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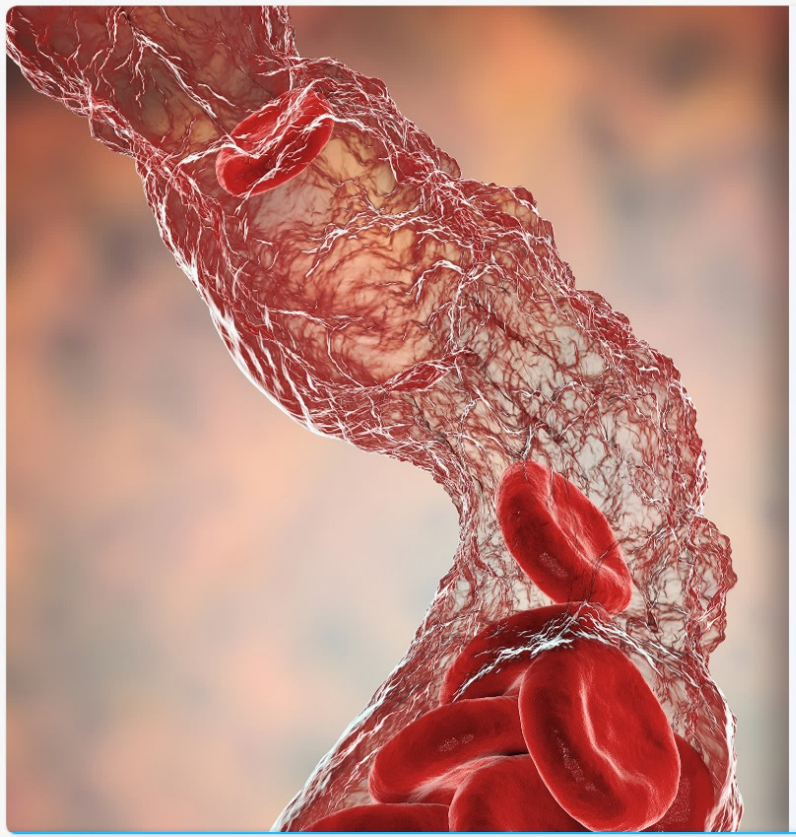

We're starting soon!

# The Role of DOACs in the management of VTE: RCT and RWE perspectives

## Presenters

**Conrad Strydom**
Webinar Host

**Dr Alexander Cohen**
Webinar Host

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WEBINARJAM

16° | ENG US | 06:31 PM 2024/09/11

# The Role of DOACs in th[T] and RWE Perspectives





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RSA September2024

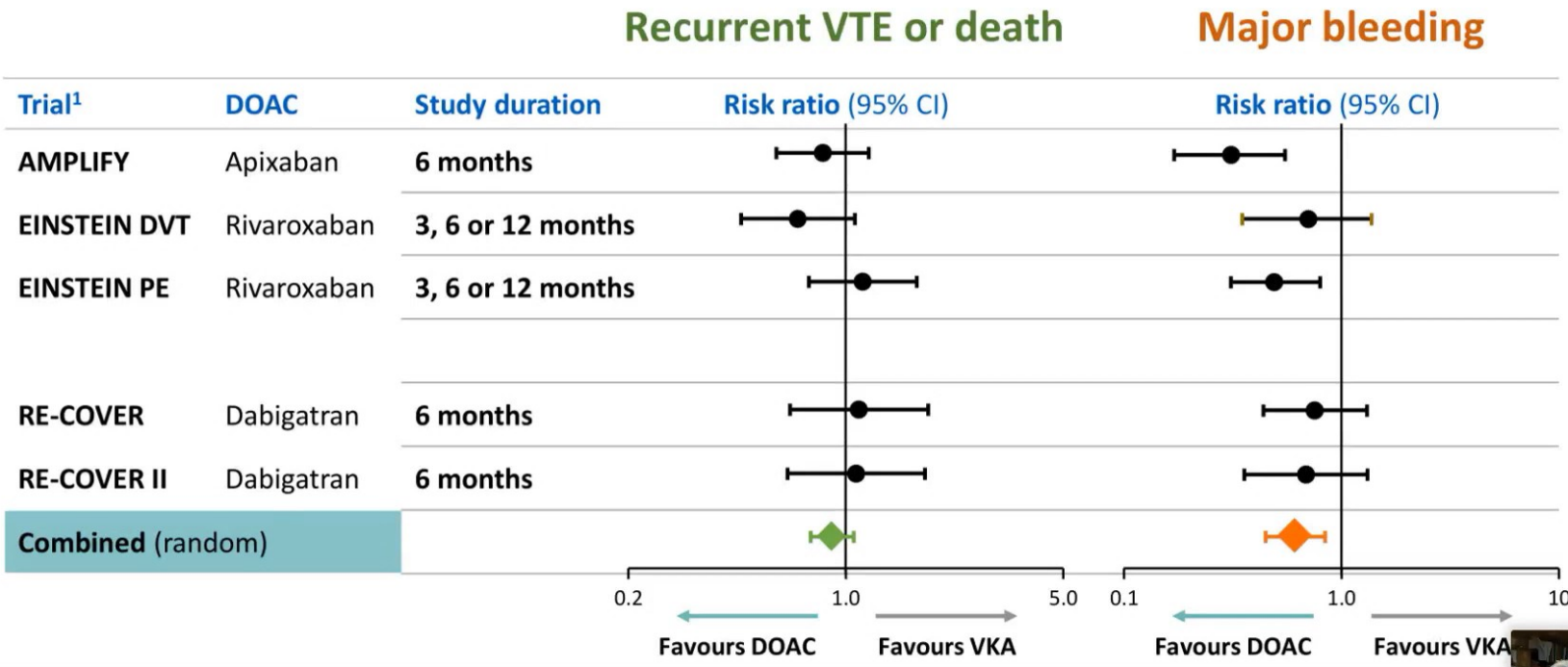
# Conclusions at the beginning

- DOACs are the treatment of choice for patients with VTE
- DOACs have different safety profiles
- Apixaban has a strong comparative safety profile for
  - The acute and long-term and extended treatment of VTE
  - The management of high-risk patients
  - The treatment of cancer associated VTE (CAT) and extended treatment of CAT
- More studies are needed in many areas such as chronic liver disease, thrombocytopoenia, dosing and extended therapy.

# My talk today:

- Describe RCT for DOACs and VTE for both treatment and primary prevention
- Examine real-world evidence (RWE) on the application of DOACs in VTE management and prophylaxis,
- Describe RCT for DOACs and Cancer associated VTE for both treatment and primary prevention
  - Caravaggio
  - Eve and APICAT
- Examine real-world evidence (RWE) on the application of DOACs in VTE management.

# Meta-analysis: DOACs for treatment of VTE
## (separate comparisons with VKA)

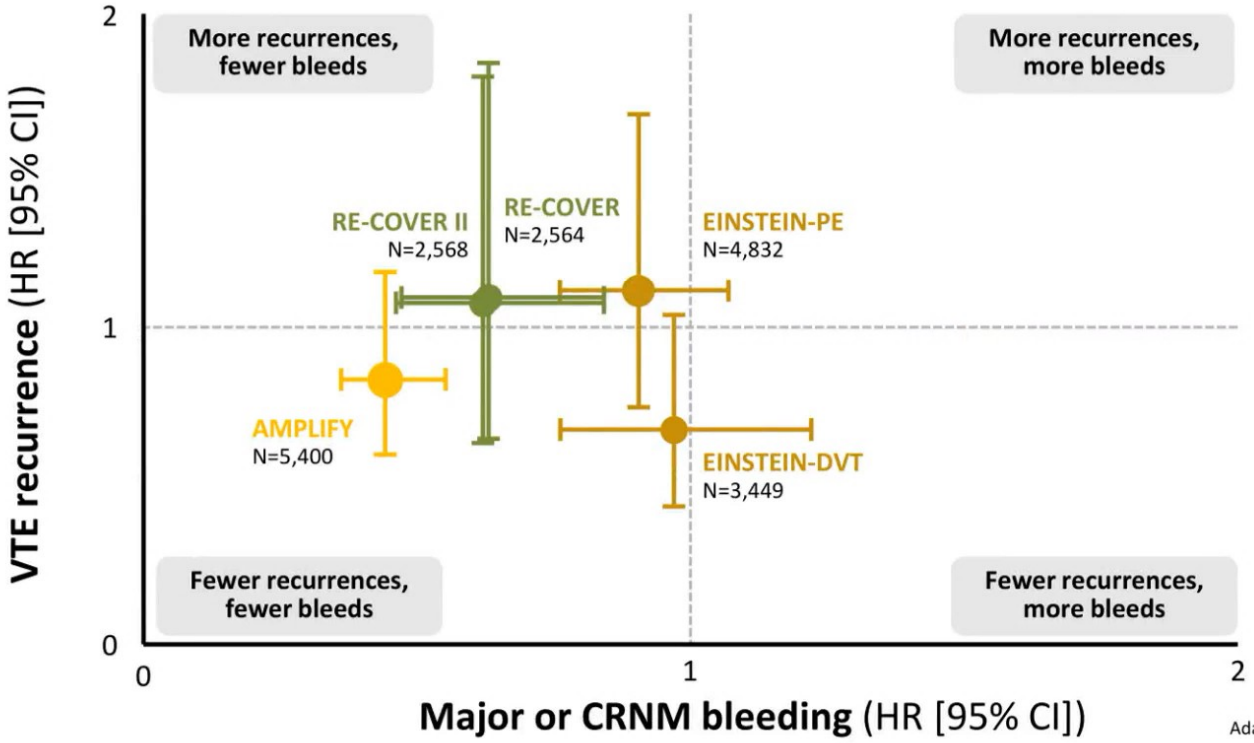



**There are no head-to-head randomised clinical trials comparing the DOACs.**
**Comparisons cannot be made between individual DOACs based on these data**

CI, confidence interval; DOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism

Adapted from Van Es N, et al. Blood 20

# Efficacy and safety of DOACs vs VKA in acute VTE



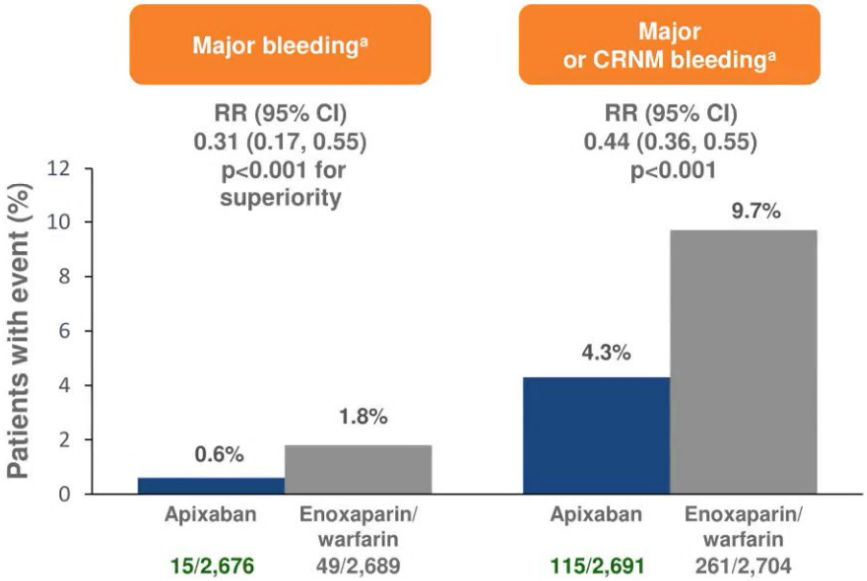

Adapted from Cohen AT et al. Adv Ther

Cohen AT et al. Adv Ther 2014;31:473–93

There are no head-to-head randomised clinical trials comparing
Comparisons cannot be made between individual DOACs based

# AMPLIFY: Major bleeding and major or CRNM bleeding for apixaban versus enoxaparin/warfarin

## AMPLIFY trial safety outcomes at 6 months[1]




## AUB events[b] of women in the AMPLIFY trial[2]

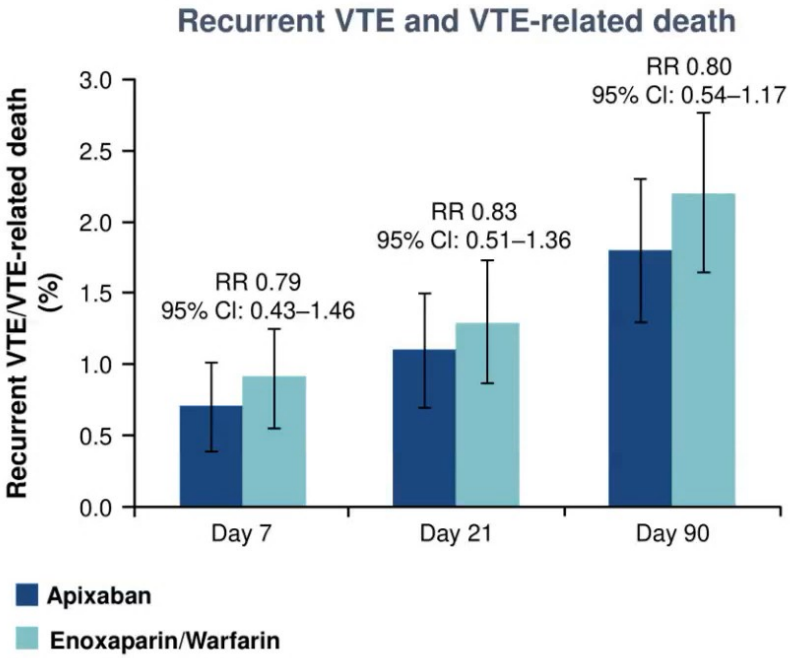
| Clinical outcome | Treatment (N) | Events, n (%) |
|---|---|---|
| Major vaginal bleeding | Apixaban 1,122 | 1 (<0.1) |
| | Enoxaparin/warfarin 1,106 | 0 (0) |
| CRNM vaginal bleeding | Apixaban 1,122 | 28 (2.5) |
| | Enoxaparin/warfarin 1,106 | 24 (2.1) |

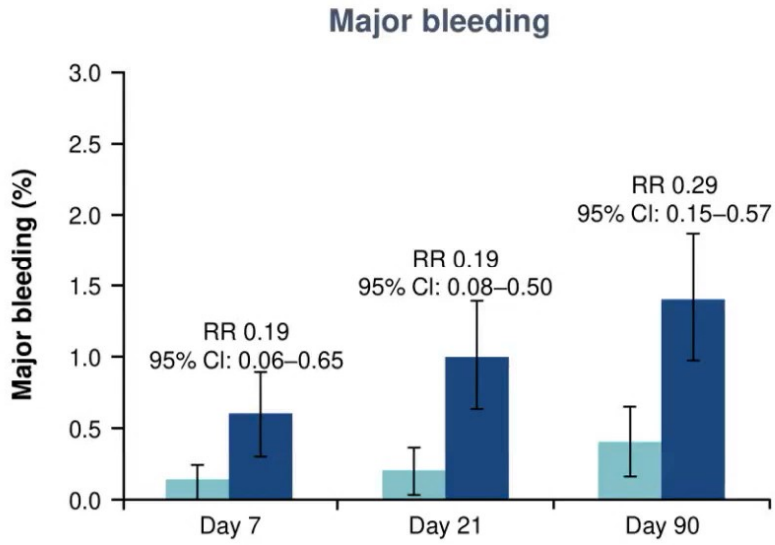
The severity of clinical presentation and course of the bleeds was **mild in 75%** of the cases in both groups[2]

[a]For patients who had more than one event, only the first event was counted. [b]AUB was, according to FIGO, defined as prolonged menstrual bleeding, intermenstrual bleeding, heavy menstrual bleeding or menstrual blood loss cau
requiring an unscheduled contact with a physician, or intervention, or adaptation of anticoagulant therapy.
AUB, abnormal uterine bleeding; CI, confidence interval; CRNM, clinically relevant non-major; FIGO, The International Federation of Gynecology and Obstetrics; RR, relative risk.

