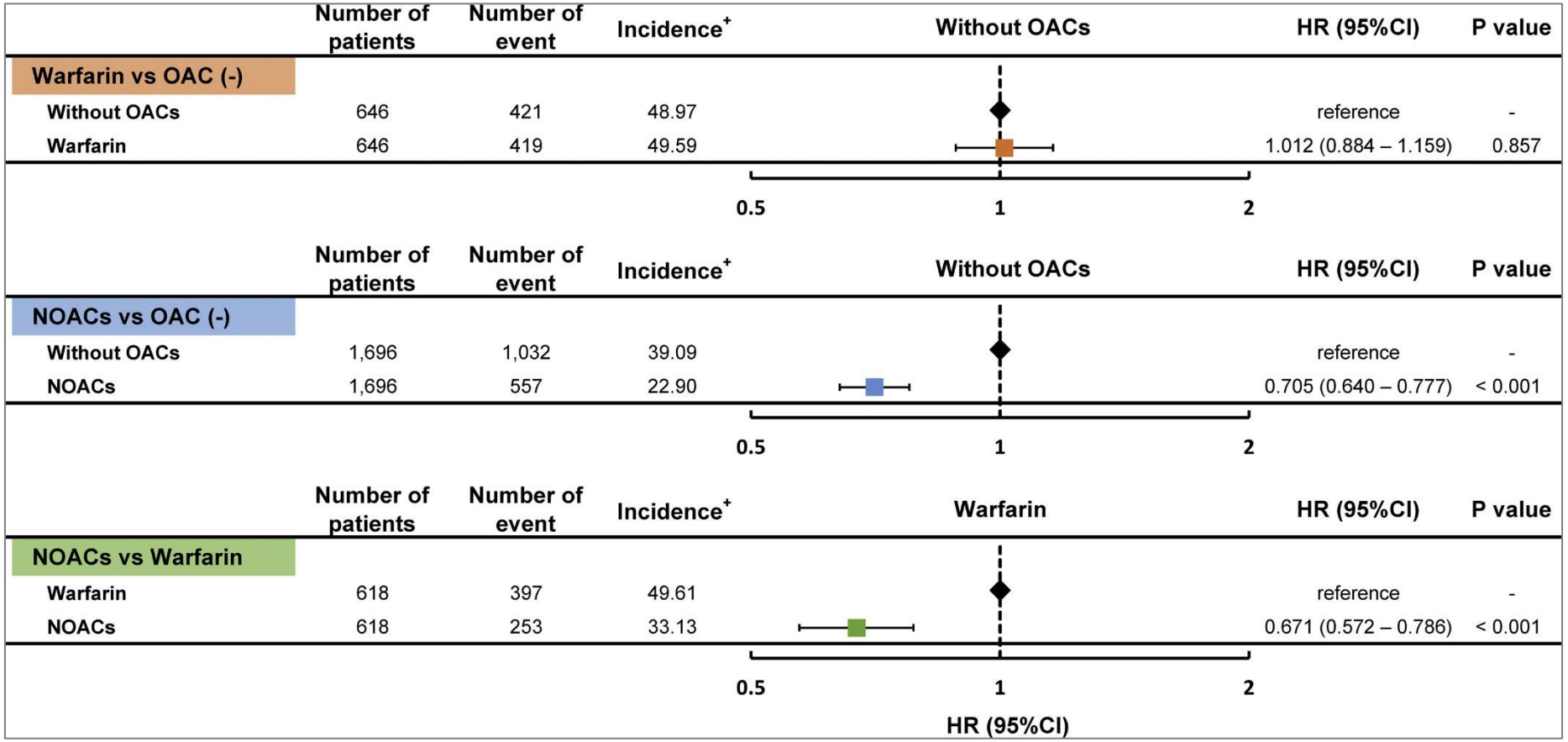


- **Outcomes:** composite of ischemic stroke, ICH, major bleeding or mortality.

Chao TF. Heart Rhythm. 2021.

Ischemic stroke, ICH, major bleeding or mortality

Propensity score matching



*Per 100 person-years.

