Cobrra and Managing complex patients with insights from RCTs and RWE

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VTE and Stroke prevention in high-risk subpopulations of patients with non-valvular atrial fibrillation

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PP-ELI-GLB-1130 | February 2026
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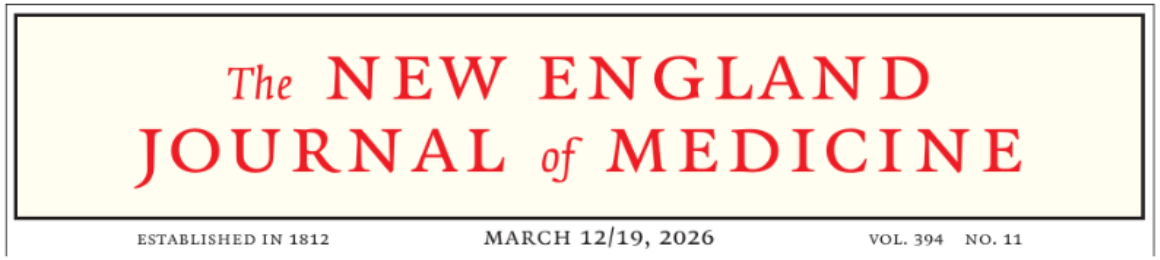
COBRRA:
Bleeding risk with apixaban vs. rivaroxaban in acute venous thromboembolism[1]



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 12/19, 2026 VOL. 394 NO. 11

Bleeding Risk with Apixaban vs. Rivaroxaban in Acute Venous Thromboembolism

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1. Castellucci LA, *et* al. NEJM 2026;394(11):1051–1060.

Audience poll

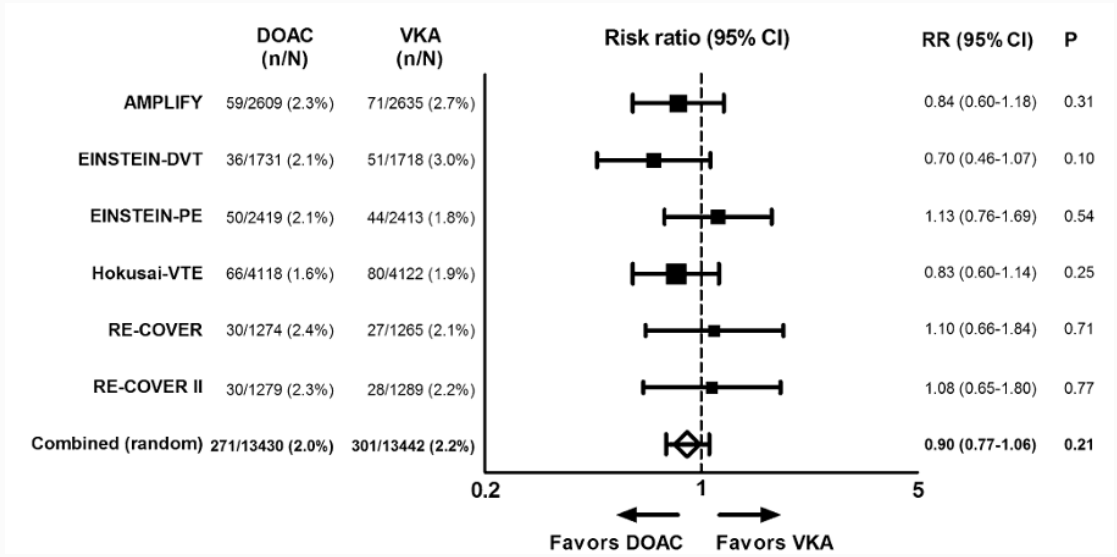
When selecting a DOAC for the treatment of acute VTE, which endpoint most strongly influences your choice?

A	Major bleeding
B	Clinically relevant nonmajor bleeding
C	Composite clinically relevant bleeding (major and nonmajor)
D	Recurrent VTE
E	I consider bleeding outcomes and recurrent VTE together, no single endpoint dominates
F	I don’t commonly treat patients with VTE

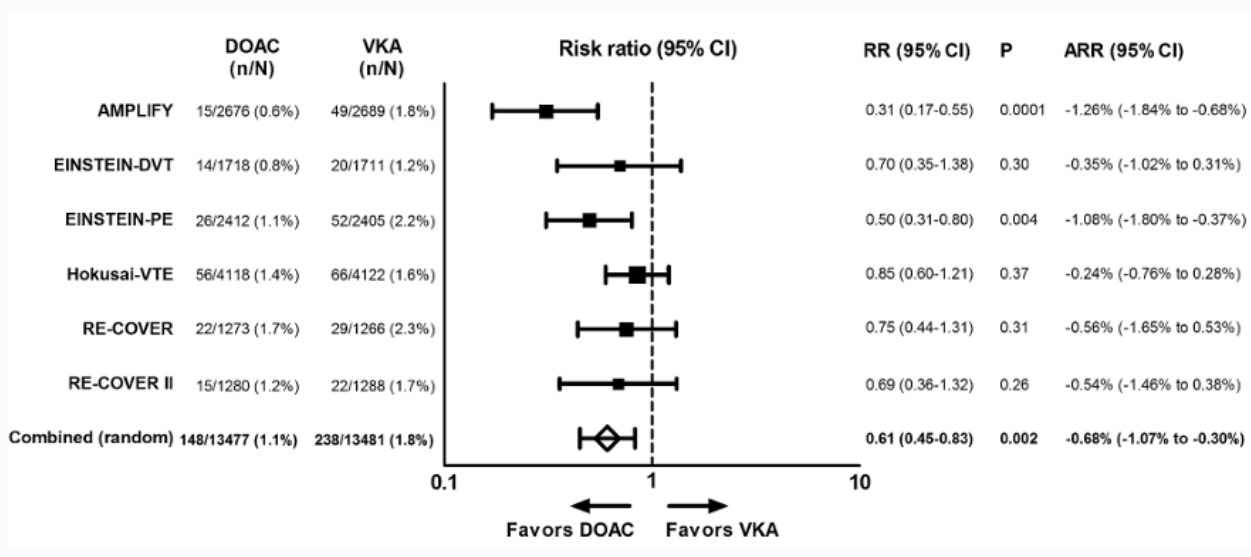
DOACs vs. VKAs in VTE therapy: Meta-analysis of Phase 3 trials[1]

This meta-analysis consolidates data from six large Phase III trials involving ~27,000 patients, assessing the efficacy and safety of DOACs vs. VKAs in managing acute symptomatic VTE, including DVT and PE

First recurrent or VTE-related death



Major bleeding



Images sourced from van Es N *et al*. 2014.

Prevention of **recurrent VTE** (including VTE-related death) was **comparable** with DOACs vs VKAs (2.0% vs 2.2%; RR 0.90, 95% CI 0.77–1.06), consistent with noninferiority and no heterogeneity across studies (I^2 = 0%).

DOACs significantly reduce the risk of major bleeding vs. VKAs by approximately 39%, including marked reductions in intracranial and fatal bleeding (*P*=0.002)

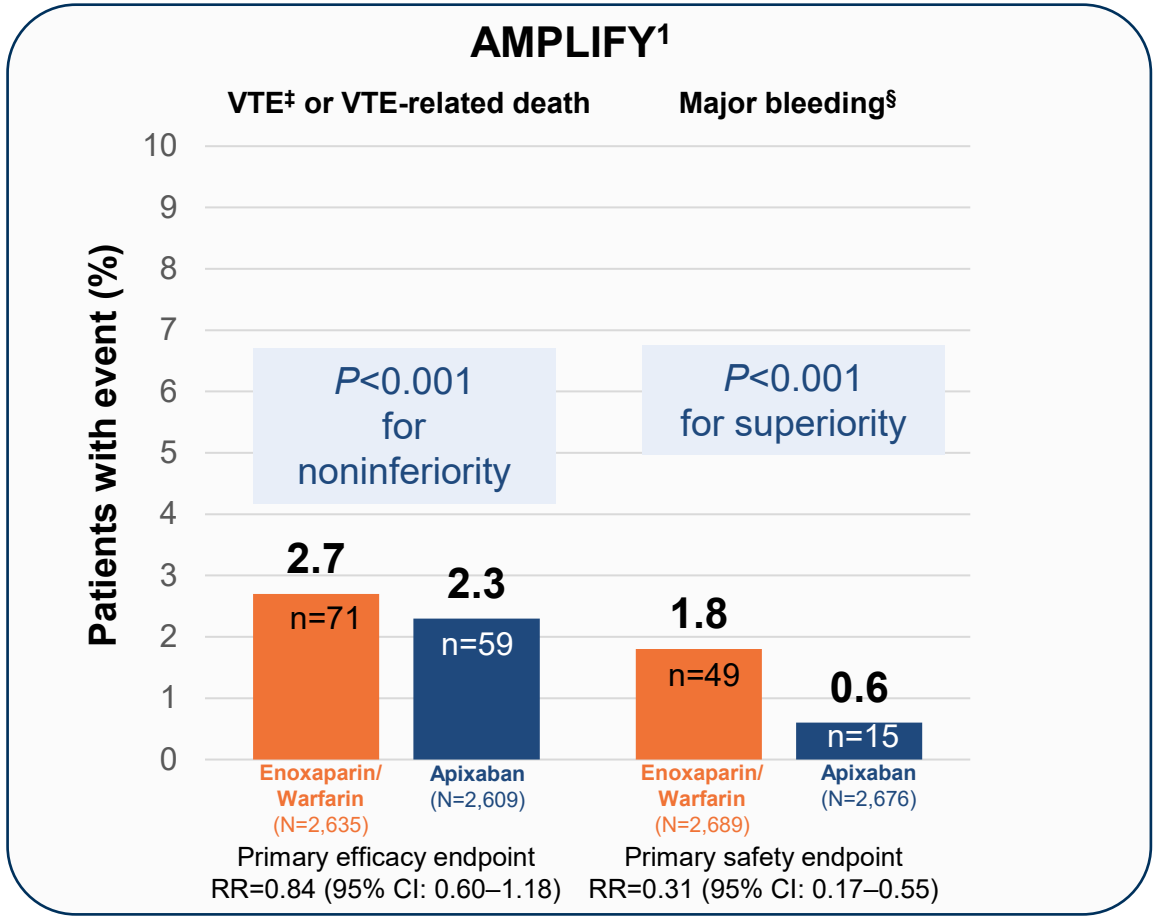
Clinical trials of DOACs cannot be directly compared.

ARR=absolute risk reduction; CI=confidence interval; DOAC=direct oral anticoagulant; DVT=deep vein thrombosis; PE=pulmonary embolism; RR=response rate; VKA=vitamin K antagonist; VTE=venous thromboembolism.

1. van Es N *et al*. Blood 2014; 124(12): 1968–1975.