1. Agnelli G, et al. *N Engl J Med.* 2013;369:799–808; 2. Brekelmans MPA, et al. *Thromb Hemost.* 2017;117:809–15.

# Early time courses of recurrent VTE and bleeding



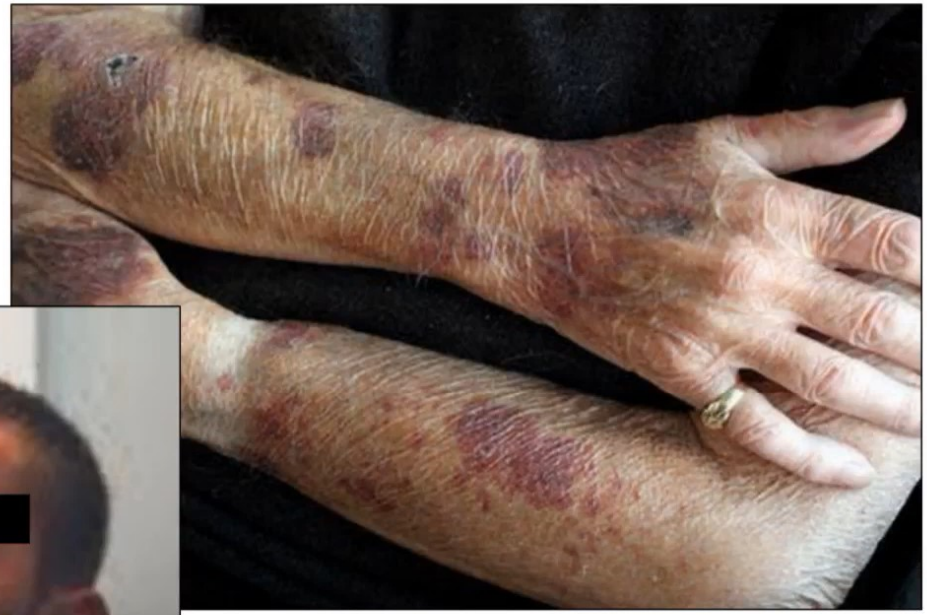




| | | | | |
|---|---|---|---|---|
| **CRNM bleeding:** | RR | 0.65 | 0.35 | 0.41 |
| | CI | 0.38–1.13 | 0.24–0.52 | 0.31–0.54 |

CRNM: clinically relevant non-major.

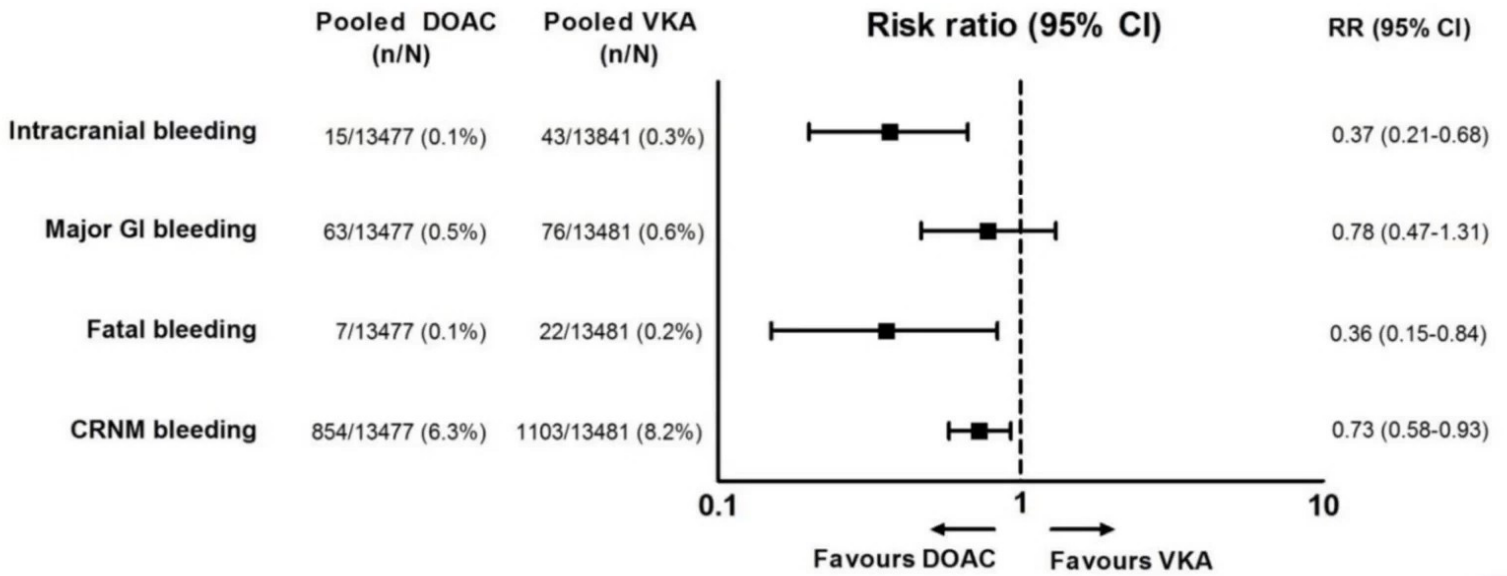
Raskob G, et al. Thromb Haemos

# Bleeding



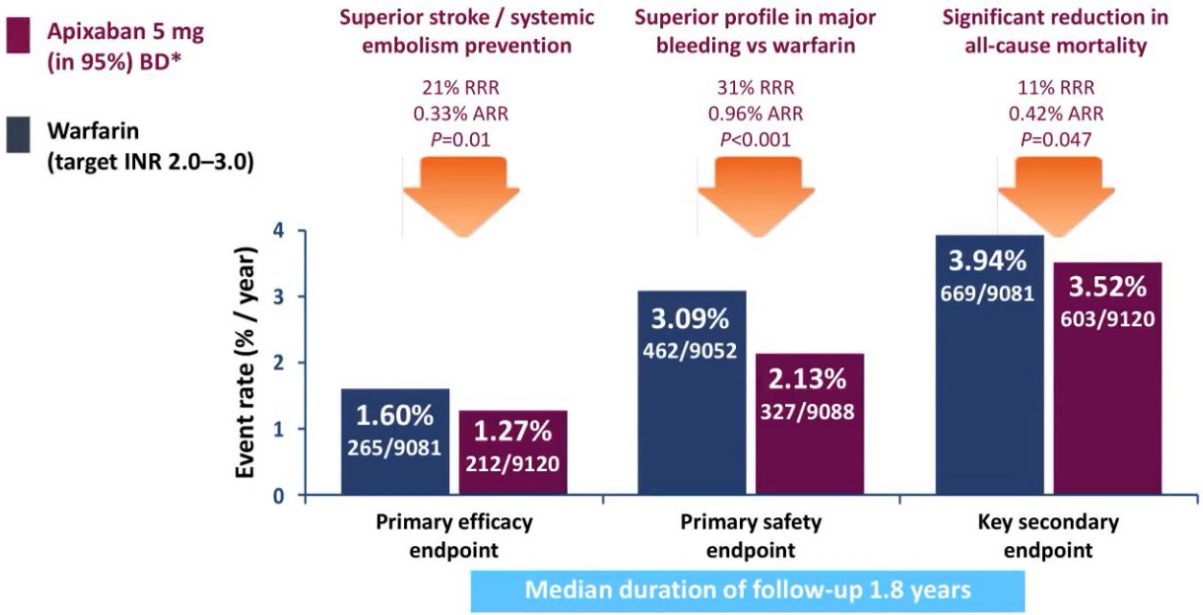
All photos of patients are with permission

# Bleeding components




van Es N, et al. *Blood* 2014;

# Apixaban is the only oral anticoagulant to demonstrate superiority vs warfarin in all of the following three outcomes in AF patients

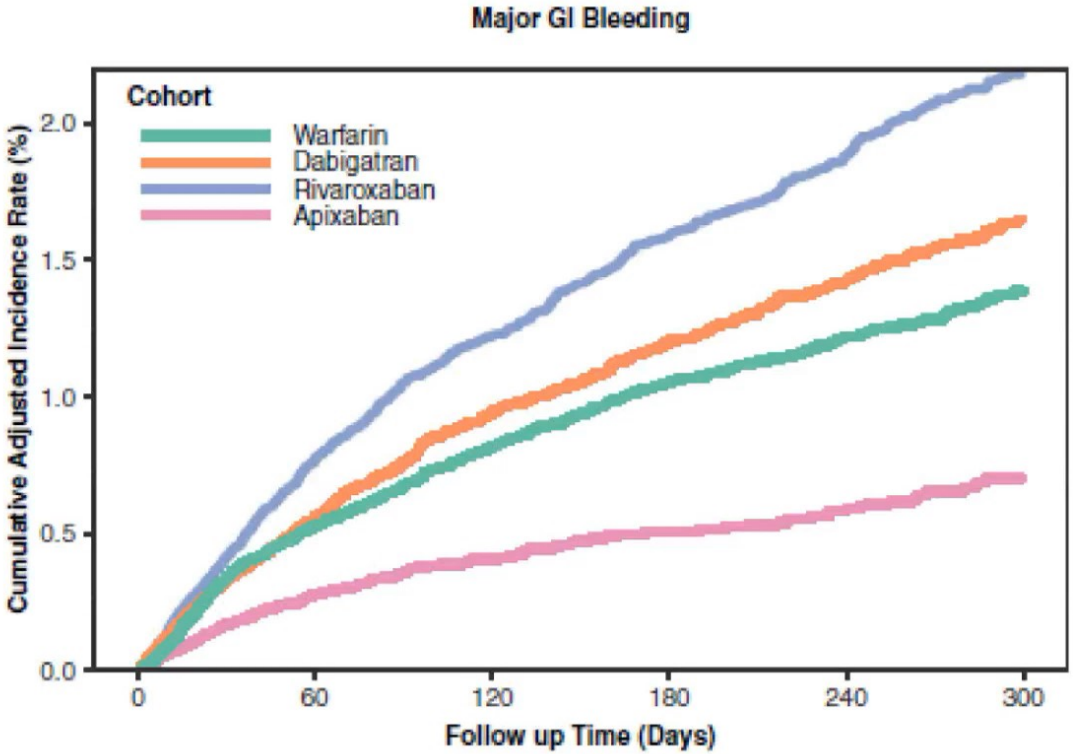



- Pre-specified hierarchical sequential testing was performed first on stroke/systemic embolism (primary efficacy endpoint) for non-inferiority, then for superiority, then on major bleeding, and finally on death from any cause (secondary endpoint)

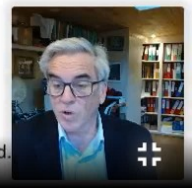
**Patients with ≥2 of the following received a reduced dose of apixaban 2.5 mg BD: age ≥80 years, body weight ≤60 kg a serum creatinine level ≥1.5 mg/dL (133 µmol/L). Per the SmPC, patients with the exclusive criterion of severe renal impairment (CrCl 15–29 mL/min) should also receive the lower dose of apixaban 2.5 mg twice daily. This new criterion differs from the trial conduct.*
*ARR, absolute risk reduction; RRR, relative risk reduction.*

1. Adapted from Granger et al. *N Engl J Med*. 2011;365:981–992; 2. Apixaban

# Adjusted KM Plots for Major GI Bleeding in patients with AF

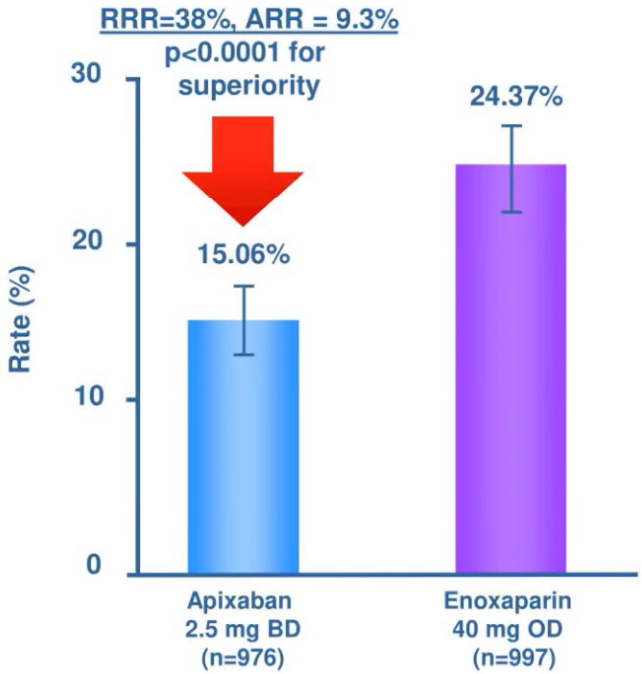



Graham DJ et al. Am J of Med.



# ADVANCE-2: In TKR, apixaban 2.5 mg BD superior to enoxaparin 40 mg OD for 10-14 days in reducing total VTE/all-cause death