CI = confidence interval; CKD = chronic kidney disease; GI bleeding = gastrointestinal; HR = hazard ratio; ICH = intra-cranial hemorrhage; NOACs = non-vitamin K antagonist OACs; OACs = oral anticoagulants.

Chao TF. Heart Rhythm. 2021

Annals of Internal Medicine

ORIGINAL RESEARCH

Frailty and Clinical Outcomes of Direct Oral Anticoagulants Versus Warfarin in Older Adults With Atrial Fibrillation

A Cohort Study

Dae Hyun Kim, MD, MPH, ScD; Ajinkya Pawar, PhD; Joshua J. Gagne, PharmD, ScD; Lily G. Bessette, BS; Hemin Lee, MD, MPH; Robert J. Glynn, ScD, PhD; and Sebastian Schneeweiss, MD, ScD

- **Design:** 1:1 propensity score-matched retrospective study, Medicare, US, 2010-2017.
- **Study population:** patients with AF who filled a prescription for 1 OAC.
- **Frailty:** nonfrailty - a **CFI** <0.15, prefrailty - **CFI** 0.15-0.24, frailty - **CFI** ≥0.25.
- **Primary outcome:** composite of death, ischemic stroke, or major bleeding.
- **Follow-up:** median, 72-84 days.

Primary Funding Source: National Institute on Aging.

Kim DH. Ann Intern Med. 2021.

Death, Ischemic Stroke, or Major Bleeding

Outcomes	Apixaban Cohort			
	Rate per 1000 Person-Years		HR (95% CI)	RD (95% CI)
	Warfarin (n = 109 369)	Apixaban (n = 109 369)		
Composite event				
Total	92.3	60.1	0.68 (0.65 to 0.72)	−32.2 (−36.1 to −28.3)
Nonfrail	37.6	21.9	0.61 (0.52 to 0.71)	−15.7 (−20.4 to −11.0)
Prefrail	86.0	54.2	0.66 (0.61 to 0.70)	−31.8 (−36.7 to −26.9)
Frail	226.2	157.6	0.73 (0.67 to 0.80)	−68.7 (−85.3 to −52.0)
P value for heterogeneity	-	-	0.080	<0.001

Outcomes	Dabigatran Cohort				Rivaroxaban Cohort			
	Rate per 1000 Person-Years		HR (95% CI)	RD (95% CI)	Rate per 1000 Person-Years		HR (95% CI)	RD (95% CI)
	Warfarin (n = 79 365)	Dabigatran (n = 79 365)			Warfarin (n = 137 972)	Rivaroxaban (n = 137 972)		
Composite event								
Total	65.6	63.5	0.98 (0.92 to 1.05)	−2.2 (−6.5 to 2.1)	83.7	77.8	0.98 (0.94 to 1.02)	−5.9 (−9.4 to −2.4)
Nonfrail	31.4	25.4	0.81 (0.68 to 0.97)	−6.1 (−11.2 to −0.9)	37.2	31.6	0.88 (0.77 to 0.99)	−5.6 (−9.9 to −1.3)
Prefrail	64.1	62.1	0.98 (0.90 to 1.08)	−2.1 (−7.8 to 3.6)	76.7	76.5	1.04 (0.98 to 1.10)	−0.2 (−4.8 to 4.4)
Frail	160.2	170.0	1.09 (0.96 to 1.23)	9.8 (−9.9 to 29.6)	219.8	200.8	0.96 (0.89 to 1.04)	−19.0 (−35.2 to −2.9)
P value for heterogeneity	-	-	0.027	0.23	-	-	0.026	0.040