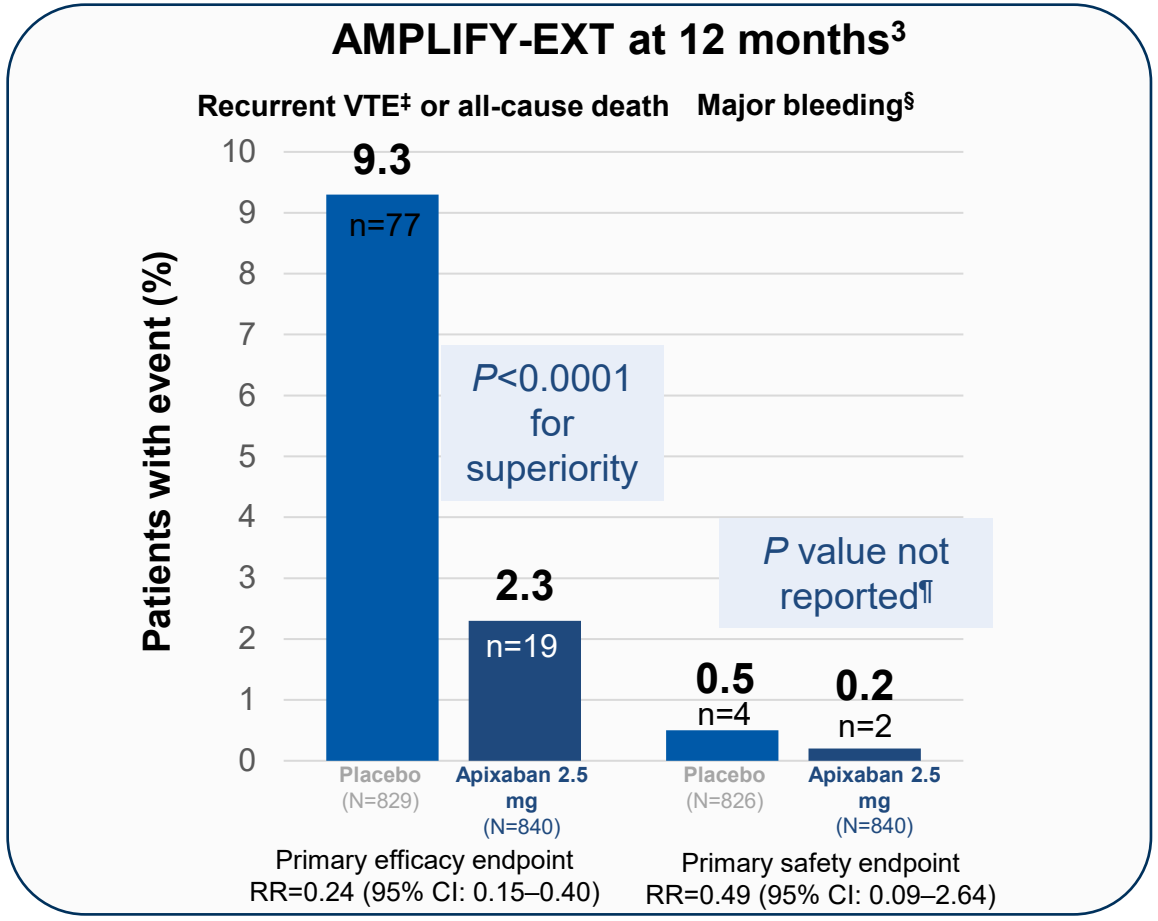
AMPLIFY was a Phase III pivotal trial that led to the approval of apixaban for VTE[1]

- Efficacy and safety of apixaban vs. enoxaparin/warfarin
  - Patients with VTE >6 months[1]*



Adapted from Agnelli G *et al*. 2013.

- Efficacy and safety of two doses of apixaban vs. placebo
  - Extended treatment of VTE over 6–12 months[2]†



Adapted from Agnelli G *et al*. 2013.

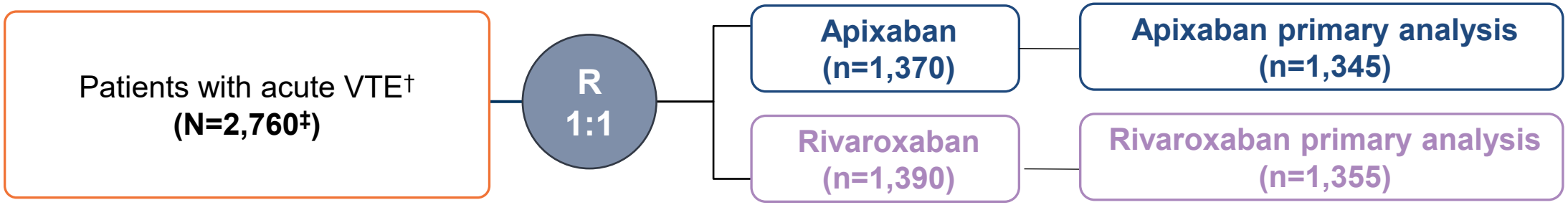
*AMPLIFY is a randomised, double-blind study comparing apixaban with conventional therapy in 5,395 patients with acute VTE; †AMPLIFY-EXT is a randomised, double-blind study comparing two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with VTE who had completed 6–12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy; ‡Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE); §Events associated with each endpoint were counted once per patient, but patients may have contributed events to multiple endpoints; ¶A difference of 0.2 percentage points; 95% CI: -0.3 to 0.8.
CI=confidence interval; DVT=deep vein thrombosis; RR=response rate; VTE=venous thromboembolism.

1. Agnelli G *et al*. N Engl J Med 2013; 369(9): 799–808; 2. Agnelli G *et al*. N Engl J Med 2013; 368(8): 699–708; 3. ELIQUIS (apixaban) Summary of Product Characteristics. September 2025. Available at www.ema.europa.eu..

COBRRA study overview[1]

Study design: Independently funded and sponsored, multicentre, pragmatic, prospective, randomised, open-label, blinded-endpoint (PROBE) trial across 32 sites (Canada, Australia, Ireland)

Objective: To determine whether apixaban is superior to rivaroxaban for risk reduction of clinically relevant bleeding* with 3-months' treatment for VTE



Primary outcome:
Adjudicated clinically relevant bleeding*

Secondary outcomes (adjudicated):
- Major bleeding
- Clinically relevant nonmajor bleeding
- Recurrent symptomatic (composite of recurrent DVT or PE)
- Mortality (from bleeding, recurrent VTE, any cause)
- Medication adherence at each follow-up visit

COBRRA is the first DOAC vs. DOAC head-to-head trial comparing apixaban and rivaroxaban

*Composite of major bleeding and CRNM bleeding. The primary outcome was clinically relevant bleeding, a composite of major bleeding or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). Major bleeding was defined as overt bleeding that occurred in a critical site, was associated with a decrease of at least 2 g per deciliter in the hemoglobin level, led to transfusion of 2 or more units of packed red cells, or contributed to death. Clinically relevant nonmajor bleeding was defined as bleeding that did not meet the definition for major bleeding but met at least one of the following criteria: resulted in medical intervention by a health care professional, led to hospitalization or an increased level of care, or prompted face-to-face evaluation by a health care professional. A blinded adjudication of events was conducted by a central adjudication committee;†Recurrent deep vein thrombosis was defined by a noncompressible area in the popliteal vein or more proximal vein on compression ultrasonography that was not present at the time of diagnosis or by a constant intraluminal filling defect in the popliteal vein or more proximal veins on venography. Recurrent pulmonary embolism was defined by abnormalities on ventilation–perfusion scanning, including a new unmatched segmental or more proximal perfusion defect; an intraluminal filling defect in a segmental or more proximal vessel on computed tomographic pulmonary angiography that was previously free of thrombi; or a constant intraluminal filling defect or a cutoff of a vessel of more than 2.5 mm in diameter on pulmonary angiography; ‡A total of 18 randomised patients did not receive treatment: 4 withdrew consent, 13 were lost to follow-up, 1 died.
CRNM=clinically relevant nonmajor; DVT, deep vein thrombosis; Hb=haemoglobin; HCP=healthcare professional; ISTH=International Society on Thrombosis and Haemostasis; PE, pulmonary embolism; R=randomisation; RBC=red blood cell; VTE=venous thromboembolism.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

Study population and methods of analysis

KEY INCLUSION CRITERIA:

Adults (aged ≥18 years) with acute, symptomatic, proximal lower extremity DVT, or segmental or more proximal PE

KEY EXCLUSION CRITERIA:

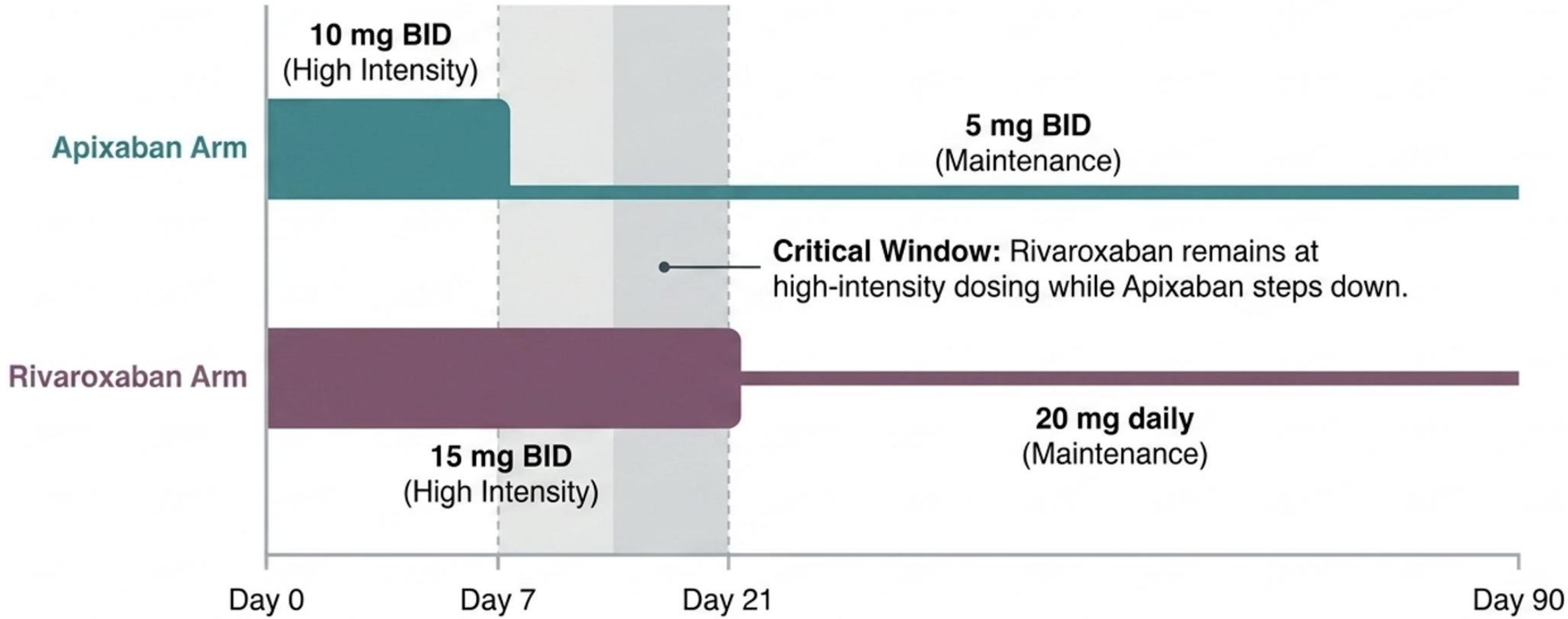
- >72 h therapeutic anticoagulation immediately before the enrolment visit
- CrCl <30 ml/min
- Active malignancy
- Another indication for long-term anticoagulation therapy, such as AF
- Any contraindication to study drug (active bleeding, Child-Pugh B or C liver disease, interacting medication, pregnancy or breastfeeding, weight >120 kg)

STATISTICAL ANALYSIS:*

- Primary analysis of the ITT population: Chi-square test and unadjusted OR with 95% CI
- A time-to-event analysis of the primary outcome was conducted with the Kaplan–Meier method.
- Relative risks and their corresponding 95% confidence intervals were calculated for all primary and secondary outcomes. Because the event of interest is rare (incidence, <10%), the odds ratios were expected to be similar to the relative risks

*The trial was powered (80%, α=0.05) to detect a 33% lower risk of clinically relevant bleeding with apixaban vs rivaroxaban, assuming event rates of 5.4% vs 8.1%, requiring 2760 participants (1380 per group).
CI=confidence interval; CrCL=creatinine clearance; DVT=deep vein thrombosis; h, hour; ITT=intention-to-treat; OR=odds ratio; PE=pulmonary embolism.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