**Primary efficacy outcome: Total VTE/all-cause death***

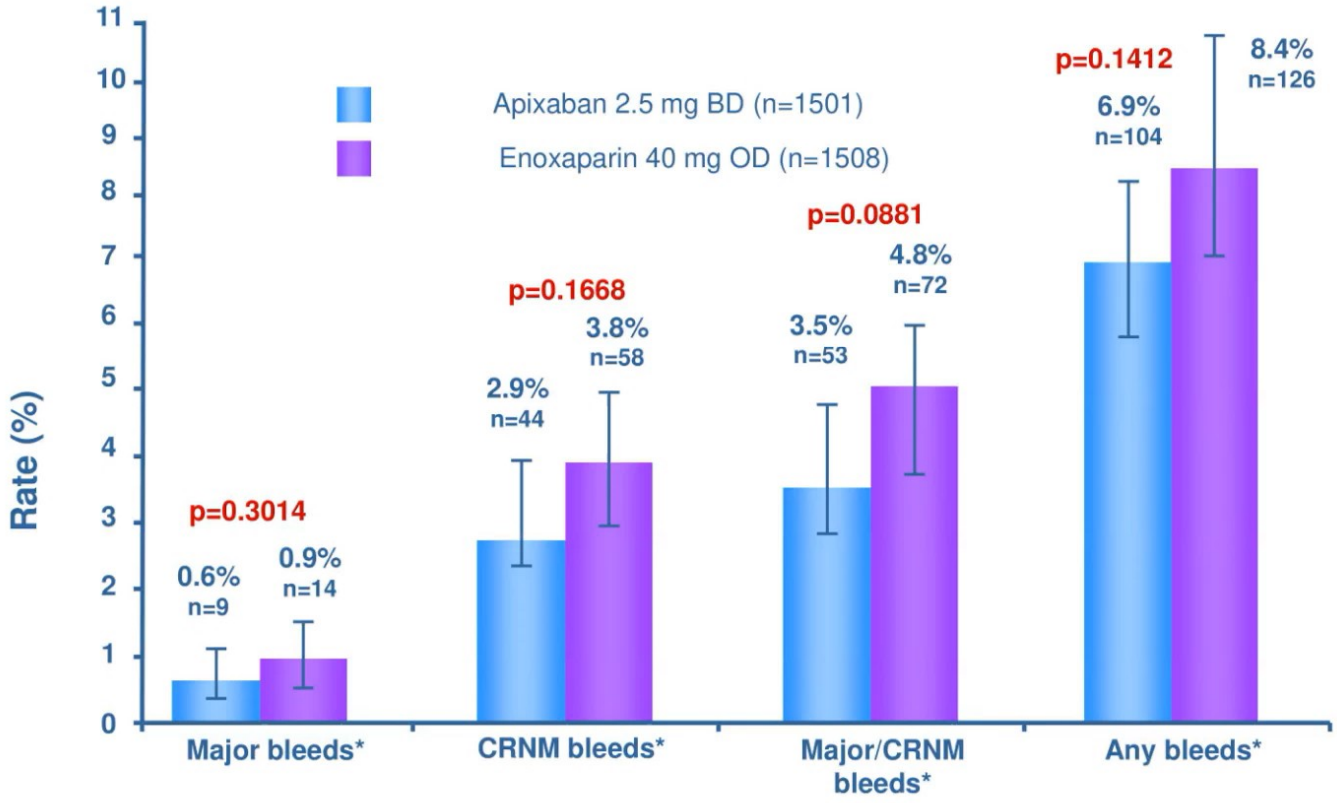



*Treatment period
n = no. of patients included in primary efficacy analysis

**RR: 0.62**
**(95% CI: 0.51–0.74)**
**p<0.0001 for non-inferiority and superiority**

Lassen et al. Lancet 201

# ADVANCE-2: In TKR, no increase in bleeding with apixaban 2.5 mg BD *vs* enoxaparin 40 mg OD



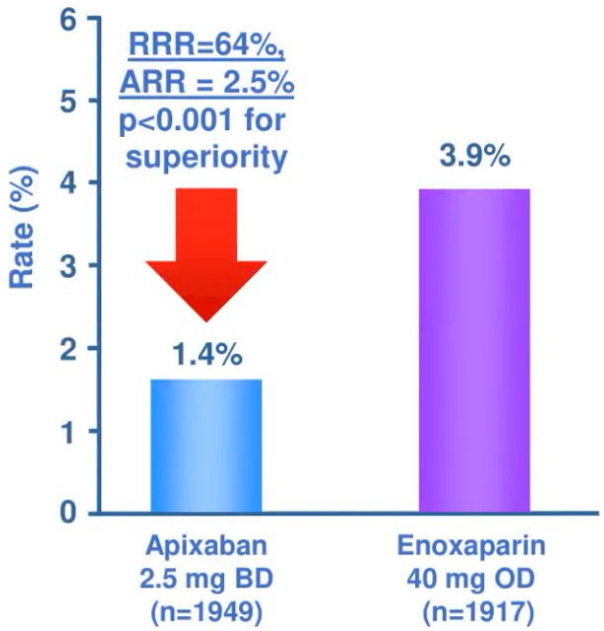

**There was no fatal bleed in either study group**

*Treatment period

Data from Lassen et al. Lancet 2

# ADVANCE-3: In THR, apixaban 2.5 mg BD superior to enoxaparin 40 mg OD for 32-38 days in reducing total VTE/all-cause death

## Primary efficacy outcome: Total VTE/all-cause death*

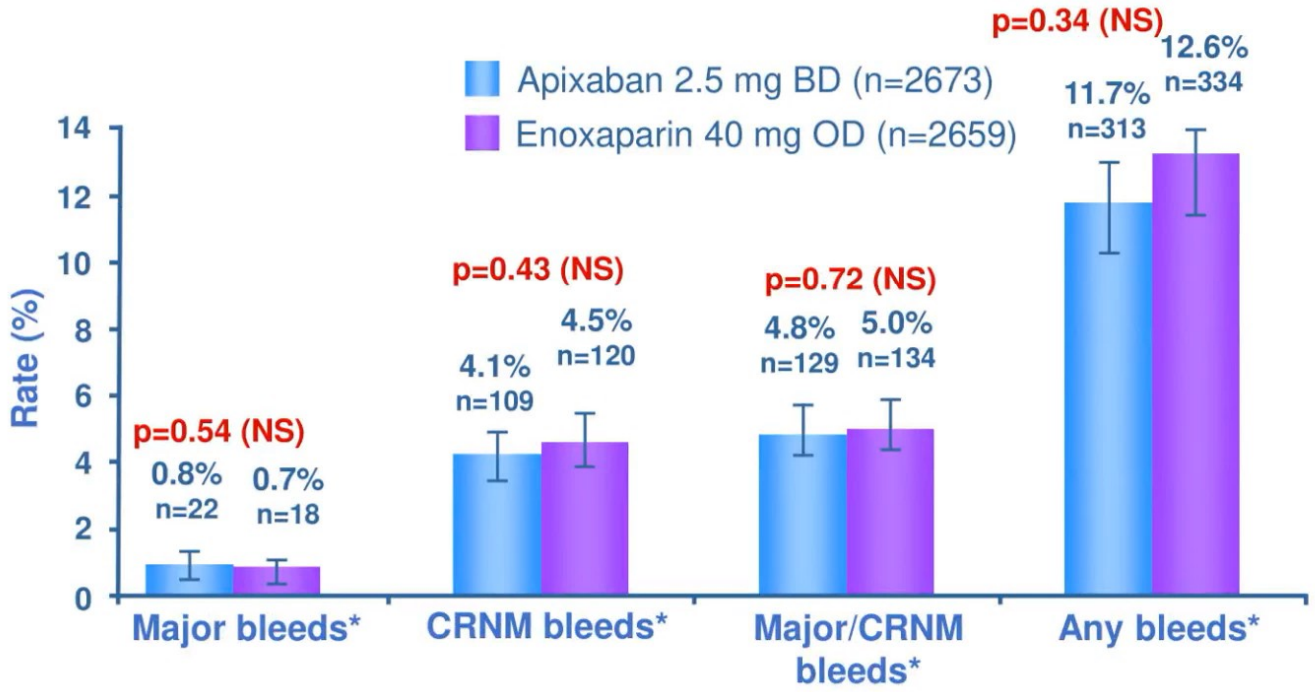



**RR: 0.36**
**(95% CI: 0.22–0.54)**
**p<0.001 (one sided for non-inferiority and two sided for superiority)**

*Treatment period
n = no. of patients included in primary efficacy analysis

Lassen et al. N Engl J Med 201

# ADVANCE-3: In THR, no increase in bleeding with apixaban 2.5 mg BD *vs.* enoxaparin 40 mg OD



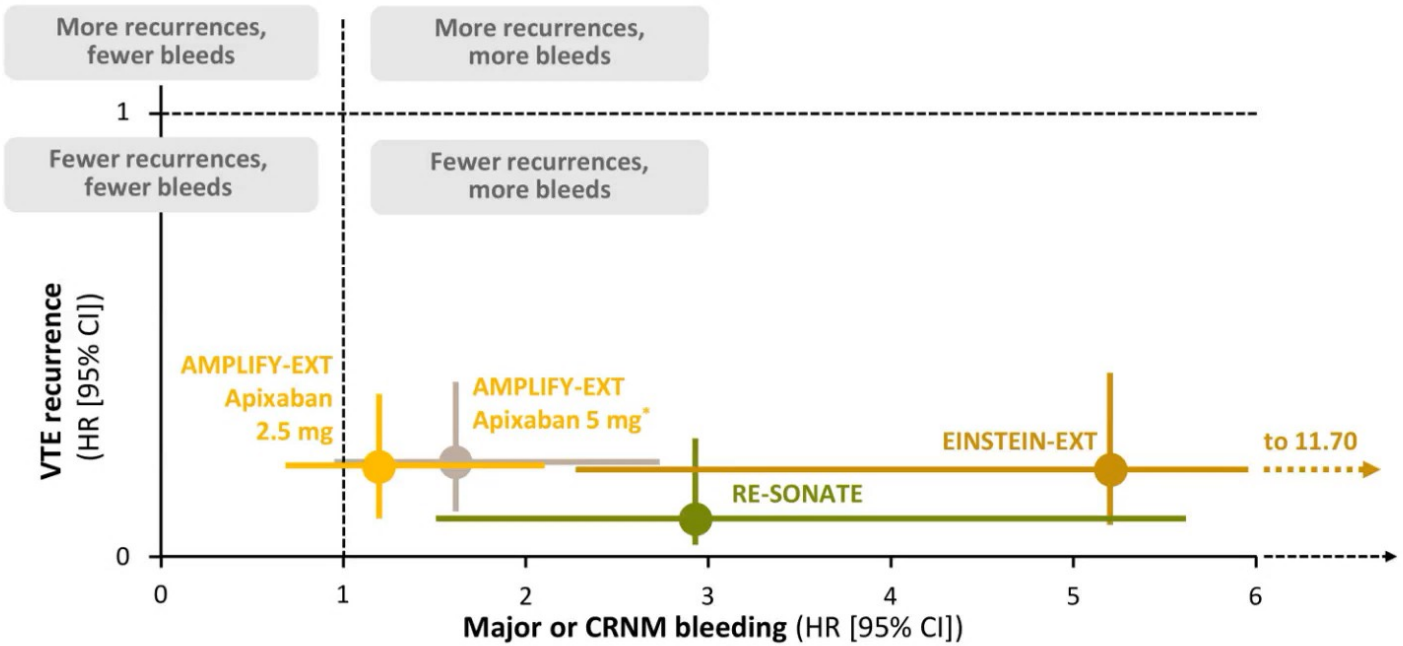

**There was no fatal bleed in either study group**

* Treatment period

NS: not statistically significant

Lassen et al. N Engl J Med 2

# Efficacy and safety of DOACs vs placebo in extended VTE treatment[1]




Head-to-head studies do not exist, therefore comparisons between agents cannot be made

*Only the 2.5 mg BID dose of apixaban is licensed for prevention of recurrent DVT/PE[2]


1. Cohen AT et al. Adv Ther 2
2. Apixaban SmPC. Available at http://www.

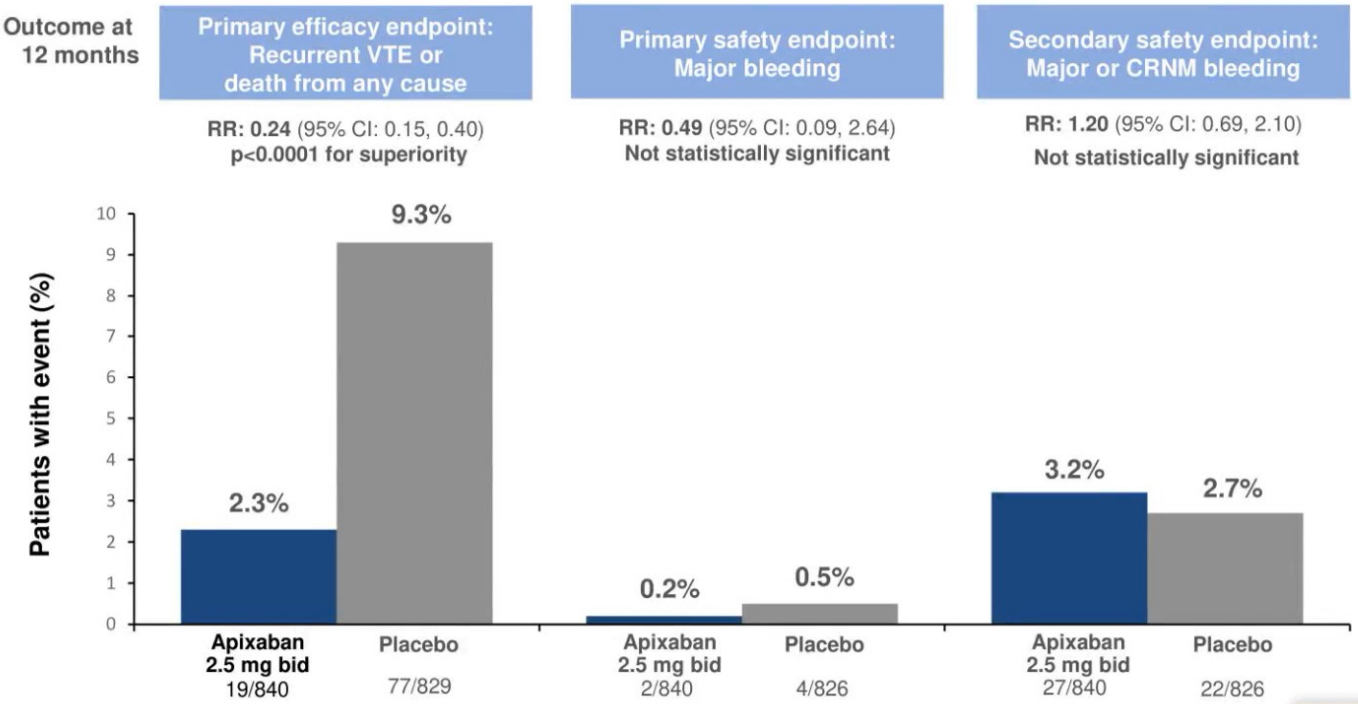

# AMPLIFY-EXT: Apixaban Efficacy and Bleeding Profile Versus Placebo

**Randomized, double-blind, placebo-controlled study**[1]

2,482 patients who had received 6–12 months of prior standard anticoagulant therapy or apixaban

**Apixaban 2.5 mg or 5 mg[a] bid versus placebo**

12-month treatment duration

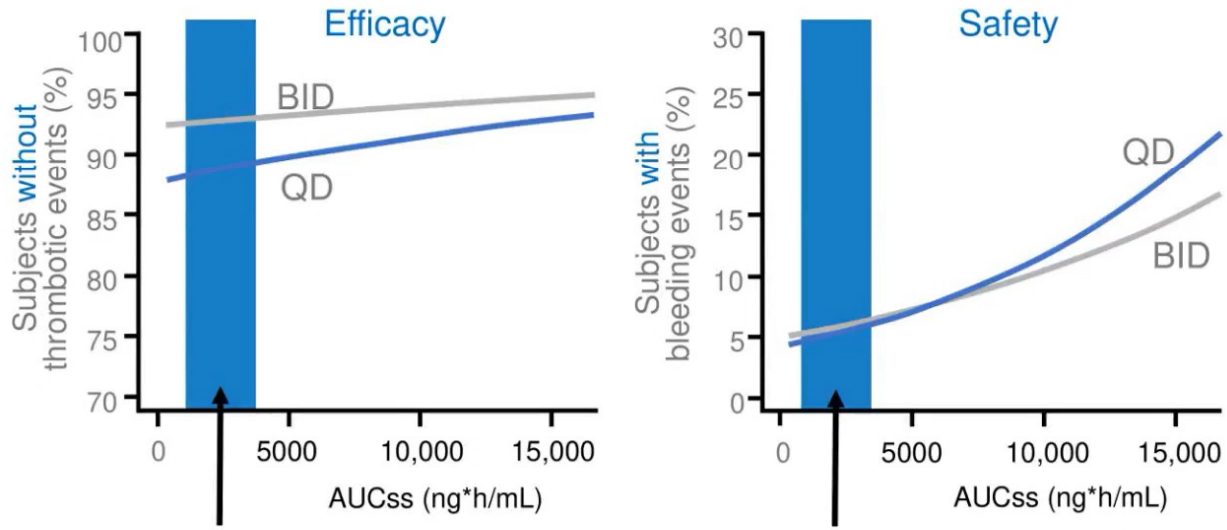



[a]Apixaban 5 mg bid is not a licensed dose for prevention of recurrent VTE. Results shown for apixaban arm are for licensed dose of apixaban 2.5 mg bid only.[2]
bid, twice daily; CI, confidence interval; RR, relative risk; VTE, venous thromboembolism.