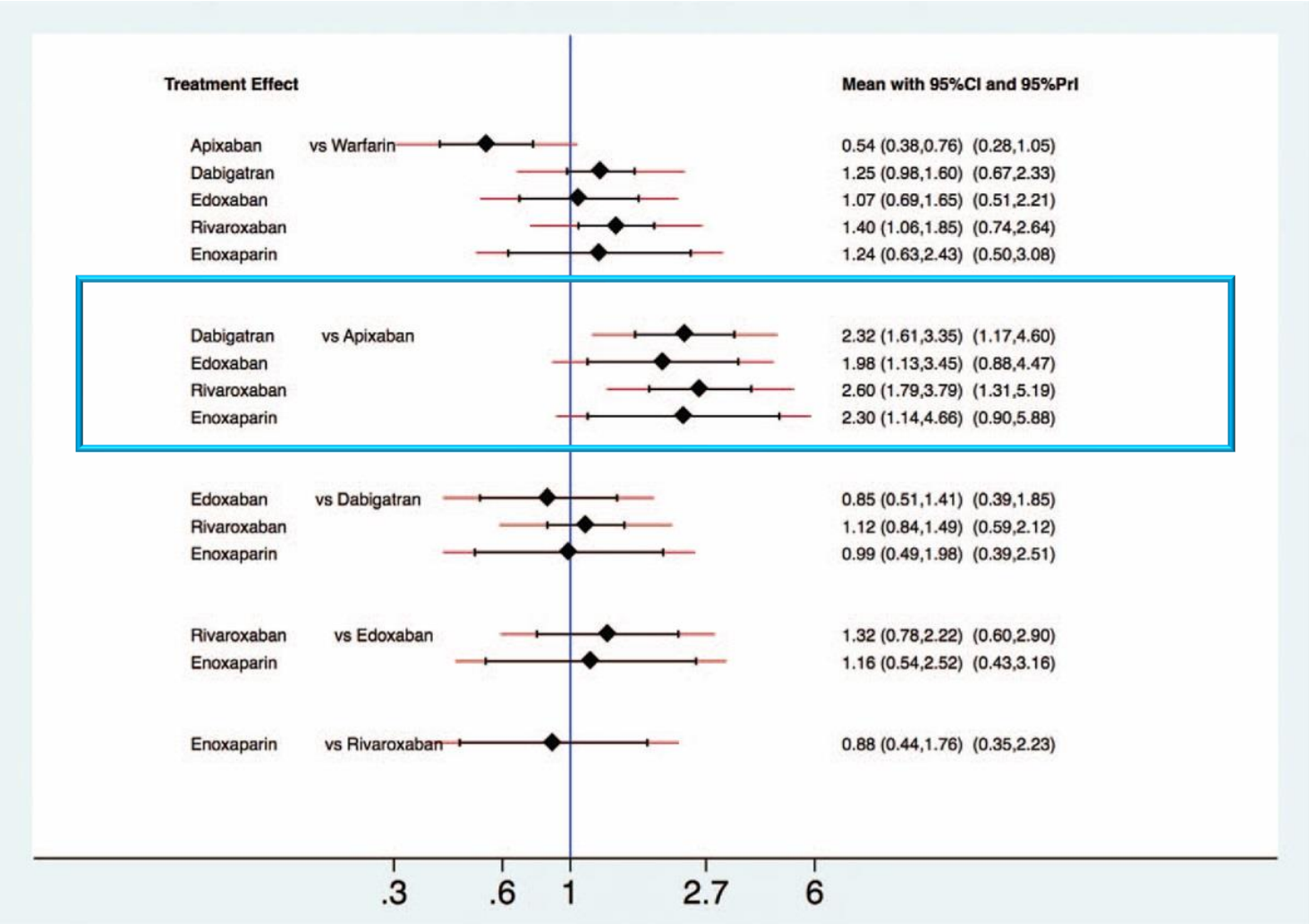
CONCLUSION:

For older adults with AF, apixaban was associated with lower rates of adverse events across all frailty levels. Dabigatran and rivaroxaban were associated with lower event rates only among non-frail patients.

Kim DH, et al. Ann Intern Med. 2021

- **Design:** network meta-analysis of 29 RCTs and 4 observational studies.
- **Study population:** 387,194 patients treated with NOACs or conventional coagulation therapy (VKA and LMWH) for approved indications (VTE, stroke prevention in AF).
- **Primary outcome:** major GI bleeding.