Dosing Regimens: Apixaban vs. Rivaroxaban



Baseline characteristics*

	Rivaroxaban (n=1,355), %†	Apixaban (n=1,345), %†
Mean age, years (SD)	**58.5 (15.8)**	**58.0 (16.3)**
Female	**42.7**	**44.4**
Race‡		
White	89.9	87.9
Black	3.2	3.8
Asian	2.3	2.7
Hispanic/Latino	1.0	1.6
Indigenous/Aboriginal	0.3	0.6
Other	2.6	2.8
Mean BMI, kg/m^2 (SD)	**28.9 (5.1)**	**29.1 (5.2)**
CrCl <50 ml/min	**4.6**	**4.5**
Continued antiplatelet use	**2.6**	**2.7**
Qualifying VTE event¶		
DVT without PE	53.0	51.4
PE with or without DVT	47.0	48.6
Unprovoked	78.6	76.0
Provoked	21.4	23.9

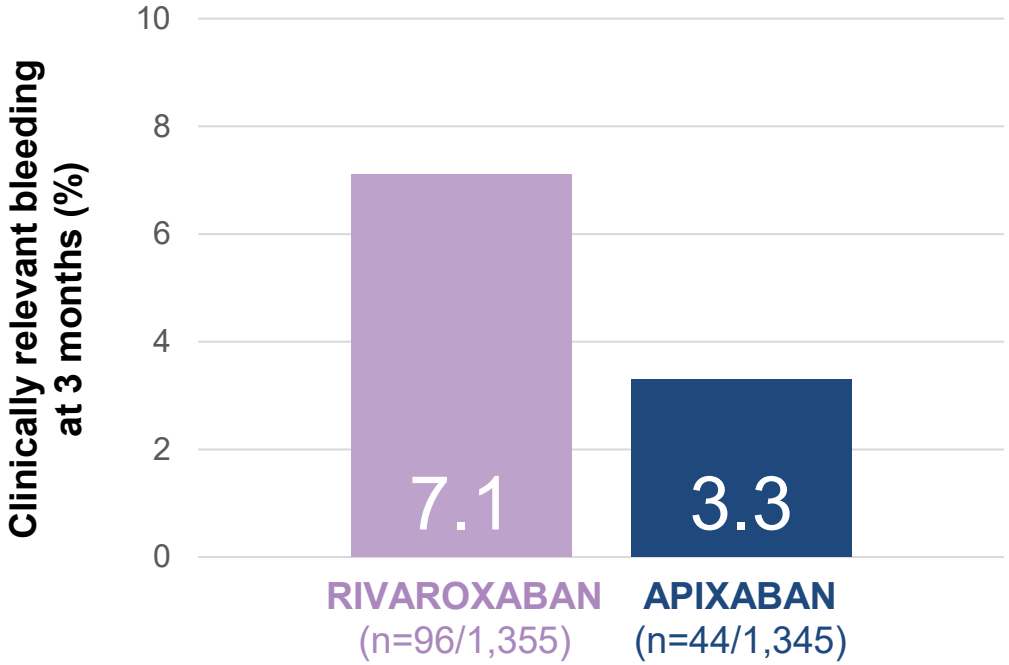
Adapted from Castellucci LA, *et al*. 2026.

*This is not an exhaustive list; †n(%) unless stated otherwise; ‡Total <100% based on data from oral presentation. Race presented for 1,336 participants receiving apixaban and 1,345 participants receiving rivaroxaban. Provokedvs. unprovoked VTE presented for 1,344 patients receiving apixaban; ¶Controlled antiplatelet use.
BMI=body mass index; CrCl=creatine clearance; DVT=deep vein thrombosis; PE=pulmonary embolism; SD=standard deviation; VTE=venous thromboembolism.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

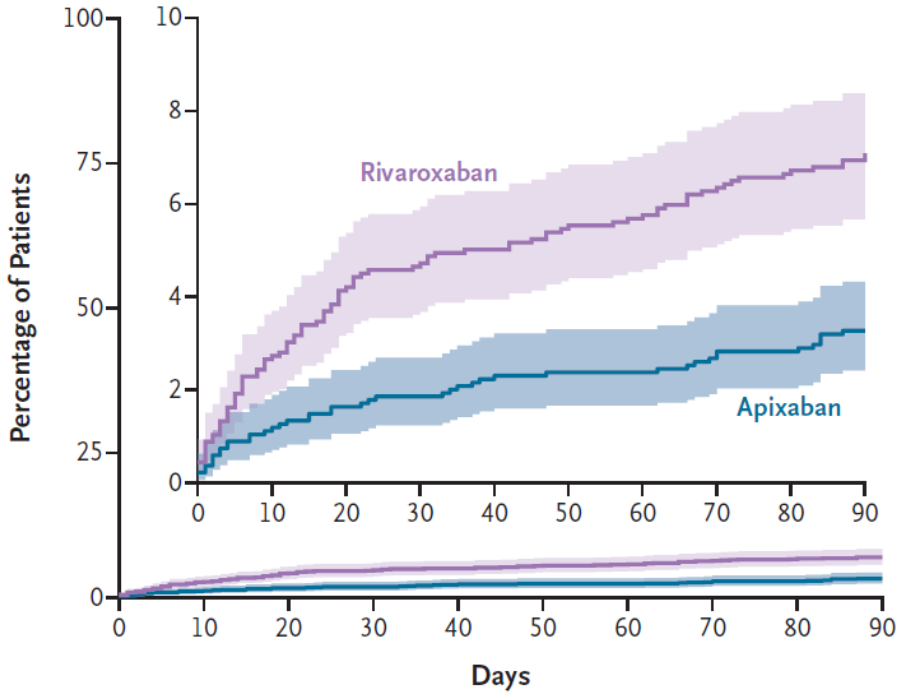
Apixaban significantly reduced the risk of clinically relevant bleeding vs. rivaroxaban for the treatment of acute VTE at 3 months; findings were consistent across prespecified subgroups

Clinically relevant bleeding at 3 months*

RR=0.46 (95% CI: 0.33–0.65); *P*<0.001



Time to clinically relevant bleeding*



No. at Risk

Rivaroxaban	1355	1319	1299	1292	1287	1281	1278	1270	1265	1261
Apixaban	1345	1330	1323	1320	1315	1313	1313	1309	1307	1301

The above figures have been adapted from Castellucci LA, *et al*. 2026.

*Clinically relevant bleeding was defined as a composite of major bleeding or clinically relevant non-major bleeding.
CI=confidence interval; RR=relative risk; VTE=venous thromboembolism.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

Relative Risk

0.46

A 54% relative reduction in clinically relevant bleeding

Absolute Risk Reduction

3.8%

The pure percentage point difference

Number Needed to Treat (NNT)

~27

Treating 27 patients with Apixaban instead of Rivaroxaban prevents one bleeding event over 3 months

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Breakdown: Major bleeding occurred in 0.4% (Apixaban) vs 2.4% (Rivaroxaban). CRNM bleeding occurred in 2.9% vs 4.9%.

The relative risk of experiencing either a major or clinically relevant nonmajor bleed were lower among patients who received apixaban vs. rivaroxaban (secondary outcome)*†

Secondary outcomes Event rates shown as n (%)	**Rivaroxaban** (n=1,355)	**Apixaban** (n=1,345)	**RR (95% CI)‡**
Major bleeding¶	32 (2.4)	5 (0.4)	0.16 (0.06–0.40)
Clinically relevant nonmajor bleeding events	67 (4.9)	39 (2.9)	0.59 (0.40–0.86)

The above table has been adapted from Castellucci LA, *et al*. 2026.

There were no cases of fatal bleeds in the study

*A total of 42 patients who received treatment did not complete the study: 1.2% (n=17/1,362) in the apixaban group and 1.8% (n=25/1,380) of the rivaroxaban group; †The definitions of outcomes, treatment period, follow-up period, and the patient population were different in this study compared with AMPLIFY; ‡Analyses of secondary outcomes were not adjusted for multiplicity, and the widths of the confidence intervals should not be used in place of hypothesis testing.
CI=confidence interval; RR=relative risk.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

Clinically relevant nonmajor and major bleeding events were more common with rivaroxaban vs. apixaban

Sites of bleeding Event rates shown as n (%)	**Rivaroxaban** (n=1,355)	**Apixaban** (n=1,345)
Clinically relevant nonmajor bleeding		
Gastrointestinal	13 (0.96)	8 (0.59)
Vaginal*	22/578 (3.81)	16/597 (2.68)
Hematuria	17 (1.25)	4 (0.30)
Major bleeding		
Gastrointestinal	10 (0.74)	0 (0.0)
Vaginal*	8/578 (1.38)	1/597 (0.17)

The above table has been adapted from Castellucci LA, *et al*. 2026.

*The denominator denotes the number of female participants randomized in each treatment group.
GI=gastrointestinal.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

Rates of recurrent VTE and all-cause mortality were similar across both treatment groups*†

Secondary outcomes Event rates shown as n (%)	**Rivaroxaban** (n=1,355)	**Apixaban** (n=1,345)	**RR (95% CI)‡**
Recurrent VTE	14 (1.0)	15 (1.1)	1.08 (0.52–2.23)
All-cause mortality	4 (0.3)	1 (0.1)	0.25 (0.03–2.26)

The above table has been adapted from Castellucci LA, *et al*. 2026.

There were no cases of fatal recurrent VTE in the study

Serious adverse events that were unrelated to bleeding or VTE occurred in 36 patients (2.7%) in the apixaban group and 30 patients (2.2%) in the rivaroxaban group

*A total of 42 patients who received treatment did not complete the study: 1.2% (n=17/1,362) in the apixaban group and 1.8% (n=25/1,380) of the rivaroxaban group; †The definitions of outcomes, treatment period, follow-up period, and the patient population were different in this study compared with AMPLIFY; ‡Analyses of secondary outcomes were not adjusted for multiplicity, and the widths of the confidence intervals should not be used in place of hypothesis testing.
CI=confidence interval; RR=relative risk; VTE=venous thromboembolism.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

Limitations of analysis

KEY LIMITATIONS:

- Open-label design may have introduced ascertainment bias
- The short follow-up duration of 3 months limits extrapolation of the results beyond this time frame
- Bleeding definitions did not incorporate healthcare resource utilisation or patient-reported bleeding severity and quality-of-life impact
- Findings not generalisable to patients with other conditions (e.g. AF, cancer-associated VTE, or extended-duration treatment for prevention of VTE recurrence)
- Study not powered to detect differences in the risk of recurrent VTE; findings should not be extrapolated to other indications

AF=atrial fibrillation; QoL=quality of life; VTE=venous thromboembolism.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

Complete Medication Adherence at 3 Months

65.7%

APIXABAN

75.1%

RIVAROXABAN

Summary

COBRRA is the first DOAC vs. DOAC head-to-head trial and demonstrated that at 3 months of treatment, **APIXABAN** vs. **RIVAROXABAN** was associated with:

↓ **Significantly reduced clinically relevant bleeding (primary outcome)**	**3.3% vs. 7.1%** RR*=0.46 (95% CI: 0.33–0.65); *P*<0.001
↓ **Reduced major bleeding (secondary outcome)†**	**0.4% vs. 2.4%** RR=0.16 (0.06–0.40)
↓ **Reduced clinically relevant nonmajor bleeding events (secondary outcome)**	**2.9% vs. 4.9%** RR=0.59 (0.40–0.86)
↔ **Similar rates of recurrent VTE (secondary outcome)**	**1.1% vs. 1.0%** RR=1.08 (0.52–2.23)
↔ **Similar rates of all-cause mortality (secondary outcome)**	**0.1% vs. 0.3%** RR=0.25 (0.03–2.26)

*Odds ratios were prespecified for the primary analysis, with relative risks additionally calculated at the request of the journal editors. Because bleeding events were rare (<10%), odds ratios and relative risks were expected to be similar; †Secondary outcomes were not adjusted for multiplicity. The authors caution that secondary outcomes should not be used in place of hypothesis testing.
CI=confidence interval; RR=relative risk; VTE=venous thromboembolism.
Castellucci LA, *et* al. N Eng J Med 2026;394(11):1051–1060.