1. Agnelli G, et al. *N Engl J Med.* 2013;368:699–708; 2. Pfizer Laboratories (Pty) Ltd. ELIQUIS® (apixaban) 2,5 mg and 5 mg Film-coated Tablets. Approved Package Insert – 1

# The choice of the apixaban BID dosing regimen is based on a clear rationale

**To maximise efficacy without increasing bleeding risk**




Exposure range (2.5th–97.5th percentile) for 2.5 mg BID dosing regimen

AUCss, area under the plasma concentration–time curve at steady state.

*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE in patients who have been treated for 6 months

Adapted from Feng Y, et al. Po
21st Congress of ISTH, July 20
Switzerland. Poster P-M-663

# Move on to Observational or RWE

## In essence, a clinical trial can tell us what a drug does, while RWE can provide the context that tells us whether what it does actually matters.[1]



RWE, real-world evidence. 1. PMLiVE. Get Real! The Rise of Observational Data In Healthcare. A
http://www.pmlive.com/pharma_intelligence/get_real!_the_rise_of_observational_data_in_healthcare_705710. Accessed Feb

# Limitations of R




**Too Few**
– number of patients exposed

**Too Median-Aged**
– very young and very old are rarely represented in clinical trials

**Too Simple**
– patients with complicated medical conditions or receiving concomitant drugs are usually excluded
– Frail, Complex, Pregnant

**Too Brief**
– relatively short duration of observation in chronic therapy

**Too Narrow Definitions & Outcomes**
– Definitions of disease: use for other related conditions for which the risk–benefit may be different (efficacy and safety in off-label users) e.g., no atypical VTE or distal DVT

– Outcomes are strict e.g., recurren
no MI, stroke, POAD; mortality

VTE, venous thromboembolism; DVT, deep vein thrombosis; MI, myocardial infarction; POAD, peripheral occlusive arteri

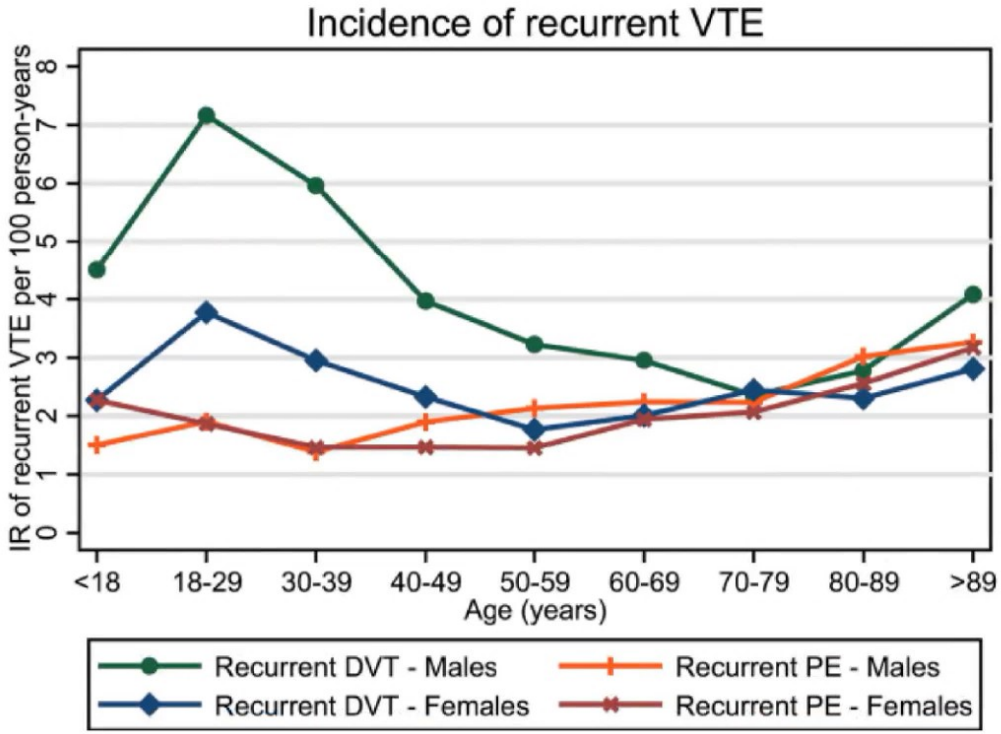
Speake

# Epidemiology examining disease burden and risk

- Smoking and Lung cancer
- Cholesterol and CVD
- Bimodal distribution of age and risk of recurrent VTE

VTE, venous thromboembolism; CVD, cardiovascul

# Incidence rates of DVT recurrence are highest in the young



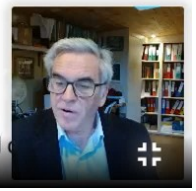

n=24,332

Martinez C, Cohen AT et al. Thromb Haem 2014;

# Comparative pharmacoepidemiology

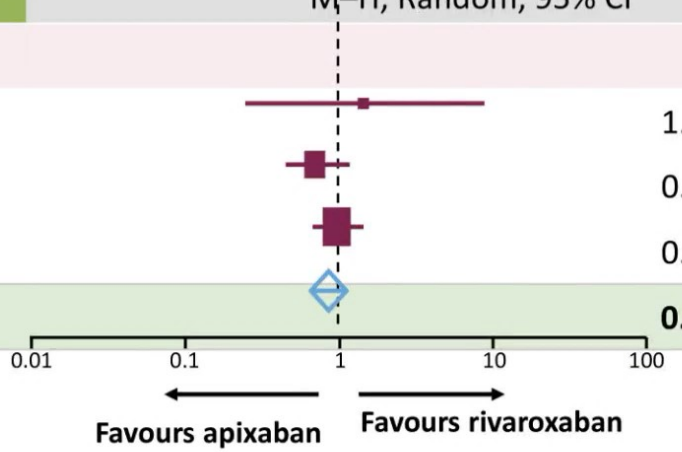
- Where there is insufficient data to allow conclusions
  - MA maintains randomisation
  - Large observational studies

- Where there are no head to head comparisons
  - NMA for RCT (observational)
  - Comparative pharmacoepidemiology
  - MA of comparative pharmacoepidemiology



# Aryal meta-analysis: Apixaban vs rivaroxaban for VTE in clinical practice Recurrent VTE outcomes

| Study | Events/Total Apixaban | Events/Total Rivaroxaban | Risk ratio M–H, Random, 95% CI |
|---|---|---|---|
| **Recurrent VTE** | | | |
| **Bott-Kitslaar 2018** | 3/302 | 2/298 | 1.48 (0.25–8.79) |
| **Dawwas 2019** | 20/3,091 | 108/12,163 | 0.73 (0.45–1.17) |
| **Sindet-Pedersen 2018** | 33/1,504 | 148/6,683 | 0.99 (0.68–1.44) |
| **Total** | **56/4,897** | **258/19,144** | **0.89** (0.67–1.19) |




**Head-to-head studies do not exist and direct comparisons between agents cannot be made**

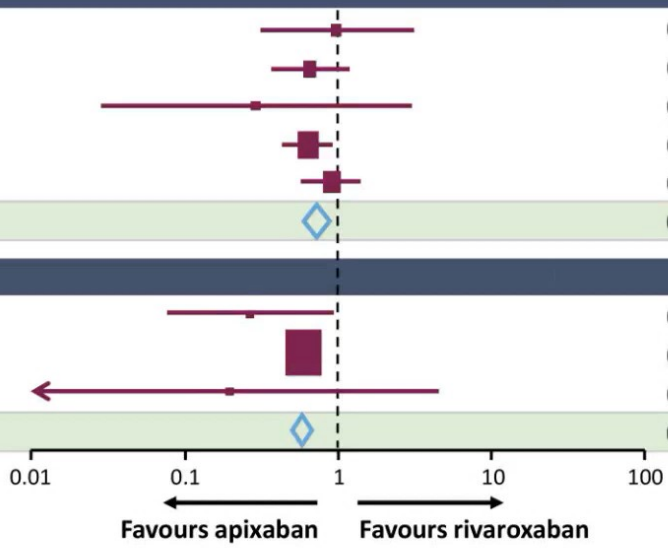
Heterogeneity: $Tau^2$=0.00; $Chi^2$=1.31, df=2 (p=0.52); $I^2$=0%. Test for overall effect: Z=0.76 (p=0.45).

M–H: Mantel–Haenszel.

Aryal MR, et al. *Blood Adv* 20

# Aryal meta-analysis: Apixaban vs rivaroxaban
# Bleeding outcomes

| Study | Events/Total Apixaban | Events/Total Rivaroxaban | Risk ratio M–H, Random, 95% CI |
|---|---|---|---|
| **Major bleeding** | | | |
| **Bott-Kitslaar 2018** | 6/302 | 6/298 | 0.99 (0.32–3.02) |
| **Dawwas 2019** | 14/3,091 | 84/12,163 | 0.66 (0.37–1.15) |
| **Howe 2018** | 1/24 | 2/14 | 0.29 (0.03–2.93) |
| **Lutsey 2019** | 38/6,638 | 132/14,751 | 0.64 (0.45–0.92) |
| **Sindet-Pedersen 2018** | 26/1,504 | 126/6,683 | 0.92 (0.60–1.39) |
| **Total** | **85/11,559** | **350/33,909** | **0.73** (0.58–0.93) |
| **CRNM bleeding** | | | |
| **Bott-Kitslaar 2018** | 3/302 | 11/298 | 0.27 (0.08–0.95) |
| **Dawwas 2019** | 166/3,091 | 1,082/12,163 | 0.60 (0.52–0.71) |
| **Howe 2018** | 0/24 | 1/14 | 0.20 (0.01–4.60) |
| **Total** | **169/3,417** | **1,094/12,475** | **0.59** (0.50–0.70) |




**Head-to-head studies do not exist and direct comparisons between agents cannot be made**

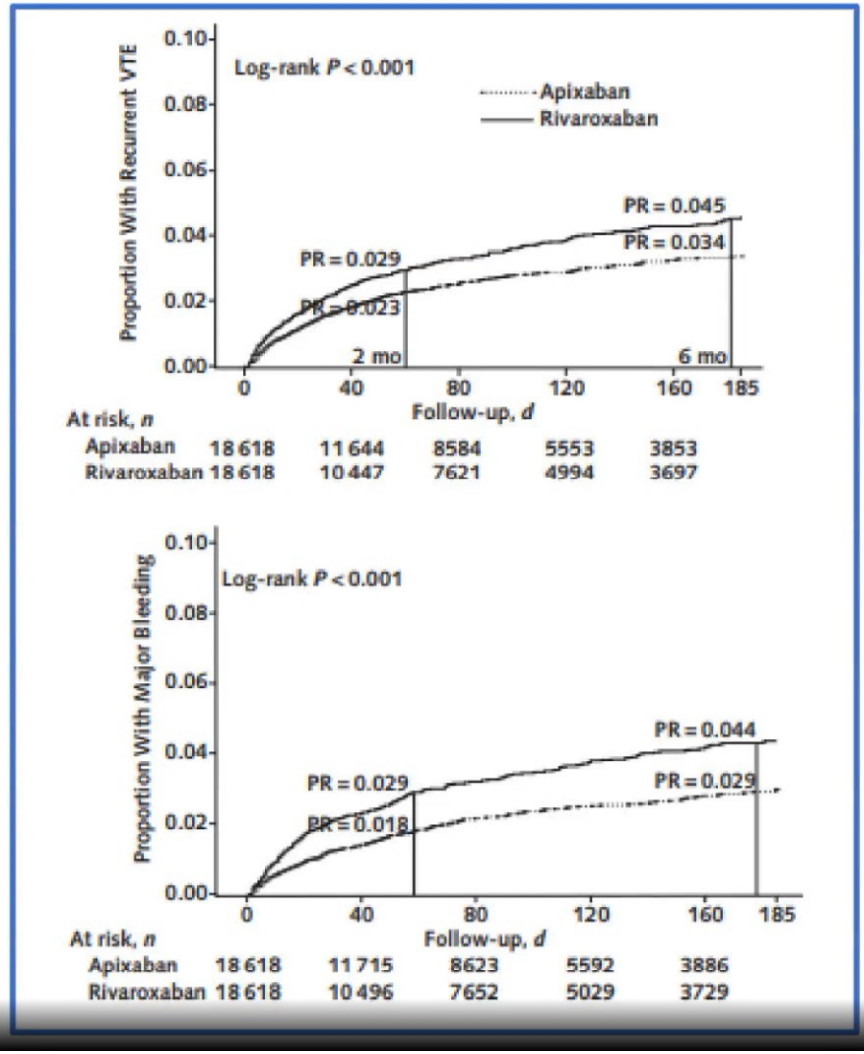
Major bleeding: Heterogeneity: $Tau^2$=0.00; $Chi^2$=2.68, df=4 (p=0.61); $I^2$=0%. Test for overall effect: Z=2.58 (p=0.010).

CRNM bleeding: Heterogeneity: $Tau^2$=0.00; $Chi^2$=2.00, df=2 (p=0.37); $I^2$=0%. Test for overall effect: Z=6.16 (p<0.00001).

Aryal MR, et al. *Blood Adv* 20

# Apixaban vs Rivaroxaban Risk for recurrent VTE and bleeding

## New users, commercial healthcare database

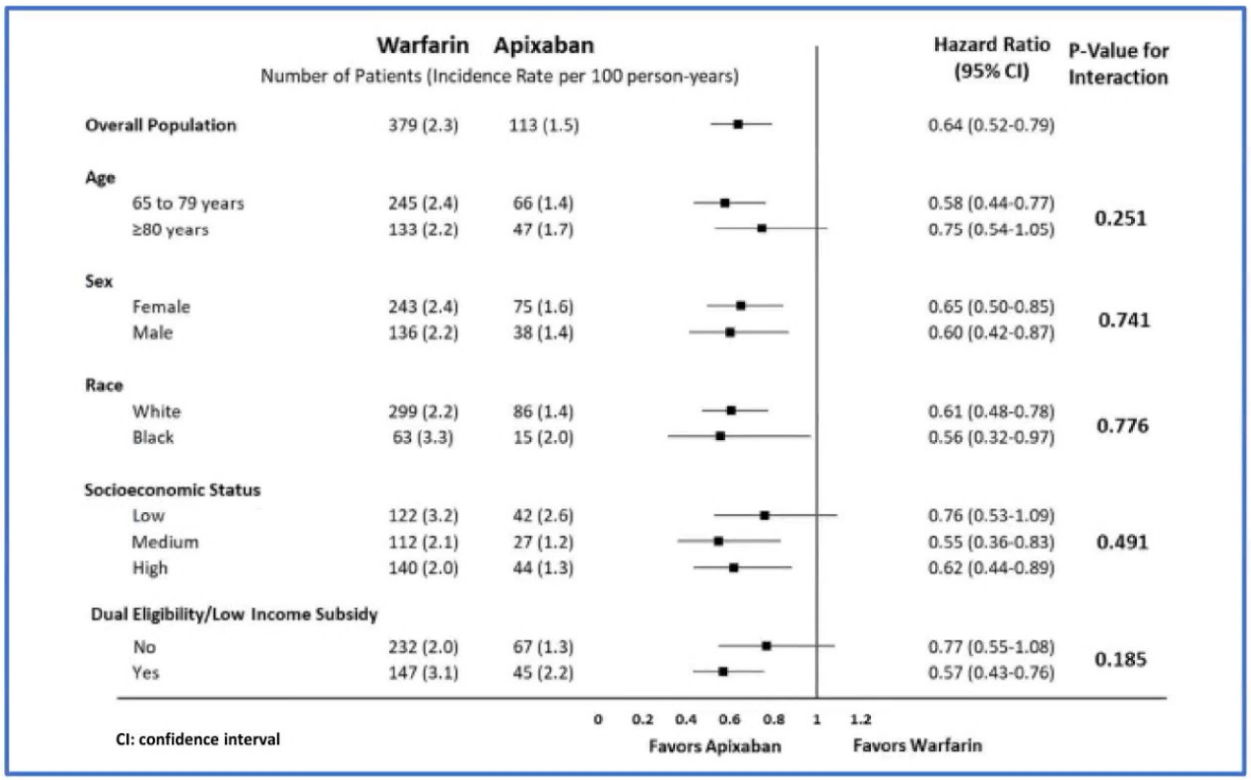



PR = probability;
VTE = venous thromboembolism

Disclaimer: Head-to-head studies do not exist and direct comparison agents cann

Dawwas GK
Ann Intern M

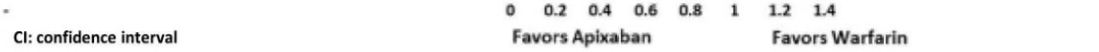
# Recurrent VTE among older patients with VTE stratified by demographic and socioeconomic factors (67,000+ patients with VTE)