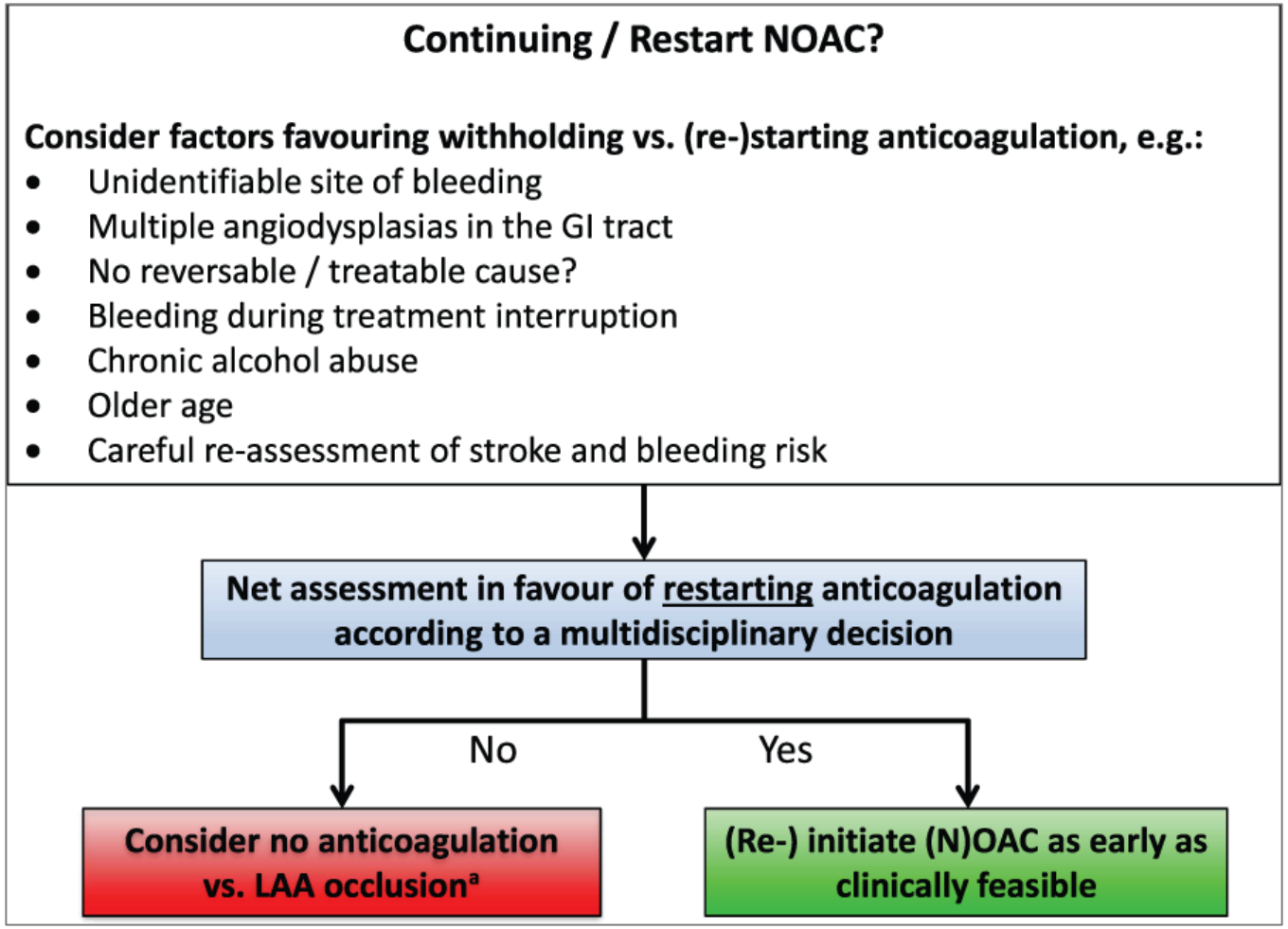
Oh HJ. Res Medicine (Baltimore). 2021.



Compared to apixaban, the remaining NOACs (dabigatran, edoxaban, and rivaroxaban) and enoxaparin were associated with increased risk of major GI bleeding.

Oh HJ. Res Medicine (Baltimore). 2021.