Audience poll

How will the COBRRA data influence your decision-making approach in anticoagulation management?

A	Significantly
B	Moderately
C	Slightly
D	Not at all
E	Not applicable to my practice

Clinical relevance

Apixaban appears safer than rivaroxaban for clinically relevant bleeding during initial treatment phase of acute symptomatic DVT

Findings specially persuasive for patients with higher perceived bleeding risk – eg. Prior bleeding concerns, non-major bleeding may be clinically disruptive

Results should not be extrapolated to cancer-associated thrombosis, atrial fibrillation, extended secondary prevention beyond 3 months

Advanced age/frailty/multimorbidity

Recommendations for oral anticoagulant use in elderly patients (aged ≥65 years) with NVAF[1]

The 2023 AGS Beers Criteria® for potentially inappropriate medication use in adults aged ≥65 years provides recommendations for oral anticoagulant use in elderly patients.[1]

*Compared with DOACs, **warfarin has higher risks of major bleeding** (particularly intracranial bleeding) and similar or lower effectiveness for the treatment of NVAF and VTE[1]*

*The recommendation for **dabigatran remains as use with caution** for the long-term treatment of NVAF and VTE… **an increased risk of GI and major bleeding** compared with alternatives such as apixaban[1]*

*At doses used for long-term treatment of VTE or NVAF, **rivaroxaban appears to have a higher risk of major bleeding and GI bleeding** in older adults than other DOACs, particularly apixaban[1]*

The 2024 ESC guidelines provide a recommendation for oral anticoagulant use in adults aged ≥75 years, specifically relating to treatment switching.[2]

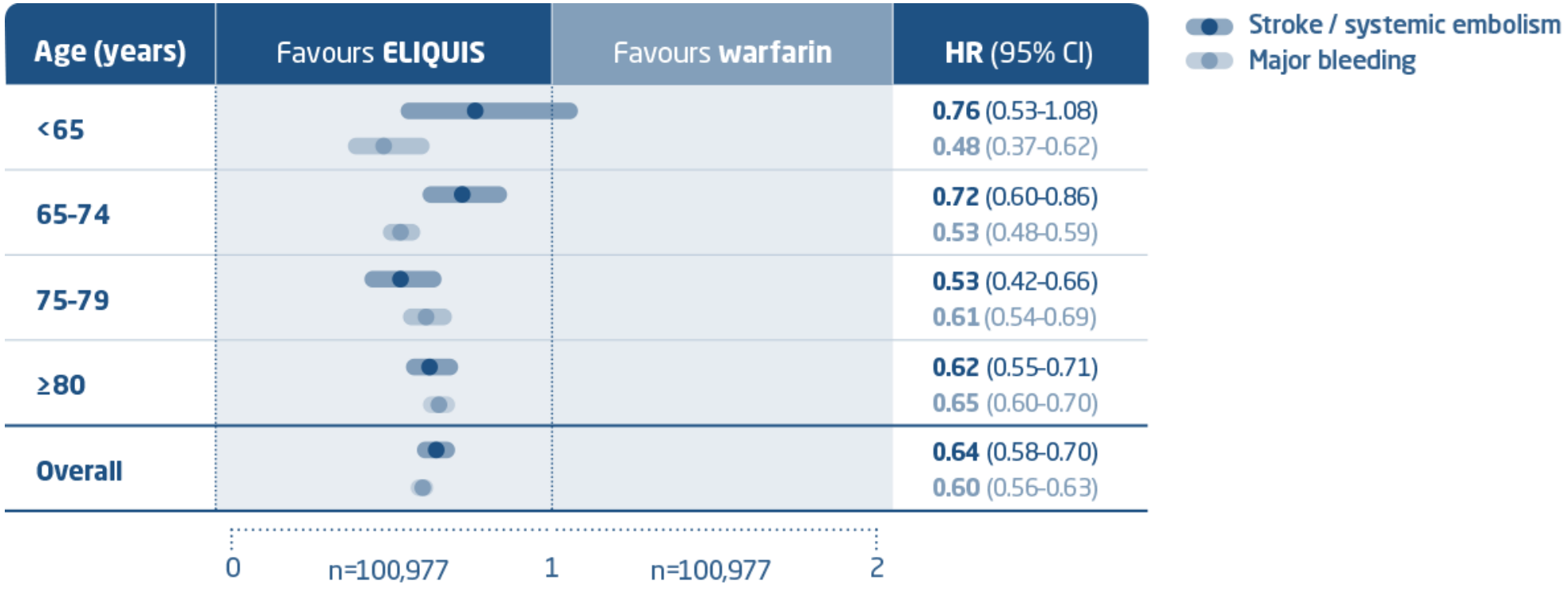
Maintaining VKA treatment rather than switching to a DOAC may be considered in patients aged ≥75 years on clinically stable therapeutic VKA with polypharmacy to prevent excess bleeding risk[2]

AGS, American Geriatrics Scciety; DOAC, direct oral anticoagulant; ESC, European Society of Cardiology; GI, gastrointestinal; NVAF, non-valvular atrial fibrillation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

1. The American Geriatrics Society. J Am Geriatr Soc 2023; 71(7): 2052–2081; 2. Van Gelder IC *et al*. Eur Heart J 2024; 45(36): 3314–3414.

ARISTOPHANES: Efficacy and safety outcomes of DOACs vs warfarin in elderly patients with NVAF*[1]

Apixaban was associated with a **lower risk of major bleeding** and a numerically lower risk of stroke/SE across age groups of patients with NVAF **aged ≥65 years** compared with warfarin.[1]



Adapted from Lip GYH, *et al*. 2018

There are no head-to-head RCTs comparing the DOACs in NVAF; direct comparisons cannot be made between individual DOACs based on these data. Real-world data have some limitations, such as the potential for selection bias, differing outcomes definitions and the potential presence of unmeasured confounders. They are able to show associations but cannot determine causality.

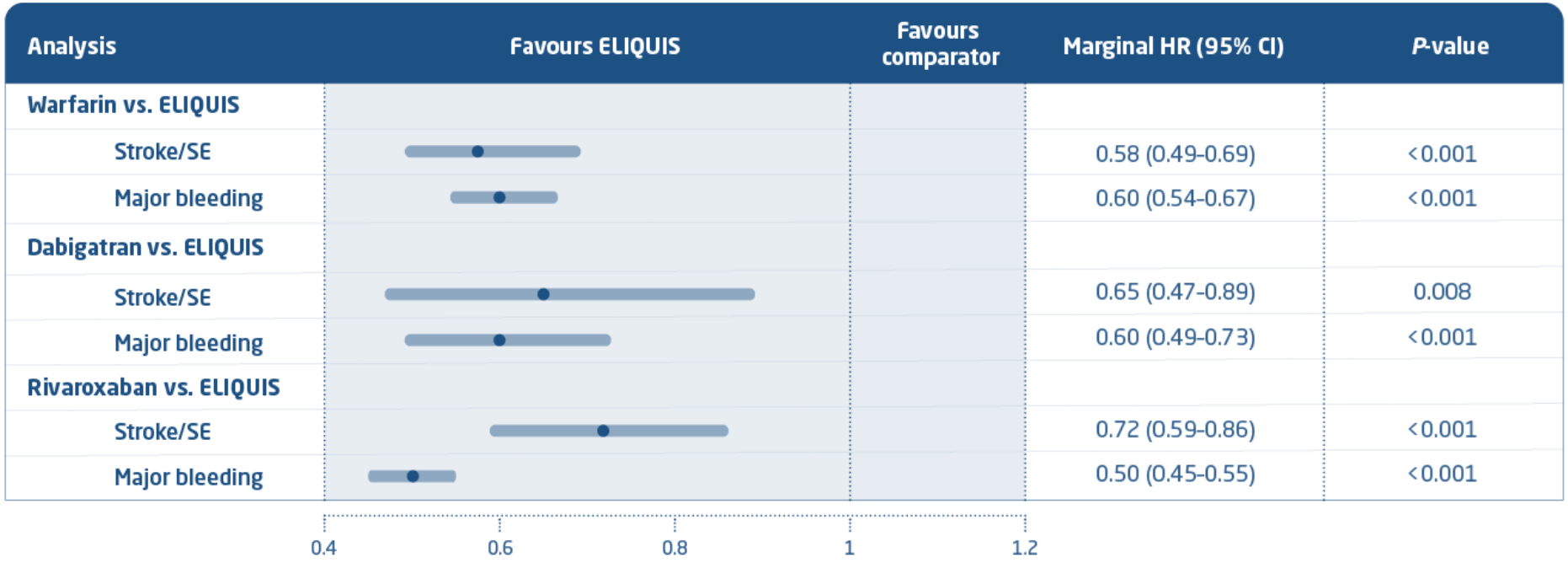
*ARISTOPHANES was a large-scale, retrospective, US real-world analysis using pooled data from the US Centers for Medicare and Medicaid Services Medicare data and four US commercial claims databases to compare stroke/SE and major bleeding amongst patients with NVAF on DOACs or warfarin.

CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; NVAF, non-valvular atrial fibrillation; RCT, randomised controlled trial; SE, systemic embolism.

1. Lip GYH *et al.* Stroke 2018; 49(12): 2933–2944.

ARISTOPHANES: Efficacy and safety outcomes of DOACs vs warfarin and DOAC vs DOAC in elderly patients aged ≥80 years with NVAF*[1]

Apixaban was associated with a **lower risk of stroke/SE and major bleeding** in patients with NVAF aged **≥80 years** compared with warfarin, dabigatran and rivaroxaban



Adapted from Deitelzweig S *et al*. 2019

There are no head-to-head RCTs comparing the DOACs in NVAF; direct comparisons cannot be made between individual DOACs based on these data. Real-world data have some limitations, such as the potential for selection bias, differing outcomes definitions and the potential presence of unmeasured confounders. They are able to show associations but cannot determine causality.

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CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; NVAF, non-valvular atrial fibrillation; RCT, randomised controlled trial; SE, systemic embolism.

1. Deitelzweig S *et al*. J Am Geriatr Soc 2019; 67(8): 1662–1671.

Overweight, Obesity and Underweight

Obesity and the impact on thrombotic conditions*

High prevalence in the US[1]	A contributing factor to VTE and AF[2,3]	Increases the risk of developing AF
• **~40%** of patients have obesity • **~8%** of patients have morbid obesity	• Inducing a **pro-thrombotic** and **pro-inflammatory** state[2,3] • **Reducing drug effect** and levels[2,3]: • Obese patients taking warfarin are less likely to achieve therapeutic INR, take longer to achieve therapeutic INR, take a higher average daily dose, and have a higher mean dose at discharge[4]	• **+49% increased risk of AF** compared to non-obese patients†[5] • Increasing patient risk for thrombotic events[6,7]