Cohen A.T., e
Ther. Sept 20
Nov;38(11):3

# Major bleeding among older patients with VTE stratified by demographic and socioeconomic factors

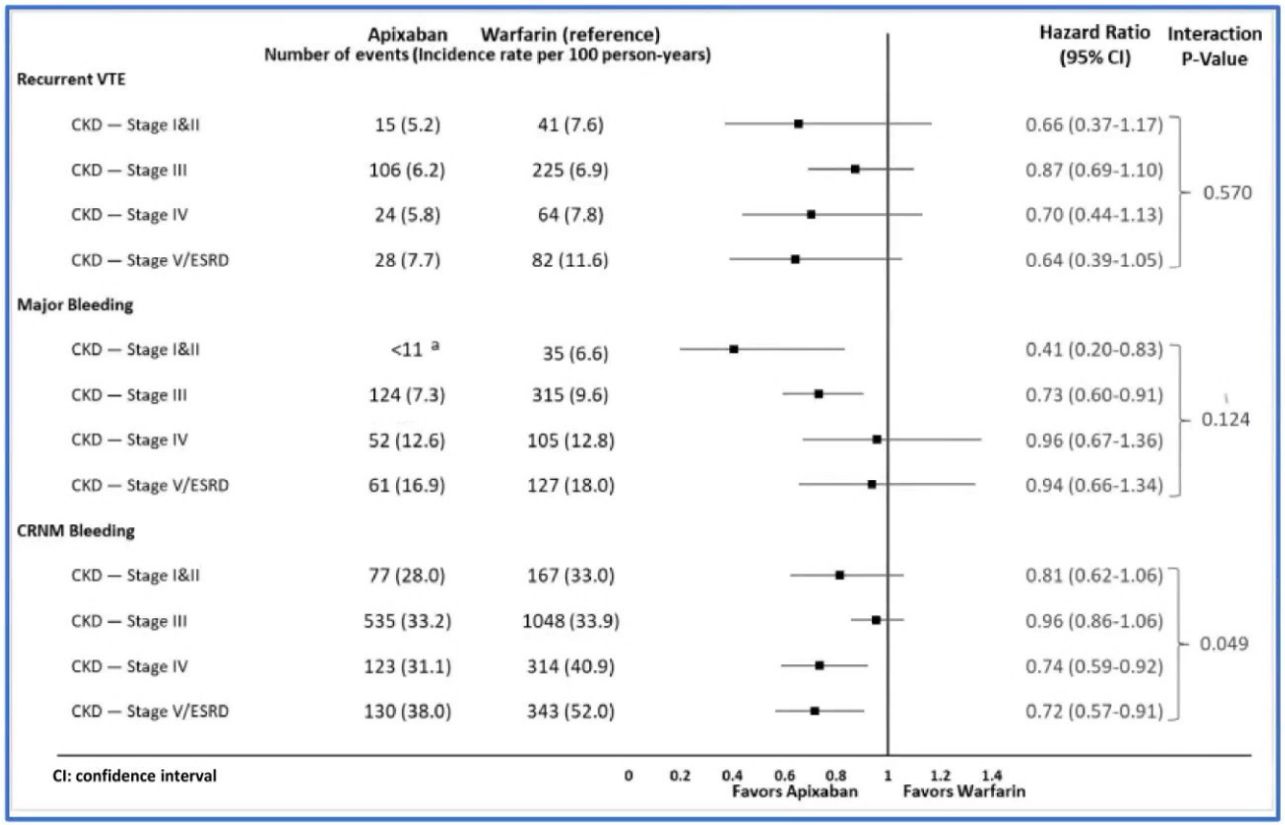
| | Warfarin Number of Patients | Apixaban (Incidence Rate per 100 person-years) | Hazard Ratio (95% CI) | P-Value for Interaction |
|---|---|---|---|---|
| **Overall Population** | 964 (5.9) | 290 (4.0) | 0.65 (0.57-0.75) | |
| **Age** | | | | |
| 65 to 79 years | 522 (5.0) | 145 (3.1) | 0.61 (0.50-0.74) | **0.257** |
| ≥80 years | 442 (7.4) | 145 (5.4) | 0.71 (0.59-0.86) | |
| **Sex** | | | | |
| Female | 656 (6.4) | 205 (4.5) | 0.66 (0.56-0.78) | **0.495** |
| Male | 309 (5.0) | 85 (3.1) | 0.60 (0.47-0.76) | |
| **Race** | | | | |
| White | 737 (5.3) | 215 (3.5) | 0.62 (0.53-0.72) | **0.548** |
| Black | 190 (10.1) | 56 (7.4) | 0.69 (0.51-0.93) | |
| **Socioeconomic Status** | | | | |
| Low | 264 (7.0) | 93 (5.7) | 0.77 (0.60-0.98) | |
| Medium | 324 (6.0) | 79 (3.5) | 0.56 (0.43-0.72) | **0.185** |
| High | 353 (5.1) | 109 (3.3) | 0.61 (0.49-0.77) | |
| **Dual Eligibility/Low Income Subsidy** | | | | |
| No | 556 (4.8) | 161 (3.1) | 0.67 (0.54-0.84) | |
| Yes | 408 (8.6) | 129 (6.3) | 0.63 (0.53-0.75) | **0.666** |




CI: confidence interval

Cohen A.T., 2021 Nov;3 5533

# Recurrent VTE, major bleeding, and clinically relevant non-major bleeding in 29,000+ chronic kidney disease on apixaban or warfarin, stratified by CKD stages

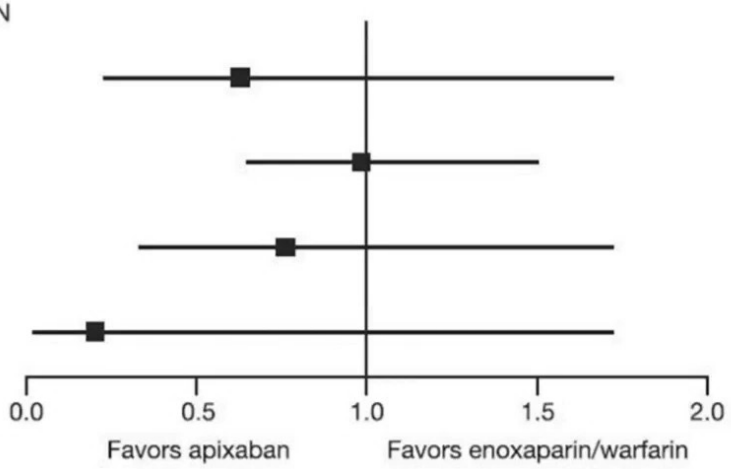



Ref: Coher
Thromb. H
Jun;122(6)

# AMPLIFY post-hoc analysis: Extremes of body weight Efficacy (recurrences) for apixaban vs enoxaparin/warfarin

**VTE or VTE-related death**

| Body weight category | Apixaban, n/N | Enoxaparin/ warfarin, n/N | RR (95% CI) | $P_{interaction}$ |
|---|---|---|---|---|
| ≤ 60 kg | 6/225 | 10/232 | 0.63 (0.23, 1.72) | 0.44 |
| > 60 to < 100 kg | 42/1870 | 43/1892 | 0.99 (0.65, 1.50) | |
| > 100 to < 120 kg | 10/368 | 13/366 | 0.77 (0.34, 1.72) | |
| > 120 kg | 1/141 | 5/142 | 0.20 (0.02, 1.72) | |



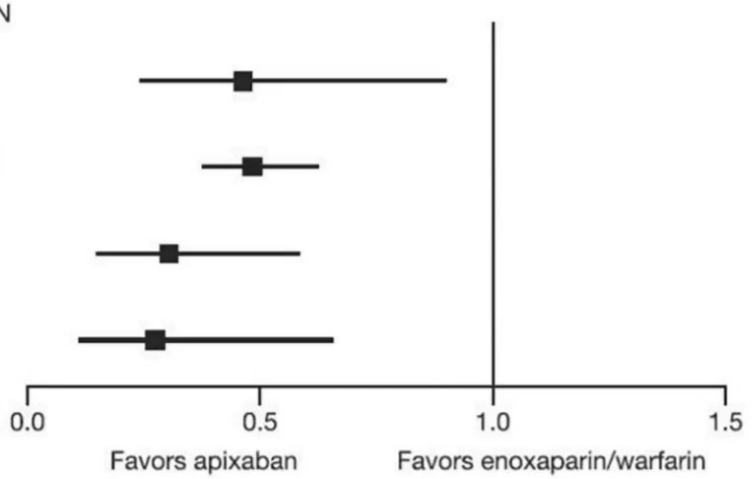

CI: confidence interval; RR: relative risk; VTE: venous thromboembolism

Cohen AT et al. Adv Ther. 2021 Jun;38(6):

# AMPLIFY post-hoc analysis: Extremes of body weight
# Major or CRNM bleeding for apixaban vs enoxaparin/warfarin

**Major or CRNM bleeding**

| Body weight category | Apixaban, n/N | Enoxaparin/ warfarin, n/N | RR (95% CI) | $P_{interaction}$ |
|---|---|---|---|---|
| ≤ 60 kg | 12/230 | 27/243 | 0.46 (0.24, 0.89) | 0.36 |
| > 60 to < 100 kg | 86/1920 | 176/1924 | 0.49 (0.38, 0.63) | |
| > 100 to < 120 kg | 11/377 | 36/372 | 0.30 (0.16, 0.58) | |
| > 120 kg | 6/144 | 22/146 | 0.28 (0.12, 0.66) | |




CI: confidence interval; CRNM: clinically relevant non-major; RR: relative risk

Cohen AT et al. Adv Ther. 2021 Jun;38(6):

# Risk of recurrences and bleeding among VTE patients stratified by obesity status in 155,000 patients analysed with IPTW and Cox regression

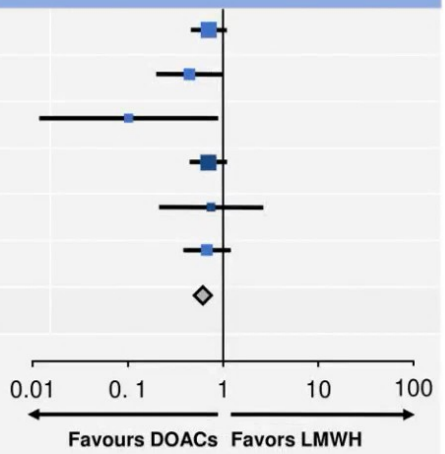
| | Warfarin No. of Events (IR) | Apixaban No. of Events (IR) | Hazard Ratio (95% CI) | P-Value for Interaction |
|---|---|---|---|---|
| **Recurrent VTE** | | | | |
| Non-Obese | 1422 (6.2) | 655 (4.6) | 0.72 (0.66—0.80) | |
| Obese/Non-Morbid | 308 (6.7) | 180 (5.7) | 0.83 (0.69—1.00) | **0.170** |
| Morbidly Obese | 350 (8.1) | 125 (5.3) | 0.63 (0.52—0.78) | |
| **Major Bleeding** | | | | |
| Non-Obese | 1315 (5.7) | 564 (4.0) | 0.68 (0.62—0.76) | |
| Obese/Non-Morbid | 287 (6.2) | 152 (4.8) | 0.76 (0.62—0.94) | **0.674** |
| Morbidly Obese | 271 (6.2) | 106 (4.5) | 0.70 (0.56—0.89) | |
| **CRNM Bleeding** | | | | |
| Non-Obese | 6630 (30.4) | 3522 (26.1) | 0.84 (0.80—0.88) | |
| Obese/Non-Morbid | 1384 (31.8) | 872 (29.2) | 0.90 (0.82—0.98) | **0.023** |
| Morbidly Obese | 1536 (38.3) | 649 (29.2) | 0.75 (0.68—0.83) | |


Cohen A.T. et al. J. Clin. Med. 08 Jan

# Cancer associated VTE
# Start with RCT

# Meta-analysis of DOACs for Ca-VTE: Recurrent Venous Thromboembolism

| Study or Subgroup | DOAC | | LMWH | | | Risk ratio | Risk ratio |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | Weight | M-H, random (95% CI) | M-H, random (95% CI) |
| HOKUSAI-VTE CANCER* | 34 | 522 | 46 | 524 | 33.5% | 0.74 [0.48, 1.14] | |
| SELECT-D | 8 | 203 | 18 | 203 | 9.3% | 0.44 [0.20, 1.00] | |
| ADAM VTE | 1 | 145 | 9 | 142 | 1.4% | 0.11 [0.01, 0.85] | |
| CARAVAGGIO | 32 | 576 | 46 | 579 | 32.0% | 0.70 [0.45, 1.08] | |
| CASTA-DIVA | 4 | 74 | 6 | 84 | 4.1% | 0.76 [0.22, 2.58] | |
| CANVAS* | 20 | 330 | 27 | 308 | 19.6% | 0.69 [0.40, 1.21] | |
| **Total (95% CI)** | | **1850** | | **1840** | **100.0%** | **0.67 [0.52, 0.85]** | |
| Total events | 99 | | 152 | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.36$, df = 5 (P= 0.50); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 3.22 (P=0.001) | | | | | | | |




**Risk of recurrence significantly lower with DOACs compared to LMWHs**

Ca-VTE, cancer-associated venous thromboembolism; CI, confidence interval; DOAC, direct-acting oral anticoagulant; LMWH, low molecular weight heparin; M-H, Mantel-Haenszel.

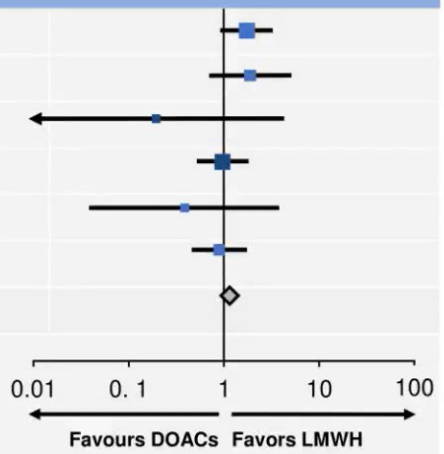
Frere C, et al. *J Hematol Oncol.* 2022;15(1):69.