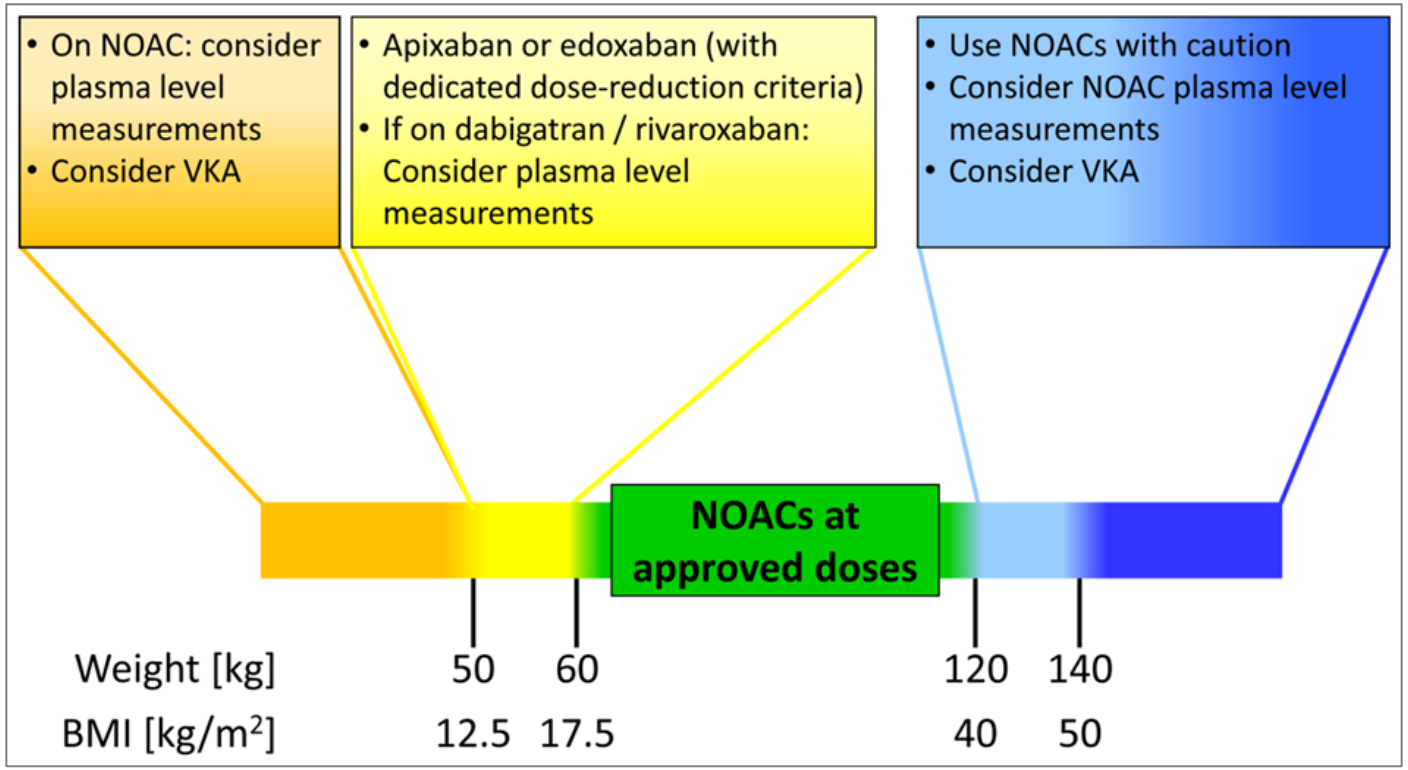
(Re-)Initiating Anticoagulation After GI Bleeding



[a] Without RCT evidence; ideally include patient in ongoing trial. GI, gastrointestinal; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant.

Steffel J. Europace. 2021.

NOACs in Under- and Overweight Patients



Both *apixaban* and *edoxaban* showed consistent efficacy and safety compared to warfarin in underweight patients when compared with the overall study population.

Steffel J. Europace. 2021.

Summary

- NOACs are recommended in preference to VKAs for stroke prevention in AF.
- Even after a decade since their arrival, adherence to NOACs is suboptimal.
- Many factors can act as barriers to NOAC implementation in clinical practice.
- Sustained adherence/persistence to long-term NOAC therapy has key role in preventing cardiovascular events and reducing cost and hospitalizations.

Thank You