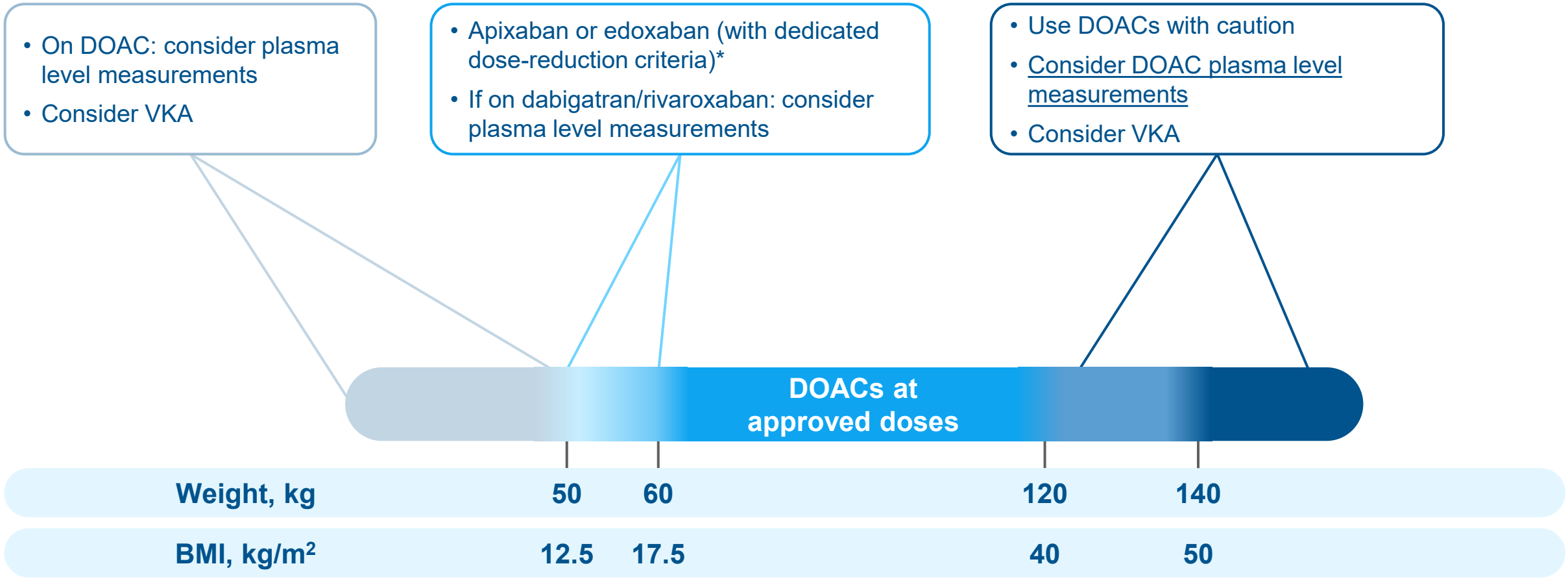
*The CDC defines obesity as BMI ≥30 kg/m^2 and severe (morbid) obesity ≥40 kg/m^2.[8] †Based on a 2007 meta-analysis, including 16 studies and 123,249 patients.[5]
AF, atrial fibrillation; BMI, body mass index; CDC, Centers for Disease Control and Prevention; INR, international normalised ratio; VTE, venous thromboembolism.
1. Fryer CD *et al.* Division of Health and Nutrition Examination Surveys. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2015–2016. National Center for Health Statistics: Health E-Stats. Available at www.cdc.gov/nchs/data/hestat/obesity_adult_15_16/obesity_adult_15_16.pdf. Accessed October 2025; 2. Huxley RR *et al.* Circulation 2011; 123(14): 1501–1508; 3. Moore T *et al.* Am J Med 2017; 130(9): 1024–1032; 4. Wallace JL *et al.* J Thromb Thrombolysis 2013; 36: 96–101; 5. Wanahita N *et al*. Am Heart J 2008; 155(2): 310-315; 6. Balu A, Lip GYH. Arch Med Sci 2025; 21(3): 775-778; 7. Tao M *et al.* Arch Med Sci 2025; 21(3): 766-774; 8. Centers for Disease Control and Prevention. Adult BMI Categories. Available at https://www.cdc.gov/bmi/adult-calculator/bmi-categories.html. Last accessed October 2025.

Issues for clinicians around obesity

- The AHA/ACC/HRS guidelines are limited around special recommendations for obese patients[1]
- Real-world evidence for antithrombotic, fixed-dose drugs in underweight and obesity are limited according to the ESC Working Group on Thrombosis[2,3]
- DOAC label language does not recommend dose adjustments for obese patients[4–6]

ACC, American College of Cardiology; AHA, American Heart Association; DOAC, direct oral anticoagulant; ESC, European Society of Cardiology; HRS, Heart Rhythm Society.
Clinical experience of Dr Steven Deitelzweig.
1. Joglar JA *et al.* Circulation 2023; 149(1): doi:10.1161/CIR.0000000000001193; 2. Gigante B et al. Eur Heart J Cardiovasc Pharmacother 2024;10(7):614–645; 3. Steffel J et al. Eurospace 2021;23(10):1612–1676; 4. ELIQUIS SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf; 5. PRADAXA SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf; 6. XARELTO SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf.

2021 EHRA Practical Guide: DOACs in patients with AF and high and low body weights[1]



Adapted from Steffel J, et al. 2021.

*2.5 mg twice daily apixaban dosing is recommended for patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL.[2] Body weight: No dose adjustment for apixaban required, unless criteria for dose reduction are met. Dose reduction to 2.5 mg bid if at least two out of three fulfilled: age ≥80 years; weight ≤60 kg; creatinine ≥1.5 mg/dL (133 µmol/L).[2]

AF, atrial fibrillation; BMI, body mass index; DOAC, direct oral anticoagulant; EHRA, European Heart Rhythm Association; VKA, vitamin K antagonist.

1. Steffel J *et al.* Europace 2021; 23(10): 1612–76; 2. ELIQUIS SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf.

ARISTOTLE subgroup analysis: Outcomes for apixaban vs. warfarin in patients with NVAF by body weight from an RCT[1]

Event	Rate per 100 pt/yr (no.)		HR (95% CI)	Interaction *P* Value*
	Apixaban	Warfarin	Apixaban Versus Warfarin	
Efficacy end points				
Stroke/SE				0.6401
≤60 kg	2.01 (34)	3.20 (52)	0.63 (0.41–0.96)	
61–120 kg	1.23 (173)	1.44 (201)	0.85 (0.70–1.05)	
>120 kg	0.44 (4)	1.13 (11)	0.39 (0.12–1.22)	
Stroke				0.8423
≤60 kg	1.95 (33)	2.95 (48)	0.66 (0.42–1.03)	
61–120 kg	1.14 (161)	1.37 (191)	0.84 (0.68–1.03)	
>120 kg	0.44 (4)	1.03 (10)	0.43 (0.13–1.36)	
Ischemic or uncertain type of stroke				0.9810
≤60 kg	1.77 (30)	1.90 (31)	0.93 (0.57–1.54)	
61–120 kg	0.91 (128)	0.98 (137)	0.93 (0.73–1.18)	
>120 kg	0.44 (4)	0.61 (6)	0.71 (0.20–2.52)	
Hemorrhagic stroke				0.0418
≤60 kg	0.18 (3)	1.10 (18)	0.16 (0.05–0.54)	
61–120 kg	0.25 (36)	0.40 (56)	0.64 (0.42–0.97)	
>120 kg	0.00 (0)	0.41 (4)	—	
All-cause death				0.3614
≤60 kg	7.00 (122)	6.33 (107)	1.10 (0.85–1.43)	
61–120 kg	3.14 (451)	3.75 (535)	0.84 (0.74–0.95)	
>120 kg	3.00 (28)	2.52 (25)	1.19 (0.69–2.04)	
Myocardial infarction				0.8694
≤60 kg	0.64 (11)	0.36 (6)	1.74 (0.64–4.71)	
61–120 kg	0.54 (76)	0.66 (92)	0.82 (0.60–1.11)	
>120 kg	0.33 (3)	0.41 (4)	0.81 (0.18–3.60)	

Event	Rate per 100 pt/yr (no.)		HR (95% CI)	Interaction *P* Value*
	Apixaban	Warfarin	Apixaban Versus Warfarin	
Safety end points				
Major bleeding				0.0158
≤60 kg	2.33 (36)	4.28 (62)	0.55 (0.36–0.82)	
61–120 kg	2.15 (277)	3.02 (379)	0.71 (0.61–0.83)	
>120 kg	1.55 (13)	2.08 (19)	0.74 (0.37–1.50)	
Major or CRNM bleeding				0.0108
≤60 kg	3.60 (55)	7.06 (101)	0.51 (0.37–0.71)	
61–120 kg	4.20 (532)	5.97 (730)	0.71 (0.63–0.79)	
>120 kg	2.77 (23)	4.83 (43)	0.58 (0.35–0.95)	
Intracranial bleeding				0.1833
≤60 kg	0.32 (5)	1.49 (22)	0.21 (0.08–0.56)	
61–120 kg	0.35 (46)	0.75 (96)	0.47 (0.33–0.67)	
>120 kg	0.00 (0)	0.43 (4)	—	
Gastrointestinal bleeding				0.1730
≤60 kg	0.90 (14)	1.09 (16)	0.84 (0.41–1.72)	
61–120 kg	0.67 (87)	0.79 (100)	0.85 (0.64–1.13)	
>120 kg	0.47 (4)	0.33 (3)	1.44 (0.32–6.42)	
Any bleeding				0.1101
≤60 kg	18.68 (244)	30.86 (344)	0.62 (0.53–0.73)	
61–120 kg	18.15 (1987)	25.29 (2528)	0.73 (0.69–0.78)	
>120 kg	16.44 (119)	25.13 (176)	0.67 (0.53–0.85)	

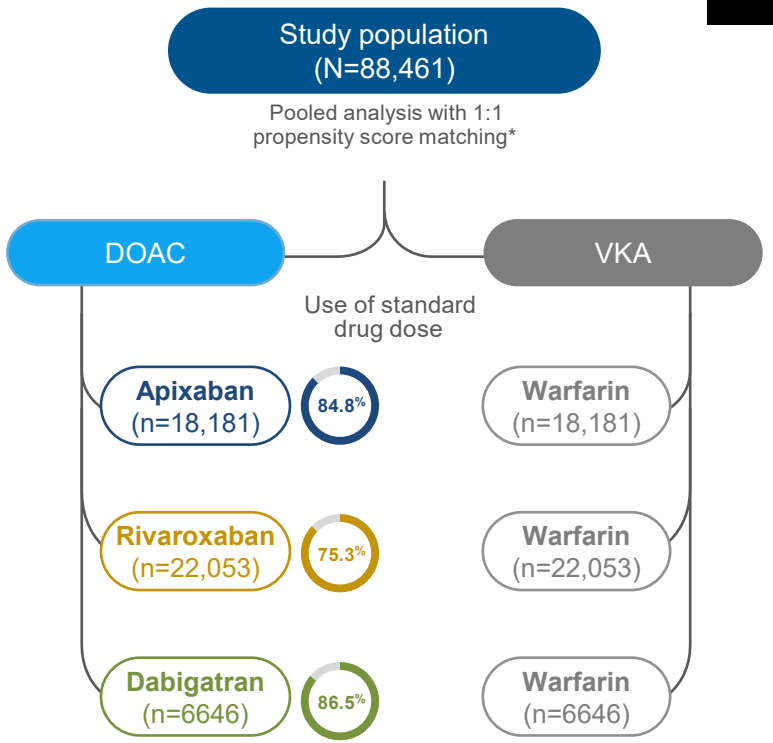
Adapted from Hohnloser *et al.* 2019.[1]

This is a subgroup analysis not included in the primary outcome analysis of the ARISTOTLE randomised controlled trial investigating the efficacy and safety of apixaban vs. warfarin in patients with NVAF (N=18,201). The primary efficacy and safety outcomes were stroke or systemic embolism and major bleeding.[1]
The distribution of patients in each individual weight group was as follows: N=1,985, ≤60 kg; N=15,172, >60 to 120 kg; and N=982, >120 kg.
*Interaction *P*-value computed with weight as continuous variable.
CI, confidence interval; CRNM, clinically relevant nonmajor; HR, hazard ratio; NVAF, non-valvular atrial fibrillation; RCT, randomised controlled trial; SE, systemic embolism.
1. Hohnloser SH *et al*. Circulation 2019; 139(20): 2292–2300.