*Edoxaban is not licenced in RSA

Adapted from Frere C, et al. J He

# Meta-analysis of DOACs for Ca-VTE: Major Bleeding

| Study or Subgroup | DOAC | | LMWH | | | Risk ratio | Risk ratio |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | Weight | M-H, random (95% CI) | M-H, random (95% CI) |
| HOKUSAI-VTE CANCER* | 29 | 522 | 17 | 524 | 29.2% | 1.71 [0.95, 3.08] | |
| SELECT-D | 11 | 203 | 6 | 203 | 12.2% | 1.83 [0.69, 4.86] | |
| ADAM VTE | 0 | 145 | 2 | 142 | 1.4% | 0.20 [0.01, 4.04] | |
| CARAVAGGIO | 22 | 576 | 23 | 579 | 30.3% | 0.96 [0.54, 1.71] | |
| CASTA-DIVA | 1 | 74 | 3 | 84 | 2.5% | 0.38 [0.04, 3.56] | |
| CANVAS* | 17 | 330 | 17 | 308 | 24.5% | 0.93 [0.49, 1.80] | |
| **Total (95% CI)** | | **1850** | | **1840** | **100.0%** | **1.71 [0.82, 1.67]** | |
| Total events | 99 | | 152 | | | | |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.66$, df = 5 (P= 0.34); $I^2 = 12\%$ | | | | | | | |
| Test for overall effect: Z = 0.85 (P=0.39) | | | | | | | |




**DOACs associated with a non-significant increase in the risk of major bleeding**

Ca-VTE, cancer-associated venous thromboembolism; CI, confidence interval; DOAC, direct-acting oral anticoagulant; LMWH, low molecular weight heparin; M-H, Mantel-Haenszel.

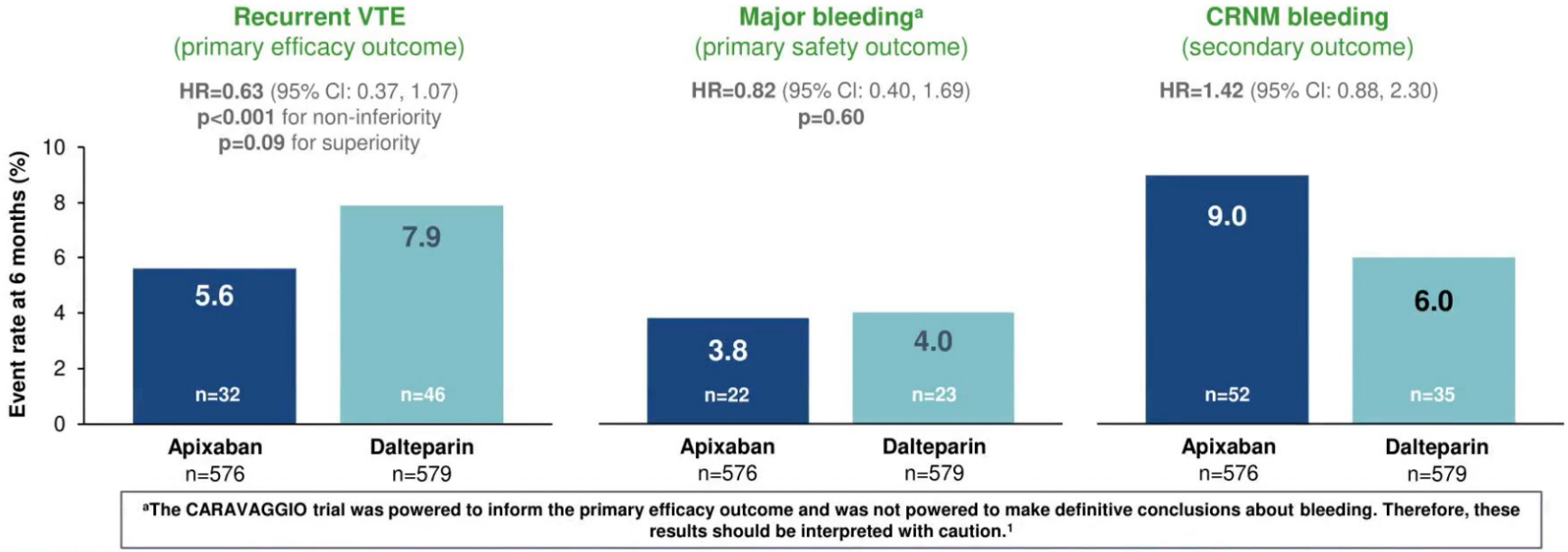
Frere C, et al. *J Hematol Oncol.* 2022;15(1):69.

*Edoxaban is not licenced in RSA

Adapted from Frere C, et al. J He

# CARAVAGGIO: Results

## Apixaban non-inferior to LMWH (dalteparin) for prevention of recurrent VTE in patients with cancer, no statistically significant increase in major bleeding[1]




[a]The CARAVAGGIO trial was powered to inform the primary efficacy outcome and was not powered to make definitive conclusions about bleeding. Therefore, these results should be interpreted with caution.[1]

**Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events. When apixaban is considered for DVT or PE treatment in patients with cancer, a careful assessment of the benefits against the risks should be made. Apixaban is contraindicated in patients with malignant neoplasms at high risk of bleeding.[2]**

576 patients received oral apixaban at a dose of 10 mg bid for first 7 days, followed by 5 mg bid.

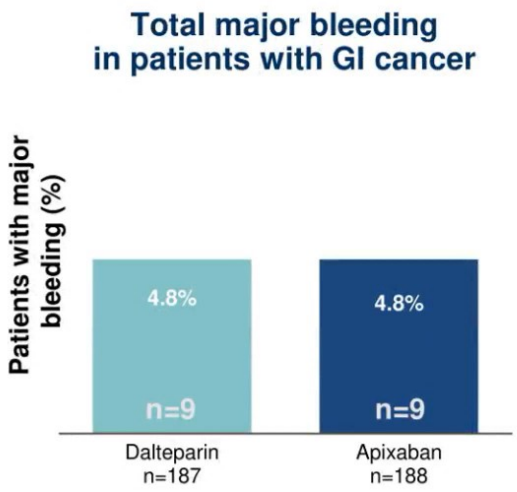
579 patients received SC dalteparin (at a dose of 200 IU per kg of body weight qd for first month, followed by 150 IU per kg qd)[1].

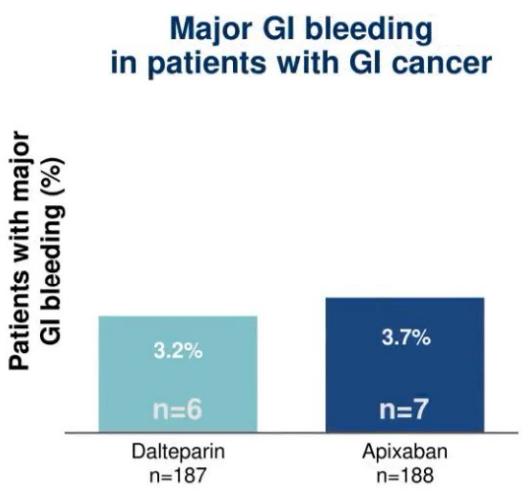
Adapted from A

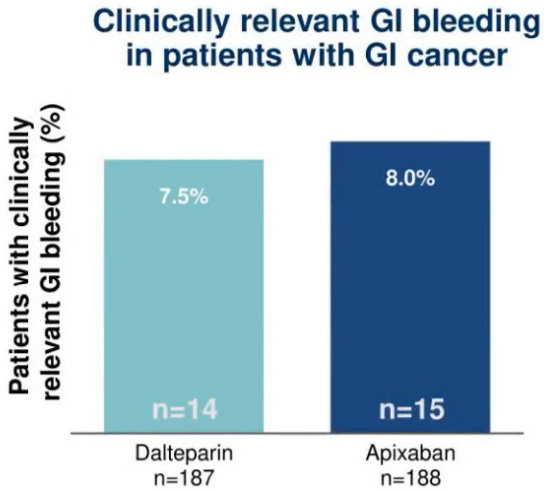
bid, twice daily; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; qd, once daily; SC, subcutaneous; UI, unit interval; VTE, venous thromboembolism.

1. Agnelli G, et al. *N Engl J Med.* 2020;382:1599–607; 2. Apixaban SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf. Update 23 June 2023 [Last accessed July 2023].

# CARAVAGGIO Subgroup Analysis: In Patients with GI Cancer,* Similar Rates of Bleeding With Apixaban vs LMWH (Dalteparin)†1




- 52 CRNM bleeding events occurred in Apixaban group vs 35 in Dalteparin group; this was mainly accounted for by events in genitourinary (20 vs 11, respectively) and upper airway (14 vs 7, respectively) tracts
- There were a total of 22 CRNM bleeding events in GI cancer patients treated with Apixaban vs 9 events for Dalteparin

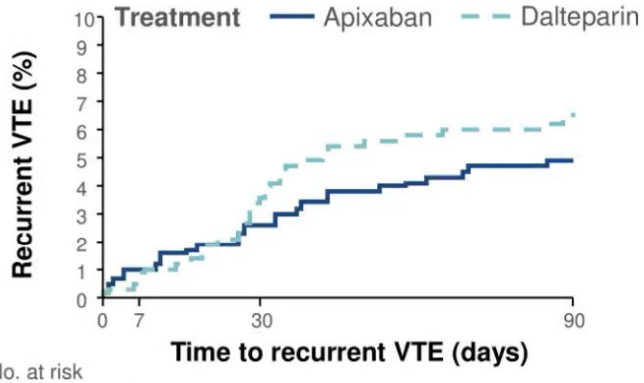
*Following cancer types considered GI cancer: upper GI, colorectal, pancreatic, or hepatobiliary. Figures in bars denote n/N.
†Study was not powered to make definitive conclusions about bleeding.[2]

CRNM, clinically relevant non-major; GI, gastrointestinal.

1. Ageno W, et al. *Thromb Haemost.* 2021;121:616-624; 2. Agnelli G, et al. *N Engl J Med.* 2020;382:1599-1607.

# CARAVAGGIO subgroup analysis: Early time course in patients with CaVTE

## Recurrent VTE



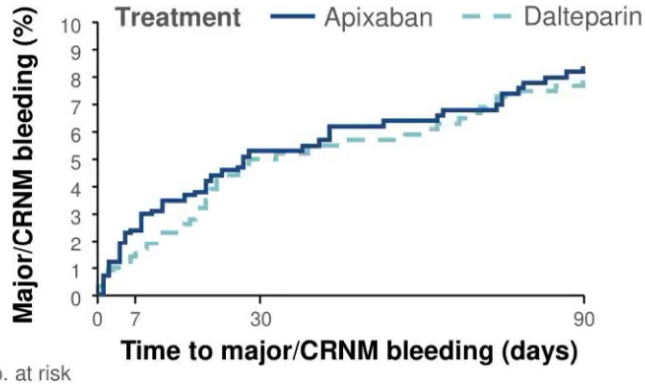

No. at risk

| | | | |
|---|---|---|---|
| Apixaban | 565 | 532 | 470 |
| Dalteparin | 568 | 522 | 453 |

| | Apixaban (n, %) | Dalteparin (n, %) | HR (95% CI) |
|---|---|---|---|
| **Day 7** | 6 (1.0) | 5 (0.9) | 1.22 (0.37, 3.98) |
| **Day 30** | 15 (2.6) | 20 (3.5) | 0.753 (0.39, 1.47) |
| **Day 90** | 27 (4.7) | 36 (6.2) | 0.75 (0.46, 1.23) |

**No significant increase in recurrent VTE at 7 days, 30 days, or 90 days for apixaban versus dalteparin**

## Major or CRNM bleeding




No. at risk

| | | | |
|---|---|---|---|
| Apixaban | 556 | 516 | 454 |
| Dalteparin | 562 | 513 | 452 |

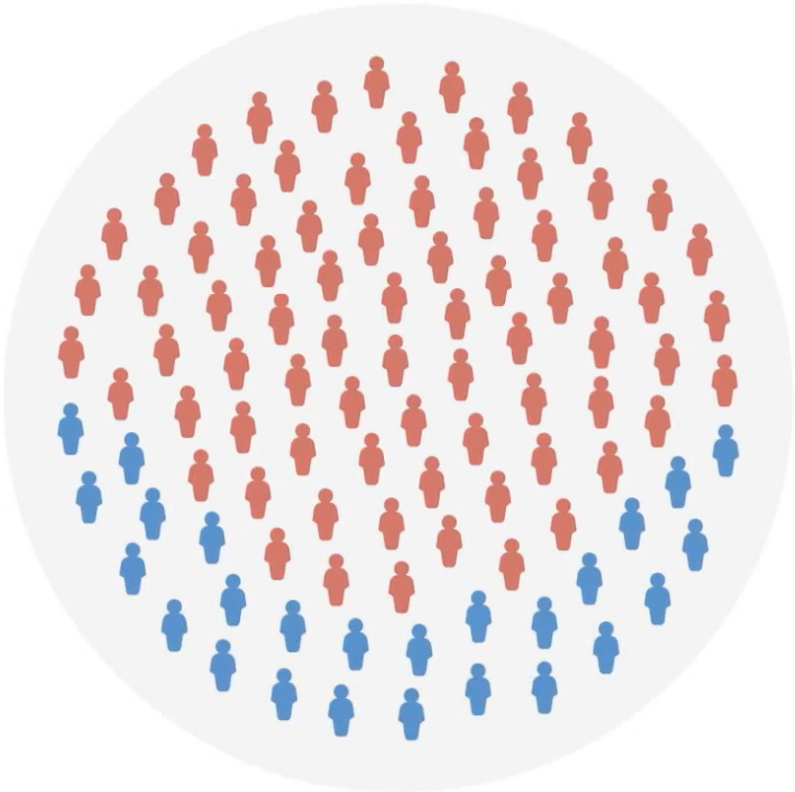
| | Apixaban (n, %) | Dalteparin (n, %) | RR (95% CI) |
|---|---|---|---|
| **Day 7** | 14 (2.4) | 10 (1.7) | 1.40 (0.63, 3.181) |
| **Day 30** | 30 (5.2) | 28 (4.8) | 1.08 (0.65, 1.78) |
| **Day 90** | 46 (8.0) | 43 (7.4) | 1.07 (0.72, 1.60) |

**No significant increase in major or CRNM bleeding at 7 days, 30 days, or 90 days for apixaban versus dalteparin**

CaVTE, cancer associated venous thromboembolism; CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio; RR, relative risk; VTE, venous thromboembolism.
Figures derived from Cohen AT, et al. Thromb Haemost. 2024 Jan 9. PMID: 38196077 2024

# CAT
# Move on to Observational or RWE

# Significant Proportion of VTE Occurs in Cancer Patients[1]



**20-30%**

Proportion of first VTE episodes that occur in patients with cancer

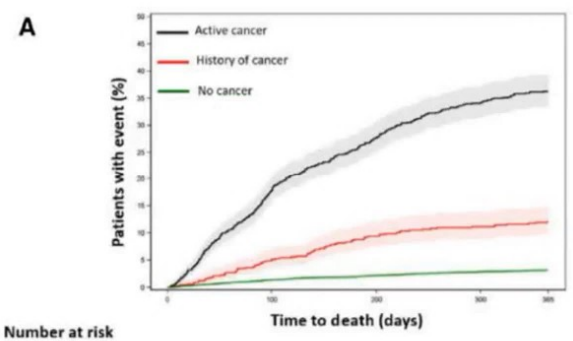
VTE, venous thrombo

1. Timp JF, et al. *Blood*. 2013;122(10):1

# GARFIELD-VTE registry: Rates of death, recurrent VTE and major bleeding are higher in patients with active cancer[1]

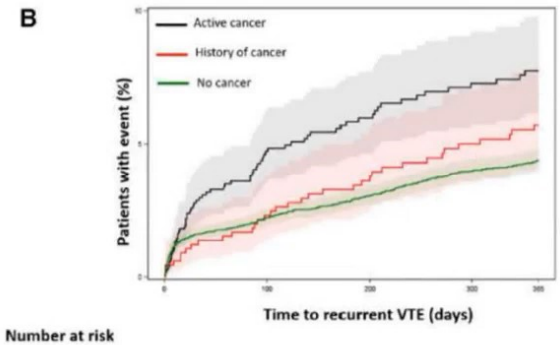
## Cumulative incidence curves for:

### All-cause mortality



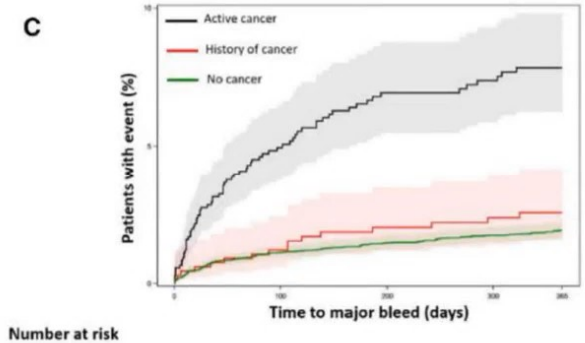

| Number at risk | | | | |
|---|---|---|---|---|
| Active cancer | 1075 | 849 | 715 | 643 |
| History of cancer | 674 | 627 | 578 | 563 |
| No cancer | 8935 | 8634 | 8266 | 8106 |

### Recurrent VTE




| Number at risk | | | | |
|---|---|---|---|---|
| Active cancer | 1075 | 812 | 681 | 606 |
| History of cancer | 674 | 613 | 558 | 536 |
| No cancer | 8935 | 8446 | 8019 | 7793 |

### Major bleeding




| Number at risk | | | | |
|---|---|---|---|---|
| Active cancer | 1075 | 818 | 683 | 615 |
| History of cancer | 674 | 622 | 571 | 555 |
| No cancer | 8935 | 8551 | 8166 | 7988 |

Rates of death, recurrent VTE, and major bleeding were higher in active cancer patients than in cancer-free patients, with hazard ratios (95% confidence intervals) of 14.2 (12.1–16.6), 1.6 (1.2–2.0) and 3.8 (2.9–5.0), respectively

Data are shown as percentage of patients with event and 95% confidence intervals

1. Weitz JI et al. J Thromb Thrombolysis 2020;50

# Three Available Risk Scores Modestly Predict Haemorrhage in Patients With Ca-VTE

| | |
|---|---|
| 1 | **HEMORR$_2$HAGES**<br>• HR 1.17%; 95% CI: 1.09 – 1.26<br>• *c*-statistic 0.57 |
| 2 | **HASBLED**<br>• HR 1.17%; 95% CI: 1.08 – 1.27<br>• *c*-statistic 0.56 |
| 3 | **VTE BLEED**<br>• HR 1.16*; 95% CI: 1.04 – 1.31<br>• *c*-statistic 0.56 |

**Conclusions**

- HEMORR2HAGES, HASBLED, and VTE BLEED risk prediction models have low predictability for bleeding in patients with Ca-VTE on anticoagulant therapy
- Risk models derived in patients with cancer are needed for accurate prediction of anticoagulant-related major bleed in cancer patients.

•Ca-VTE, cancer associated venous thromboembolism; CI, confidence interval; HR, hazard ratio.
•Sanfilippo K, et al. *Res Pract Thromb Haemost*. 2021;5(Suppl 2):Abstract OC 12.2.

# Risk of Bleeding in 15,794 Ca-VTE Subjects With 537 bleeds

**Independent predictors of significant bleeding included cancer of the:**


Bladder


Central nervous system


Cervix


Upper gastrointestinal tract


Kidney


Melanoma


Prostate

Ca-VTE, cancer-associated venous thromboembolism.

Cohen AT, et al. *Thromb Haemost.* 2024;124(4):324-336.

# Risk of Bleeding in 15,794 Ca-VTE Subjects With 537 bleeds (cont)

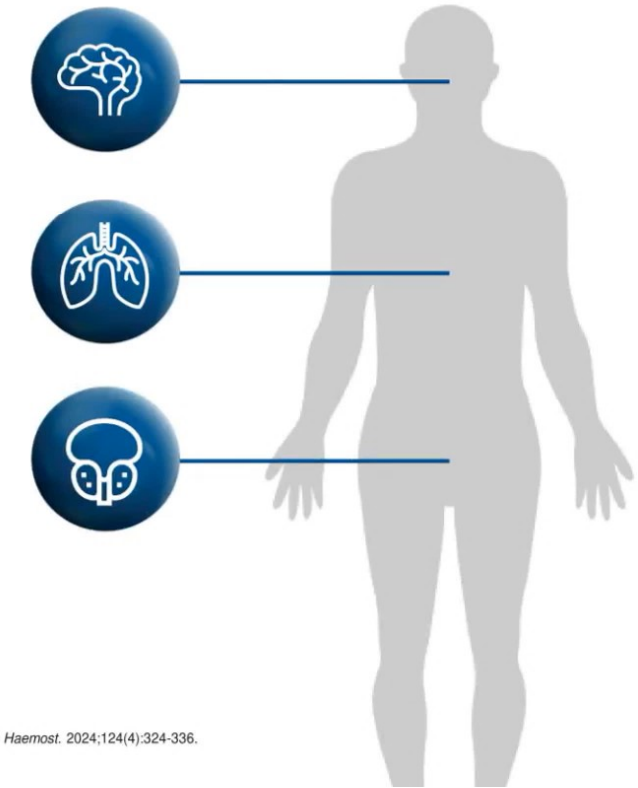
**Other independent predictors of significant bleeding :**

- Minor surgery
- Stroke
- Anemia
- History of major bleeding
- Metastases
- Minor trauma
- Gastroduodenal disease
- Coagulation disorder

Ca-VTE, cancer-associated venous thromboembolism.

Cohen AT, et al. *Thromb Haemost.* 2024;124(4):324-336.

# B-CAT Score Example



**B-CAT SCORE EXEMPLAR**

Male with prostate cancer (+1)
that has metastasized (+1)
= **2 points**

**MEDIUM RISK OF SIGNIFICANT BLEED**
in patients anticoagulated for venous thromboembolism with active cancer.

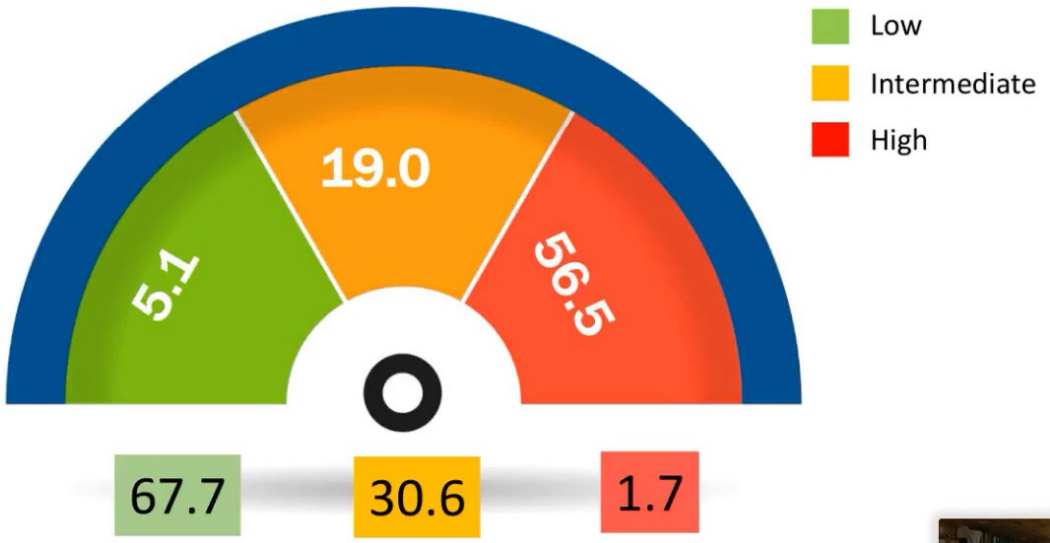
Cohen AT, et al. *Thromb Haemost*. 2024;124(4):324-336.

# Rate of Significant Bleeding in Ca-VTE in the 6 Months Post VTE Diagnosis

- 15,794 Ca-VTE Subjects With 537 significant bleeds
- 161 **major bleeds – IR 3.3**
- 376 **CRNMB-H – IR 7.7**
- 4914 person-years of observation

- **C-statistic:**
  - Significant bleeding: **0.70 (95%CI, 0.65-0.75)**

**6 Month Incidence Rate Signicant Bleeding events per 100 person-years**




- Ca-VTE, cancer-associated venous thromboembolism, CI, confidence interval; CRNMB-H, clinically-relevant non-major bleedingrequiring hospitalisation; IR, Incidence rate per 100 person-
- Cohen AT, et al. *Thromb Haemost*. 2024;124(4):324-336.

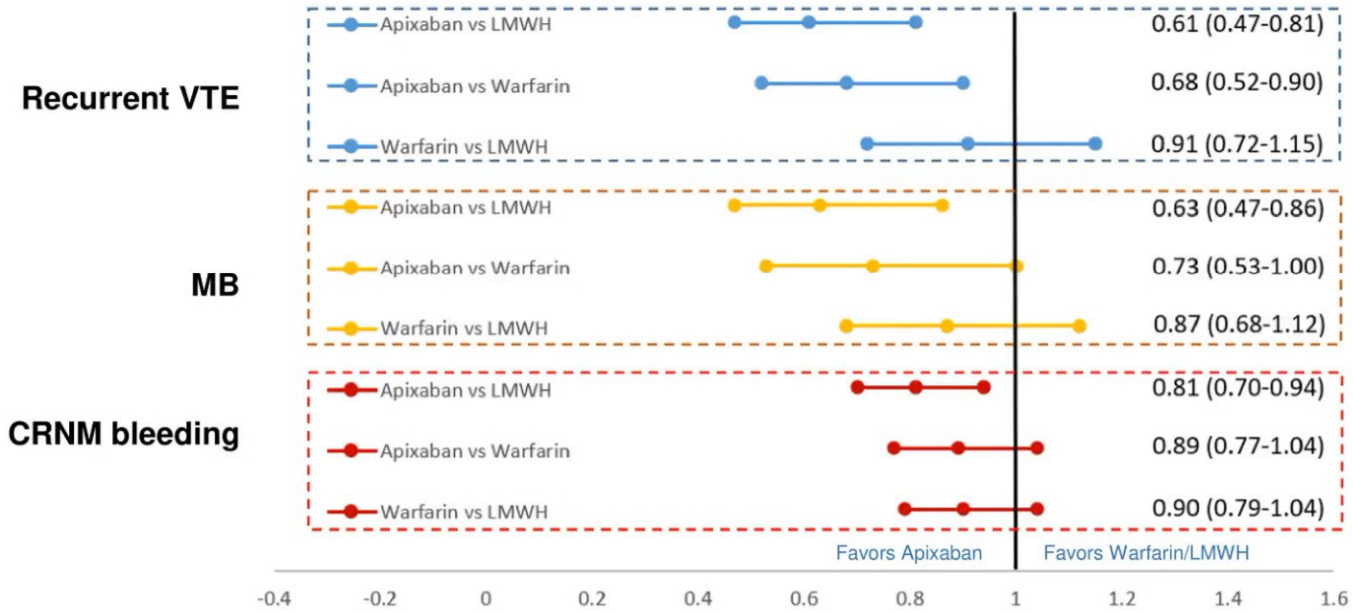
# Ca-VTE Real World Evidence: Study Population, Outcomes, and Comparison Groups

| | |
|---|---|
| **Patient population** | Patients diagnosed with VTE in setting of active cancer who newly initiated Apixaban, LMWH, or Warfarin were identified from four US commercial claims databases from 2014–2018 |
| **Primary outcomes** | Recurrent VTE, major bleeding, and CRNM bleeding |
| **Comparison groups** | Apixaban vs LMWH; Warfarin vs LMWH; Apixaban vs Warfarin |

Ca-VTE, cancer-associated venous thromboembolism; CRNM, clinically relevant non-major; DOAC, direct-acting oral anticoagulant; LMWH, low molecular weight heparin; US, United States; VTE, venous thromboembolism.

Cohen AT, et al. *Thromb Haemost.* 2021;121:383-395.

# Comparison of Recurrent VTE, Major Bleeding, and CRNM Bleeding in All Groups




**For patients with VTE and cancer, Apixaban was associated with lower risks of rVTE, MB, and CRNM bleeding when compared with LMWH.**

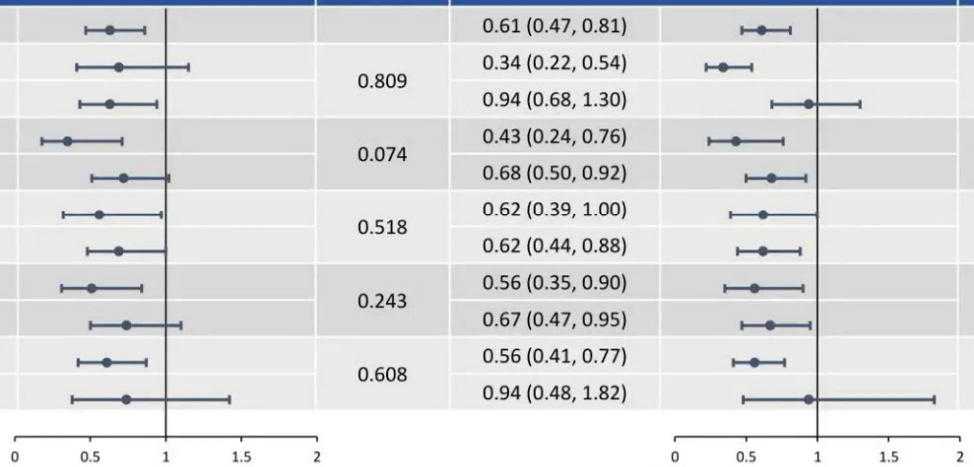
CRNM, clinically relevant non-major; LMWH, low molecular weight heparin; MB, major bleeding; rVTE, recurrent venous thromboembolism; VTE, venous thromboembolism.

Cohen A, et al. *Thromb Haemost.* 2021;121:383-395.