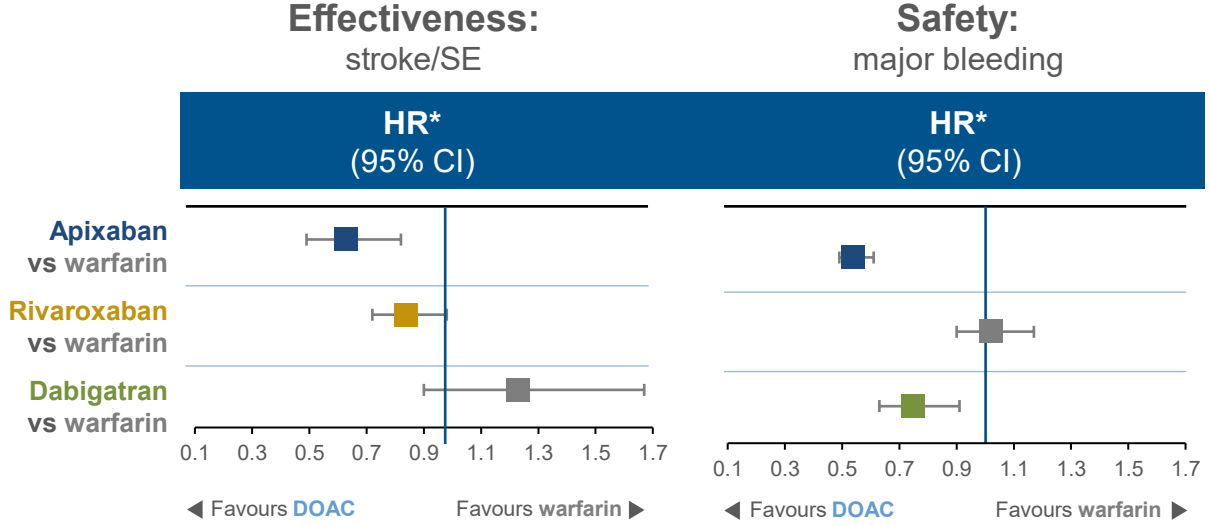
ARISTOPHANES subgroup analysis: efficacy and safety outcomes of DOACs versus warfarin in patients with NVAF and obesity[1]

Subgroup analysis: obese patients
(obesity was defined by the ICD-9-CM codes)

Patients with NVAF and a BMI ≥30 kg/m², who had ≥1 pharmacy claim for a DOAC or warfarin between 1 January 2013 and 30 September 2015



In ARISTOPHANES, patients who were obese and treated with apixaban or rivaroxaban experienced similar effectiveness and safety to the RCT trials when treated with DOACs versus warfarin



Adapted from Deitelzweig *et al.* 2020.[1]

There are no head-to-head RCTs comparing the DOACs in NVAF; direct comparisons cannot be made between individual DOACs based on these data. Real-world data have some limitations, such as the potential for selection bias, differing outcomes definitions and the potential presence of unmeasured confounders. They are able to show associations but cannot determine causality.

ARISTOPHANES was a large-scale, retrospective, US real-world analysis using pooled data from the US Centers for Medicare and Medicaid Services Medicare data and 4 US commercial claims databases to compare stroke/systemic embolism and major bleeding among patients with NVAF on DOACs or warfarin.

*Based on propensity-score-matched cohorts generated by logistic regression based on demographics, Charlson Comorbidity Index score, baseline bleeding and stroke/SE history, comorbidities and baseline comedications.

BMI, body mass index; CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; NVAF, non-valvular atrial fibrillation; RCT, randomised controlled trial; SE, systemic embolism; VKA, vitamin K antagonist.

1. Deitelzweig S *et al.* J Clin Med 2020; 9(6): 1633.

ARISTOPHANES subgroup analysis: efficacy and safety outcomes of DOACs versus warfarin in patients with NVAF and obesity[1]

Subgroup analysis: obese patients
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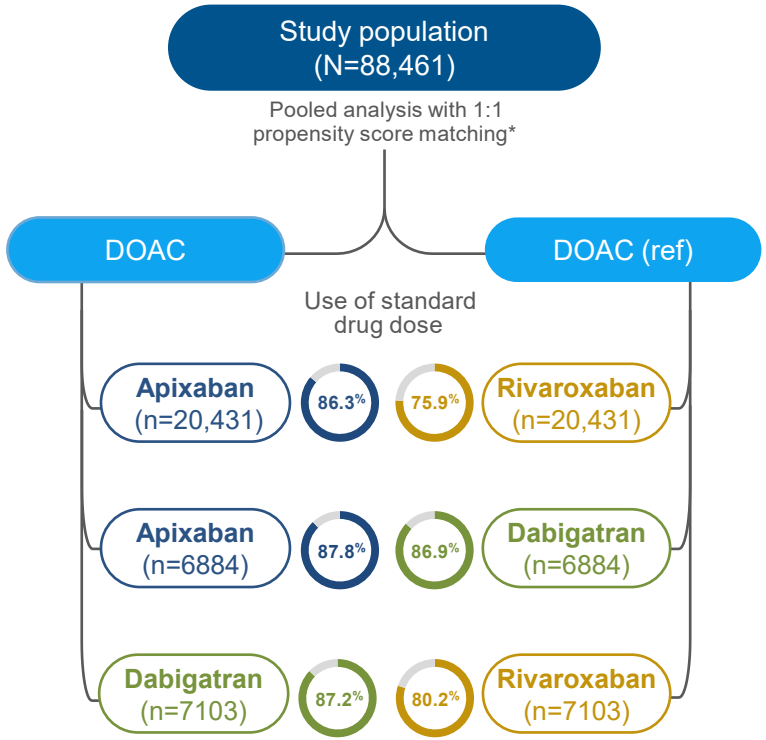
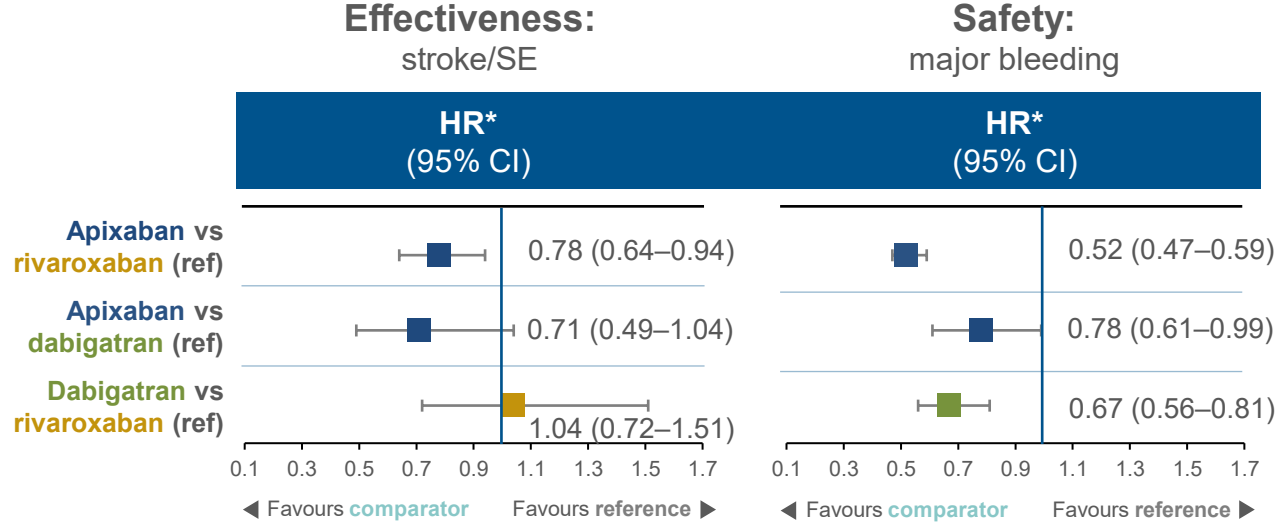


In ARISTOPHANES, patients who were obese experienced some differences in effectiveness and safety between DOACs



Adapted from Deitelzweig *et al.* 2020.[1]

There are no head-to-head RCTs comparing the DOACs in NVAF; direct comparisons cannot be made between individual DOACs based on these data. Real-world data have some limitations, such as the potential for selection bias, differing outcomes definitions and the potential presence of unmeasured confounders. They are able to show associations but cannot determine causality.

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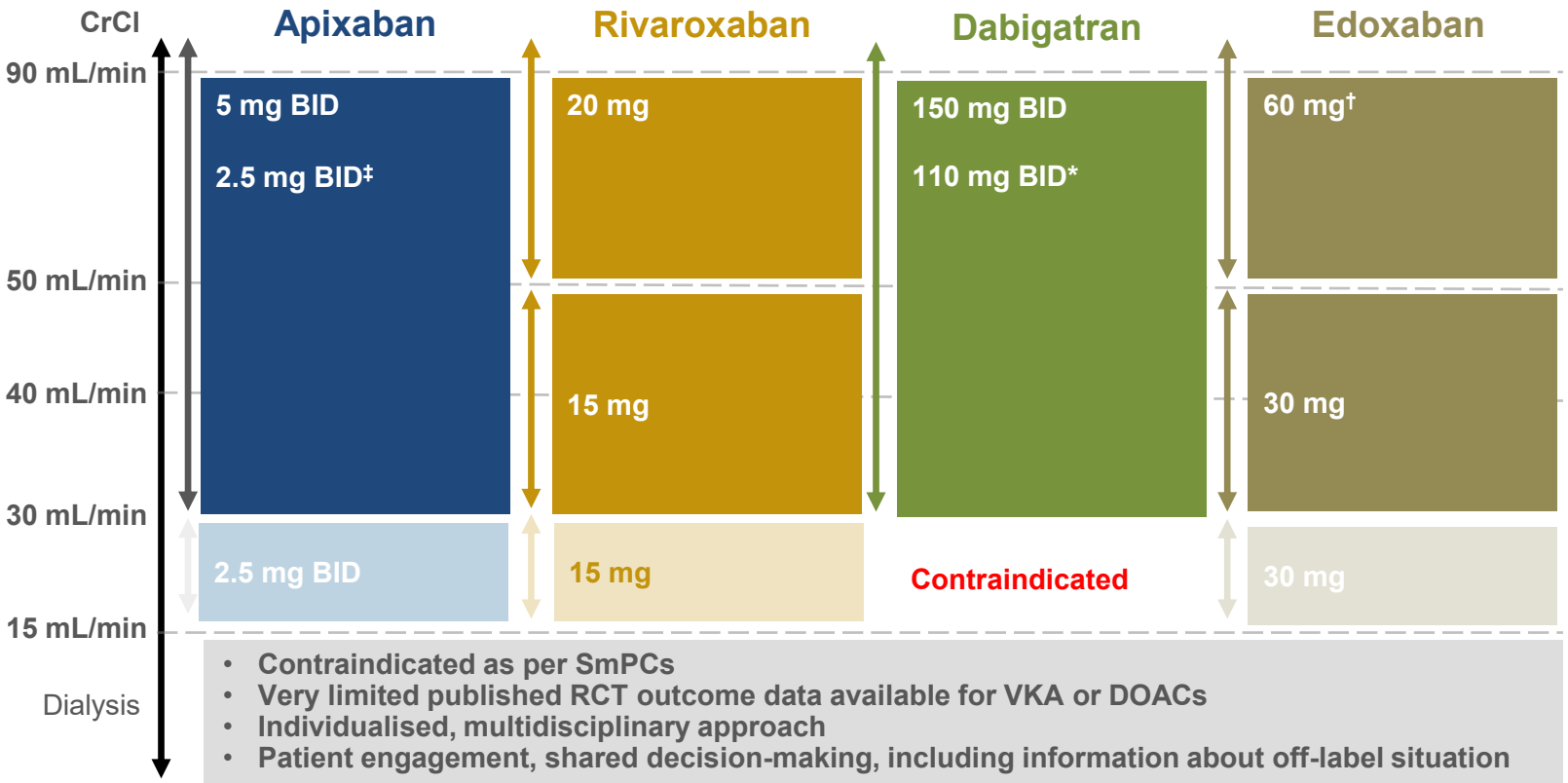
1. Deitelzweig S *et al.* J Clin Med 2020; 9(6): 1633.

Chronic kidney disease (CKD)

DOAC dosage guidance in patients with NVAF according to renal function[1–5]



Please refer to the SmPCs of individual drugs for full information on dosing and administration

Full-dose apixaban can be used in patients (according to the SmPC) **with CrCl ≥30 mL/min** (and no other dose-reduction criteria)[2]

Other DOACs: Dose reduction is required/should be considered when the patient's CrCl is ≥15–50 mL/min[§3–5]

Dabigatran is contraindicated when the CrCl is <30 mL/min;[4] for other DOACs, when the CrCl is <15 mL/min[2,3,5]

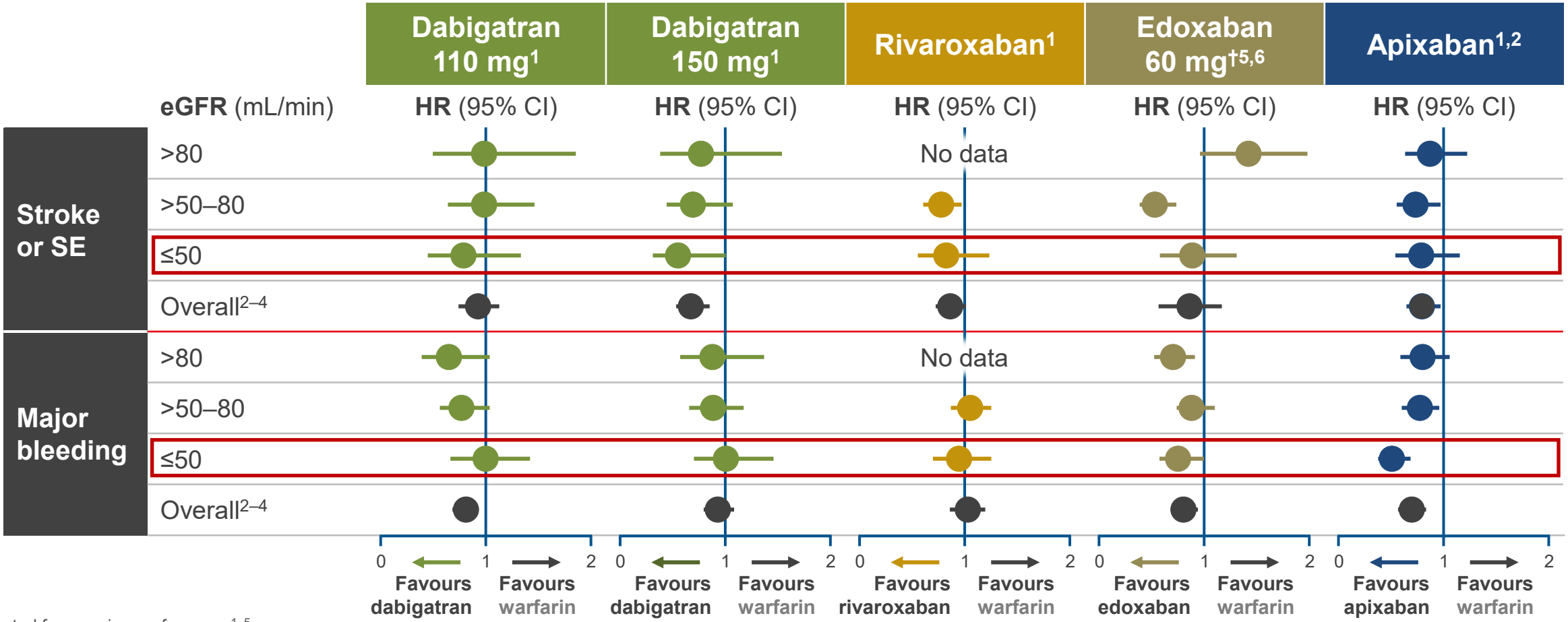
Adapted from Steffel J, et al. 2021.[1]

*110 mg bid in patients at high risk of bleeding (per SmPC)[1]; †Other dose-reduction criteria may apply (weight ≤60 kg, concomitant potent P-glycoprotein inhibitor therapy)[1]; ‡2×2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L).[1] §For edoxaban dose reduction is required/should be considered when the patient's CrCl is ≤50 mL/min.

bid, twice daily; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; NVAF non-valvular atrial fibrillation; RCT, randomised controlled trial; SmPC, Summary of Product Characteristics; VKA, vitamin K antagonist.

1. Steffel J *et al.* Europace 2021; 23(10): 1612–76; 2. ELIQUIS SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf; 3. XARELTO SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf; 4. PRADAXA SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf; 5. LIXIANA SmPC, May 2023. Available at https://www.ema.europa.eu/en/documents/product-information/lixiana-epar-product-information_en.pdf. All SmPCs available at: www.ema.europa.eu [Last accessed September 2025].

Efficacy and safety profiles of DOACs compared with warfarin in patients with or without renal impairment*[1]



Adapted from various references[1–5]

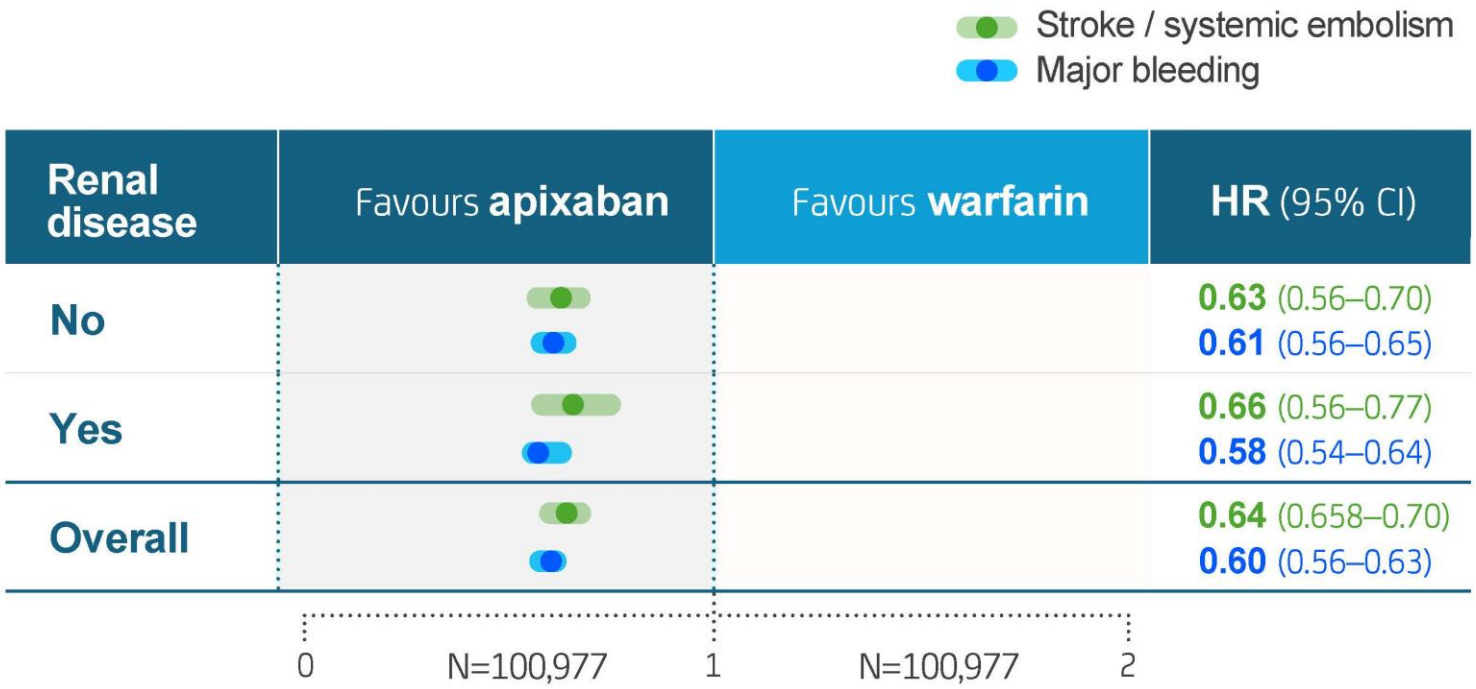
There are no head-to-head randomised clinical trials comparing the DOACs in NVAF. Comparisons cannot be made between individual DOACs based on these data.

*Review of three large, international, Phase III RCTs (ARISTOTLE for apixaban, RELY-AF for dabigatran, ROCKET-AF for rivaroxaban).[1–4] Edoxaban data were taken from the large scale, Phase III ENGAGE-AF TIMI trial investigating the safety and efficacy of edoxaban vs. warfarin in patients with NVAF[5,6]; †CrCl subgroups in the ENGAGE-AF TIMI 48 trial were 30-50mL/min (moderate dysfunction), >50–95 mL/min (mild dysfunction), and >95 mL/min (normal function) according to the Cockroft-Gault Equation. Data has been plotted according to the corresponding ranges for mild, moderate, and normal function.

CI, confidence interval; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NVAF, nonvalvular atrial fibrillation; RCT, randomised controlled trial; SE, systemic embolism.

1. Capranzano P *et al.* Expert Rev Cardiovasc Ther 2013; 11: 959–73; 2. Granger CB *et al.* N Engl J Med 2011; 365: 981–92; 3. Connolly SJ *et al.* N Engl J Med 2009; 361: 1139–51; 4. Patel MR *et al.* N Engl J Med 2011; 365: 883–91; 5. Bohula EA *et al.* Circulation 2016; 134(1): 24-36; 6. LIXIANA SmPC, May 2023. Available at https://www.ema.europa.eu/en/documents/product-information/lixiana-epar-product-information_en.pdf. [Last accessed September 2025].

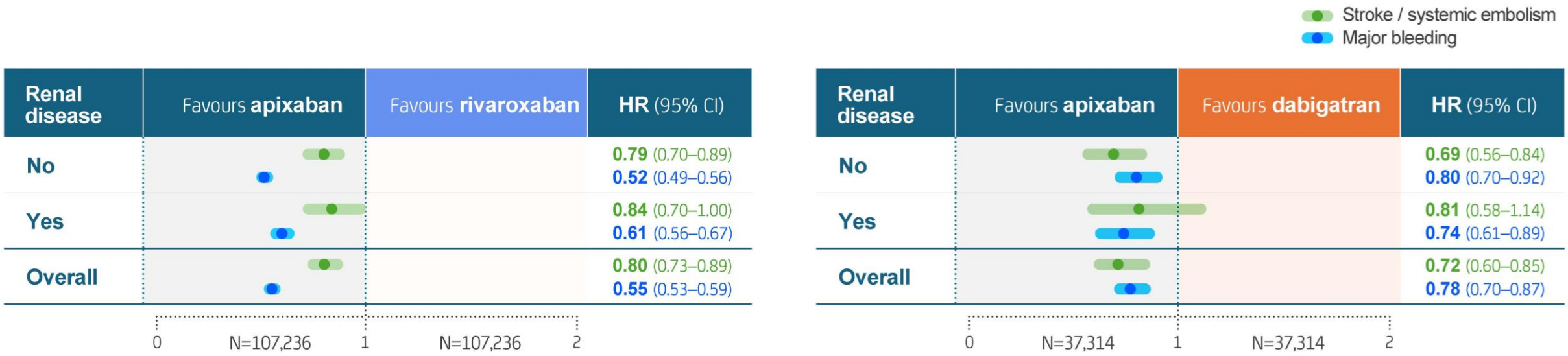
ARISTOPHANES: apixaban vs warfarin RWE in patients with NVAF and renal impairment*[1]



Adapted from Lip *et al.* 2018[1]

There are no head-to-head RCTs comparing the DOACs in NVAF. This analysis did not include edoxaban due to a limited number of eligible patients within the time period analysed.[2]
This analysis compared individual DOACs against warfarin or one another after propensity score matching to standardise characteristics, so comparisons cannot be made. These results should only be used for hypothesis generation and must be interpreted with caution. The effectiveness and safety endpoints in the DOAC RCTs were different to those in the ARISTOPHANES real-world analysis.
*ARISTOPHANES was a large-scale, retrospective, US real-world analysis using pooled data from the US Centers for Medicare and Medicaid Services Medicare data and 4 US commercial claims databases to compare stroke / systemic embolism and major bleeding among patients with NVAF on DOACs or warfarin. Cox proportional hazards regression was used to evaluate the rate of stroke / systemic embolism and major bleeding across 1:1 propensity score matched cohorts (DOAC vs. warfarin, and DOAC vs. DOAC).[1]
CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; NVAF, nonvalvular atrial fibrillation; RCT, randomised controlled trial; RWE, real-world evidence.
1. Lip GYH *et al.* Stroke 2018; 49: 2933–2944; 2. Lip GYH *et al.* Stroke 2018; 49: 2933–2944. Online Supplement.