Adapted from Cohen A, et al. Thromb

# Hazard Ratios of Recurrent VTE and Major Bleeding Among VTE Cancer Patients

| Apixaban versus LMWH (ref) | | Major bleeding | | Recurrent VTE | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | p-value for interaction | Hazard ratio (95% CI) | p-value for interaction |
| Overall population | | 0.63 (0.47, 0.86) | | 0.61 (0.47, 0.81) | |
| Metastatic diagnosis | No | 0.69 (0.41, 1.15) | 0.809 | 0.34 (0.22, 0.54) | < 0.001 |
| | Yes | 0.63 (0.43, 0.94) | | 0.94 (0.68, 1.30) | |
| Cancer treatment | No | 0.35 (0.18, 0.71) | 0.074 | 0.43 (0.24, 0.76) | 0.161 |
| | Yes | 0.72 (0.51, 1.02) | | 0.68 (0.50, 0.92) | |
| Chemotherapy | No | 0.56 (0.32, 0.97) | 0.518 | 0.62 (0.39, 1.00) | 0.990 |
| | Yes | 0.69 (0.48, 1.00) | | 0.62 (0.44, 0.88) | |
| VTE event type | PE with/without DVT | 0.51 (0.31, 0.84) | 0.243 | 0.56 (0.35, 0.90) | 0.559 |
| | DVT only | 0.74 (0.50, 1.10) | | 0.67 (0.47, 0.95) | |
| Gastrointestinal cancer | No | 0.61 (0.42, 0.87) | 0.608 | 0.56 (0.41, 0.77) | 0.173 |
| | Yes | 0.74 (0.38, 1.42) | | 0.94 (0.48, 1.82) | |



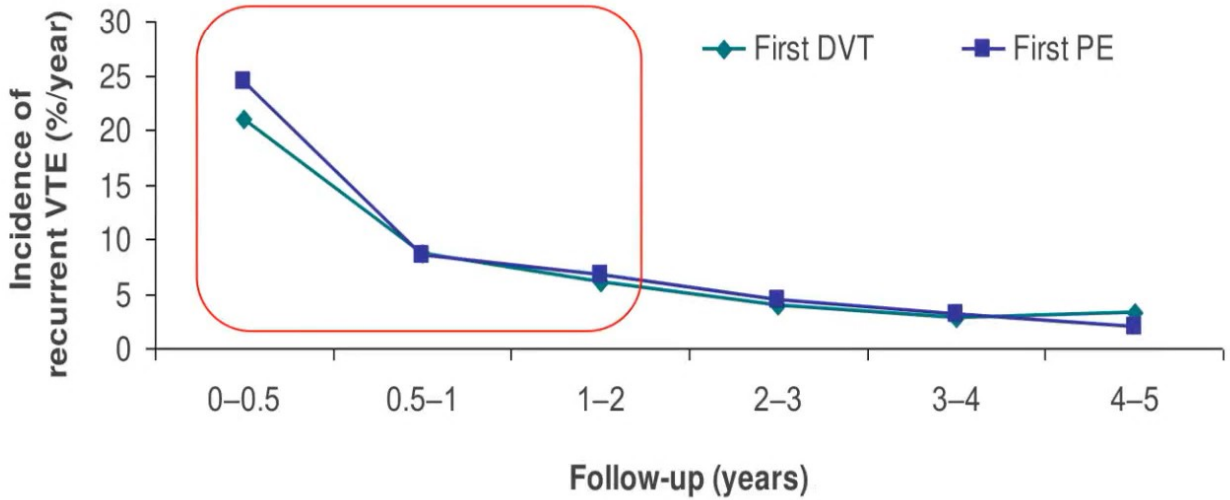

- In the overall population, apixaban had a lower risk of recurrent VTE and MB versus LMWH
- There was a significant interaction in cancer treatment strata: apixaban trended towards a lower risk of MB versus LMWH with or without cancer treatment; however, patients without cancer treatment had a larger difference versus patients with cancer treatment
- A significant interaction was observed in metastatic diagnosis strata: apixaban had a lower risk of recurrent VTE versus LMWH in patients without a metastatic diagnosis whereas apixaban had similar risk of recurrent VTE versus LMWH in patients with a metastatic diagnosis

CI, confidence interval; DVT, deep vein thrombosis; IPTW, inverse probability treatment weighting; LMWH, low-molecular-weight heparin; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembol

Cohen AT, et al. *Curr Med Res Opin*

# Recurrent VTE by Type of Event

- IR of VTE recurrence: 9.6 (95% CI: 8.8, 10.4) per 100 person-years
- Peak recurrence in first 6 months




- Cohen AT, et al. *Thromb Haemost* 2017;117:57-65.

# Ongoing Trials: Which Patients, What Dose, and for How Long?

## EVE[1]

370 DVT/PE patients with active cancer who have completed 6–12 months of anticoagulant treatment

**Aim**: to compare the safety of two doses of Apixaban for the extended treatment of patients with Ca-VTE


**Primary endpoint**: **composite of major, fatal plus CRNM bleeding**
**Secondary endpoint**: VTE recurrence

**Results presented at ISTH 2023**

## API-CAT[2]

1,722 DVT/PE patients with active cancer who have completed ≥6 months of anticoagulant treatment

**Aim**: to compare the efficacy of two doses of Apixaban for the extended treatment of patients with Ca-VTE


**Primary endpoint**: **composite of recurrent VTE or death due to PE**
**Secondary endpoints***: major and CRNM bleeding; VTE recurrence; VTE related-death; all-cause death

**Estimated study completion date: Jan 2024**

*Other secondary endpoints: adjudicated major bleeding, adjudicated composite of recurrent symptomatic VTE, VTE-related death, all-cause death, adjudicated major bleeding.
BID, twice daily.

Ca-VTE, cancer-associated venous thromboembolism; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

1. McBane RD 2nd, et al. *Eur J Haematol.* 2020;104:88-96; 2. API-CAT. Available at: https://clinicaltrials.gov/ct2/show/NCT03692065 [Last accessed Mar 2023].

# Extending VTE Secondary Prevention With Apixaban in Cancer Patients: The EVE Trial

## EVE

360 DVT/PE patients with active cancer who have completed 6–12 months of anticoagulant treatment

**Aim**: to compare the safety of two doses of apixaban for the extended treatment of patients with Ca-VTE


**Primary endpoint**: **composite of major, fatal plus CRNM bleeding.**
**Secondary endpoint**: VTE recurrence.

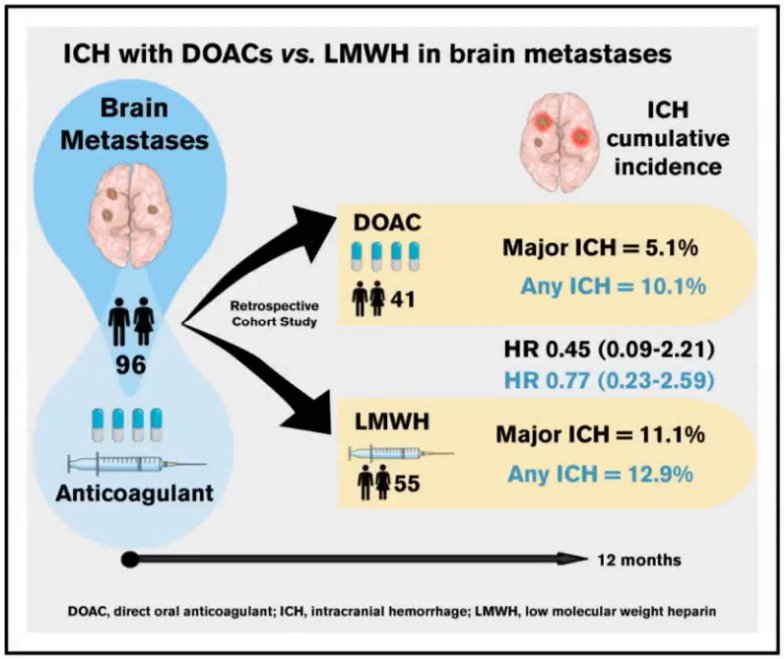
| Major and CRNM bleeding | Recurrent VTE or AT |
|---|---|
| 8.9% vs 12.2% | 5.0% vs 4.4% |
| HR = 0.72; 95% CI, 0.38-1.37; P = .39 | HR = 1.0; 95% CI, 0.40-2.53; P = 1.00 |

Apixaban 2.5 mg BID  Apixaban 5 mg BID

AT, arterial thrombosis; BID, twice daily. Ca-VTE, cancer-associated venous thromboembolism; CRNM, clinically relevant non-major; CII, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; R, randomizaton VTE, venous thromboembolism.

McBane RD 2nd, et al. *J Thromb Haemost.* S1538-7836(24)00169-7 [Epub ahead of print].

# Intracranial hemorrhage with direct oral anticoagulants in patients with brain metastases




DOAC, direct oral anticoagulant; HR, hazard ratio; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin.
Leader A, *et al. Blood Adv*. 2020;4:6291–6297.

# Observational Data in Brain Cancer: Apixaban Associated with a Lower Risk of rVTE, MB, and CRNMB.

## 30,586 active cancer patients, 5% with brain cancer

Active cancer patients starting apixaban, LMWH, or warfarin within 30 days of VTE diagnosis

4 US commercial and Medicare databases, IPTW for balancing patient characteristics, Cox proportional hazards models for outcome evaluation

Lower risk of rVTE, MB, and CRNMB with apixaban *vs* LMWH and warfarin

No significant difference between brain and other cancer patients, except for higher reduction of MB in brain cancer patients with apixaban (p=0.091, HR=0.32 *vs* HR=0.72)

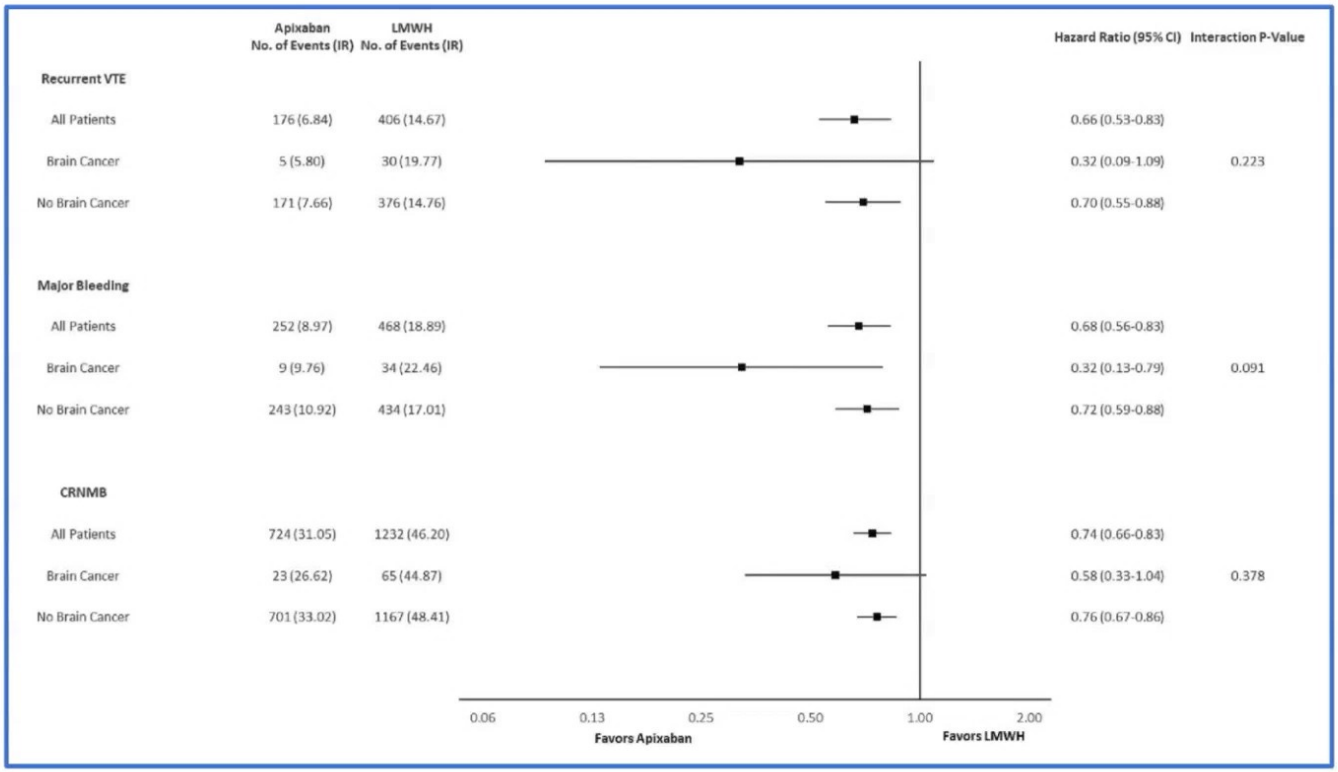
Apixaban associated with lower risk of rVTE, MB, and CRNMB across all types of cancer

Anticoagulant treatment effects were not significantly different between VTE patients with brain cancer and those with other cancer

CRNMB, clinically relevant non-major bleeding; IPTW, inverse probability treatment weighting; LMWH, low-molecular-weight heparin; MB, major bleeding; rVTE, recurrent venous thromboembolism; VTE, venous thromboembolism.

Cohen A, *et al. Thromb Res*. 2023;226:117-126.

# Risk of Recurrences and Bleeding Among 1,516 Patients with Brain Cancer and VTE Analysed with IPTW and Cox Regression

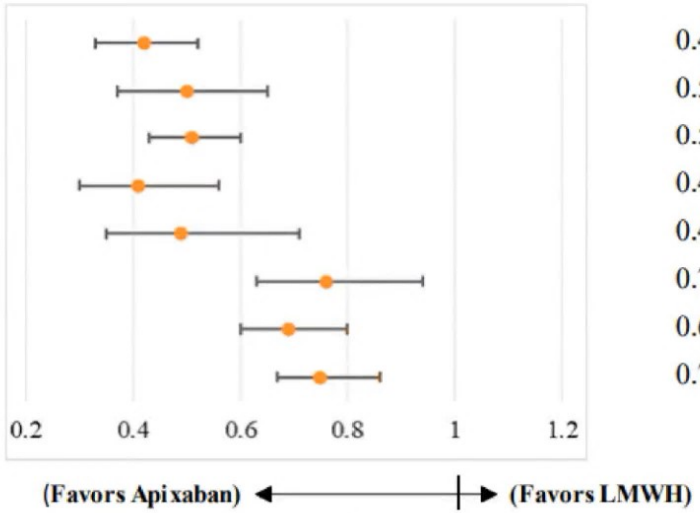



CI, confidence interval; CRNMB, clinically relevant non-major bleeding; HR, hazard ratio; IPTW, inverse probability treatment weighting; IR, incidence rate; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

Cohen A, *et al. Thromb Res.* 2023;226:117–126.

# Clinical Outcomes in Patients with Active Cancer and VTE with Extended Treatment ≥3 Months with Apixaban or LMWH[1,2]

| Outcome | Number of Events (IR per 100 person-years) | | HR (LCI-UCI) | *P*-value |
|---|---|---|---|---|
| | Apixaban n=13,564 | LMWH n=2,808 | | |
| **Recurrent VTE** | 275 (4.1) | 111 (9.6) | 0.42 (0.34-0.53) | <0.0001 |
| **Overall Major bleeding** | 418 (6.3) | 140 (12.6) | 0.50 (0.41-0.61) | <0.0001 |
| GI bleeding | 169 (2.5) | 56 (4.8) | 0.51 (0.38-0.69) | <0.0001 |
| Intracranial hemorrhage | 77 (1.1) | 31 (2.7) | 0.41 (0.27-0.63) | <0.0001 |
| Other major bleeding | 212 (3.2) | 76 (6.6) | 0.49 (0.38-0.64) | <0.0001 |
| **Overall CRNM bleeding** | 1581 (26.1) | 351 (36.0) | 0.76 (0.68-0.85) | <0.0001 |
| GI bleeding | 474 (7.2) | 118 (10.7) | 0.69 (0.56-0.84) | 0.0003 |
| Other CRNM bleeding | 1225 (19.7) | 282 (27.1) | 0.75 (0.66-0.85) | <0.0001 |




CRNM, clinically relevant non-major; GI, gastrointestinal; HR, hazard ratio; IR, incidence rate; LCI-UCI, lower confidence interval-upper confidence interval; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

1. Cohen AT *et al. JNCCN*. Accepted 2024; 2. Abstract presented at ESC 2023 Congress, August 2023.

# Conclusions at the end

- DOACs are the treatment of choice for patients with VTE
- DOACs have different safety profiles
- Apixaban has a strong comparative safety profile for
  - The acute and long-term and extended treatment of VTE
  - The management of high-risk patients
  - The treatment of cancer associated VTE (CAT) and extended treatment of CAT
- More studies are needed in many areas such as chronic liver disease, thrombocytopoenia, dosing and extended therapy.

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