ARISTOPHANES: DOAC vs. DOAC RWE (apixaban vs. rivaroxaban and dabigatran) for patients with NVAF and renal impairment*[1]



Adapted from Lip *et al.* 2018[1]

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CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; NVAF, nonvalvular atrial fibrillation; RCT, randomised controlled trial; RWE, real-world evidence.
1. Lip GYH *et al.* Stroke 2018; 49: 2933–2944; 2. Lip GYH *et al.* Stroke 2018; 49: 2933–2944. Online Supplement.

Major GI bleeding

Recommendations for oral anticoagulant use in patients with NVAF and prior bleeding[1]

Recommendations	Class[a]	Level[b]
Assessment and management of modifiable bleeding risk factors is recommended in all patients eligible for oral anticoagulation, as part of shared decision-making to ensure safety and prevent bleeding.[439–444]	I	B
Use of bleeding risk scores to decide on starting or withdrawing oral anticoagulation is not recommended in patients with AF to avoid under-use of anticoagulation.[431,445,446]	III	B

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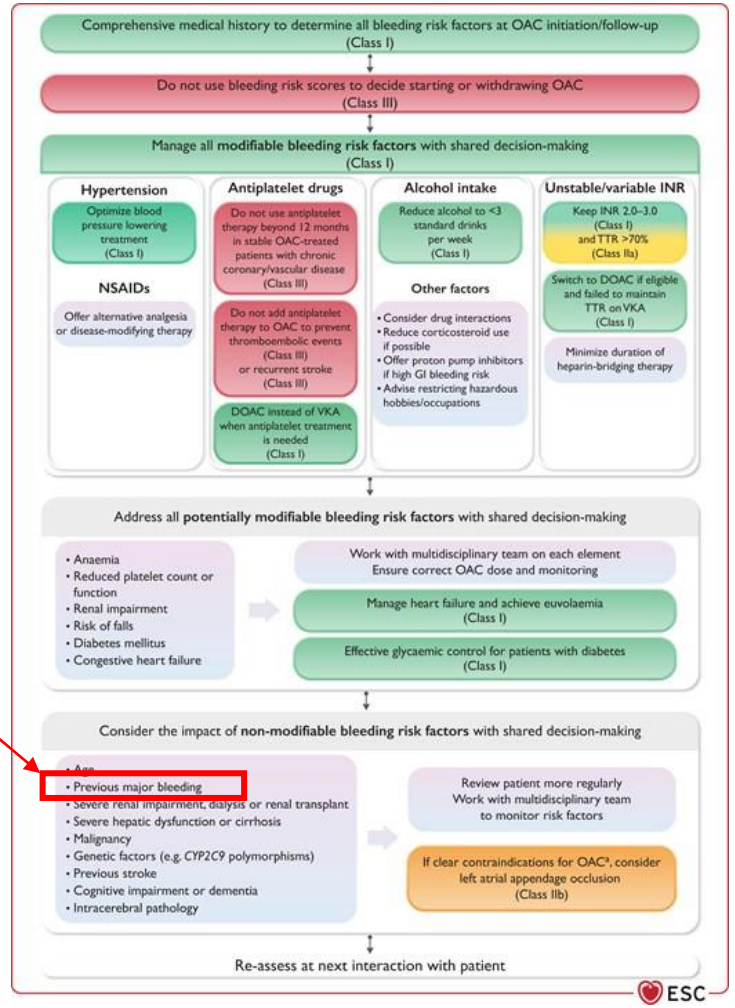
Management of NVAF after a bleeding episode[1]

- Discuss benefits and risk of restarting OAC (shared decision-making approach)
- Aim to re-initiate anticoagulation if source of bleeding has been addressed
- Assess risk of repeat bleeding
- Intensify efforts to modify bleeding risk factors
- Review choice and dose of OAC
- Institute close and ongoing monitoring



ESC guidelines do not recommend routinely switching the anticoagulant regimen of patients with AF without a clear indication to prevent recurrent embolic stroke[1]

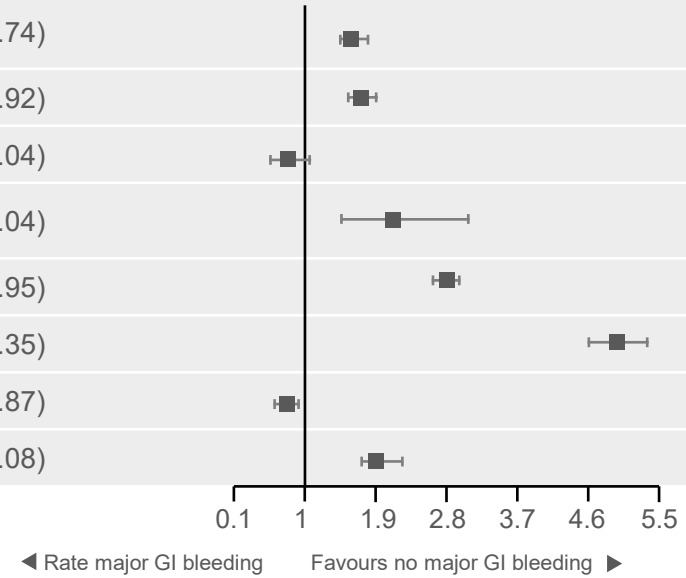
[a]Class of recommendation; [b]Level of evidence.
AF, atrial fibrillation; ESC, European Society of Cardiology; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant.
1. Van Gelder IC *et al*. Eur Heart J 2024; 45(36): 3314-3414.

ARISTOPHANES: Experiencing a major vs non-major GI bleed whilst on an OAC adversely affects stroke/SE and major bleeding risk*

A retrospective analysis using patient data from the CMS data and four US commercial claims databases (N=15,888)

PSM incidence rates and HRs of stroke/SE and major bleeding for patients with major and non-major GI bleeding on apixaban, dabigatran, edoxaban, rivaroxaban or warfarin treatment

	Major GI bleeding	Non-major GI bleeding (reference)	HR (95% CI)	p-value
	Number of events (Incidence per 100 PY)			
Stroke/SE	567 (3.75)	1,127 (2.32)	1.57 (1.42, 1.74)	<0.001
Ischaemic	471 (3.10)	858 (1.76)	1.71 (1.53, 1.92)	<0.001
Haemorrhagic	50 (0.32)	203 (0.41)	0.76 (0.56, 1.04)	0.085
SE	49 (0.32)	73 (0.15)	2.11 (1.46, 3.04)	<0.001
Major bleeding	2,339 (17.92)	2,869 (6.13)	2.79 (2.64, 2.95)	<0.001
GI	1,547 (11.21)	1,045 (2.16)	4.95 (4.57, 5.35)	<0.001
ICH	104 (0.67)	463 (0.94)	0.70 (0.57, 0.87)	0.001
Other	901 (6.15)	1,488 (3.10)	1.92 (1.76, 2.08)	<0.001



Conclusion: major GI bleeding significantly increased the risk of stroke/SE and subsequent major bleeding events compared with the risks without a major GI bleed[1]

Adapted from Deitelzweig S, *et al.* 2021[1].

There are no head-to-head RCTs comparing the DOACs in NVAF; direct comparisons cannot be made between individual DOACs based on these data. Real-world data have some limitations, such as the potential for selection bias, differing outcomes definitions and the potential presence of unmeasured confounders. They are able to show associations but cannot determine causality.

*ARISTOPHANES was a large-scale, retrospective, US real-world analysis using pooled data from the US Centers for Medicare and Medicaid Services Medicare data and four US commercial claims databases to compare stroke/SE and major bleeding amongst patients with NVAF on DOACs or warfarin.

CI, confidence interval; DOAC, direct oral anticoagulant; GI, gastrointestinal; HR, hazard ratio; ICH, intracerebral haemorrhage; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; PY, person-years; RCT, randomised controlled trial; SE, systemic embolism.

1. Deitelzweig S *et al.* Ther Adv Gastroenterol 2021; 14: 1–13.

Conclusions and key takeaways

- High-risk comorbidities and risk factors should be considered when making treatment decisions for patients with VTE and NVAF[1]
- There is a growing body of RWE for use of anticoagulant treatment in key subpopulations of patients with NVAF, including those with previous bleeding, underweight, obesity, CKD and advanced age[2-4,10–12]

Previous bleeding

- RWE shows that there is no association between resuming DOACs after a prior bleed and recurrent bleeding[3]
  - Guidelines indicate that DOAC treatment should be resumed if the source of bleeding has been addressed[1]

CKD

- Dose reductions for some DOACs should be considered in patients with low CrCl[4–7]
- RWE from ARISTOPHANES showed that outcomes with apixaban were generally consistent in patients with or without renal impairment[8]
  - Other RWE indicates that patients treated with DOACs have a lower risk of adverse renal outcomes when compared with VKA[9]

Weight

- Studies pooling DOACs show similar effectiveness and safety outcomes across weight categories[10,11]
  - The AHA/ACC/HRS guidelines do not include special recommendations for obese patients[13]

Advanced age/frailty/multimorbidity

- In ARISTOPHANES, apixaban was associated with a lower risk of stroke/SE and major bleeding vs. warfarin, dabigatran and rivaroxaban in patients with NVAF aged ≥80 years[12]
  - Guidelines indicate that OAC treatment decisions should be carefully considered in elderly patients to manage bleeding risk[14,15]

There are no head-to-head RCTs comparing the DOACs in NVAF; direct comparisons cannot be made between individual DOACs based on these data. Real-world data have some limitations, such as the potential for selection bias, differing outcomes definitions and the potential presence of unmeasured confounders. They are able to show associations but cannot determine causality.

CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; GI, gastrointestinal; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; RCT, randomised controlled trial; RWE, real-world evidence; SE, systemic embolism; VKA, vitamin K antagonist.

1. Van Gelder IC *et al.* Eur Heart J 2024; 45(36): 3314–3414; 2. Lip GYH *et al.* J Thromb Thrombolysis 2022; 54(1): 33–46; 3. Tapaskar N *et al.* Clin Gastroenterol Hepatol 2022; 20: 381–389.e9; 4. ELIQUIS SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf; 5. XARELTO SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf; 6. PRADAXA SmPC. Available at https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf; 7. LIXIANA SmPC, May 2023. Available at https://www.ema.europa.eu/en/documents/product-information/lixiana-epar-product-information_en.pdf. All SmPCs available at: www.ema.europa.eu [Last accessed September 2025]; 8. Lip GYH *et al.* Stroke 2018; 49: 2933–2944; 9. Sitticharoenchai P *et al.* J Am Heart Assoc. 2021; 10(7): e019609; 10. Deitelzweig S *et al.* J Clin Med 2020; 9(6): 1633; 11. Hohnloser SH *et al.* Circulation 2019; 139(20): 2292–2300; 12. Deitelzweig S *et al*. J Am Geriatr Soc 2019; 67(8): 1662–1671; 13. Joglar JA *et al.* Circulation 2023; 149(1): doi:10.1161/CIR.0000000000001193; 14. The American Geriatrics Society. J Am Geriatr Soc 2023; 71(7): 2052–2081; 15. Van Gelder IC et al. Eur Heart J 2024; 45(36): 3314–3414.