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ORIGINAL RESEARCH

Efficacy and Safety of Direct Oral Anticoagulants for Stroke Prevention in Older Patients With Atrial Fibrillation: A Network Meta-Analysis of Randomized Controlled Trials

Donna Shu-Han Lin, MD; Hao-Yun Lo, MD; Kuan-Chih Huang, PhD; Ting-Tse Lin, PhD; Jen-Kuang Lee, MD, PhD

Background

- Stroke prevention in older patients with AF represents a clinical dilemma and challenge.
- Older age is associated with elevated ischemic stroke and systemic embolism risks in patients with AF, and the proportion of strokes attributable to AF also increases with age. Conversely, the incidence of intracranial hemorrhages (ICHs) during warfarin therapy for stroke prevention is substantially higher in the older population, particularly in those aged >85 years.
- The introduction of direct oral anticoagulants (DOACs) has revolutionized stroke prevention in AF, with all DOACs showing superior or noninferior efficacy and safety compared with vitamin antagonists (VKAs).
- Several DOACs have published data on their efficacy and safety in the older population. However, direct comparisons between DOACs are lacking in these patients.

AIM of the study

- To compare the efficacy and safety of different DOACs in patients aged ≥75 years, with particular foci on various bleeding outcomes and the subgroup of very old patients.

Methods

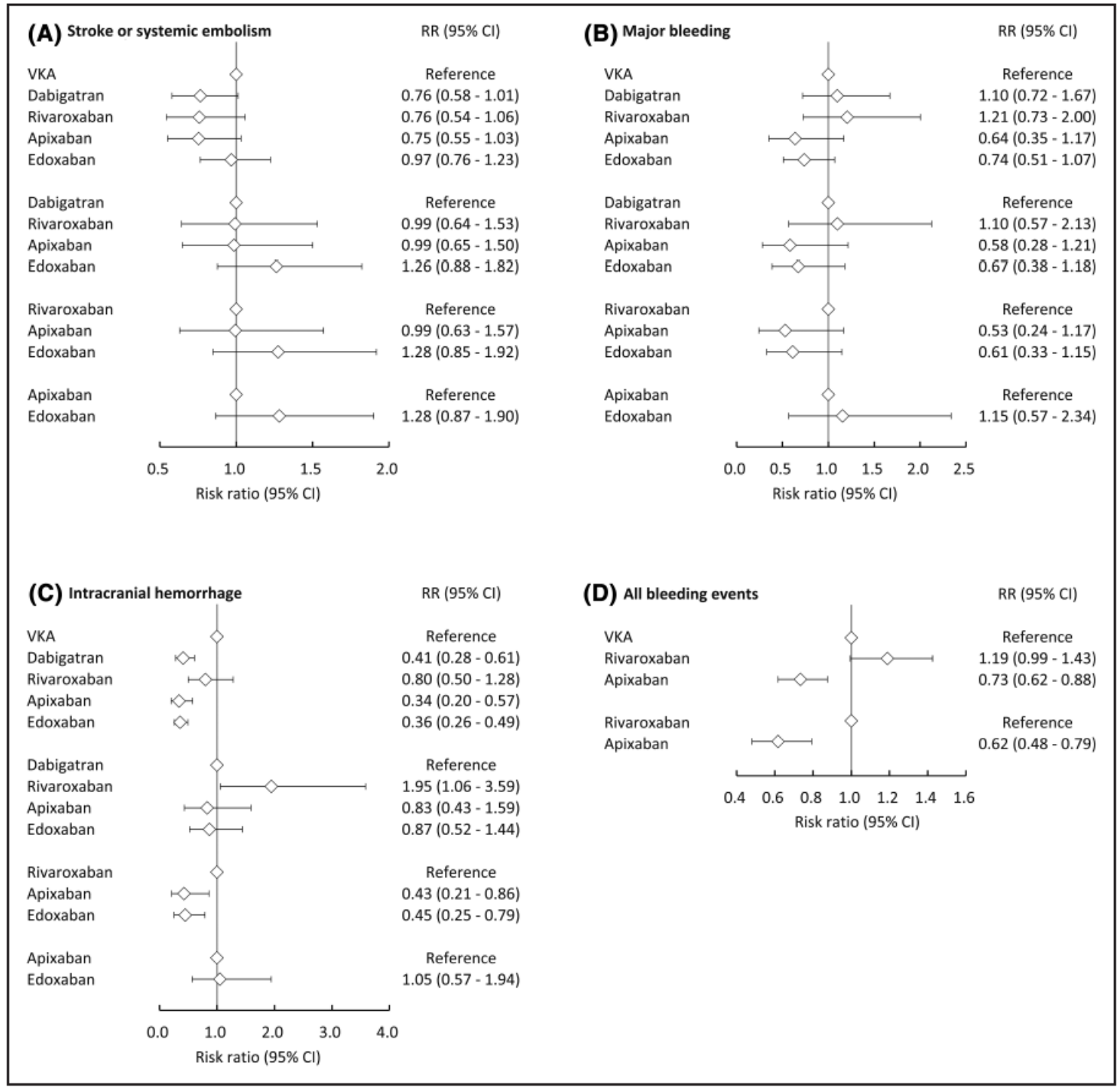
- Network meta-analysis.
- The efficacy outcome was the composite of stroke and systemic embolism.
- The safety outcomes were major bleeding, clinically relevant bleeding, and ICH.
- High- and low-dose regimens and factor IIa and Xa inhibitors were also compared.

Results: efficacy

- Across all DOACs investigated, there were no statistically significant differences in stroke or systemic embolism risks.
- Dabigatran, rivaroxaban, and apixaban had substantially but nonsignificantly lower risks than the control (VKA).
- There was a trend toward lower efficacy with edoxaban, which performed similarly to VKA in the included trials (RR, 0.97 [95% CI, 0.76–1.23]).

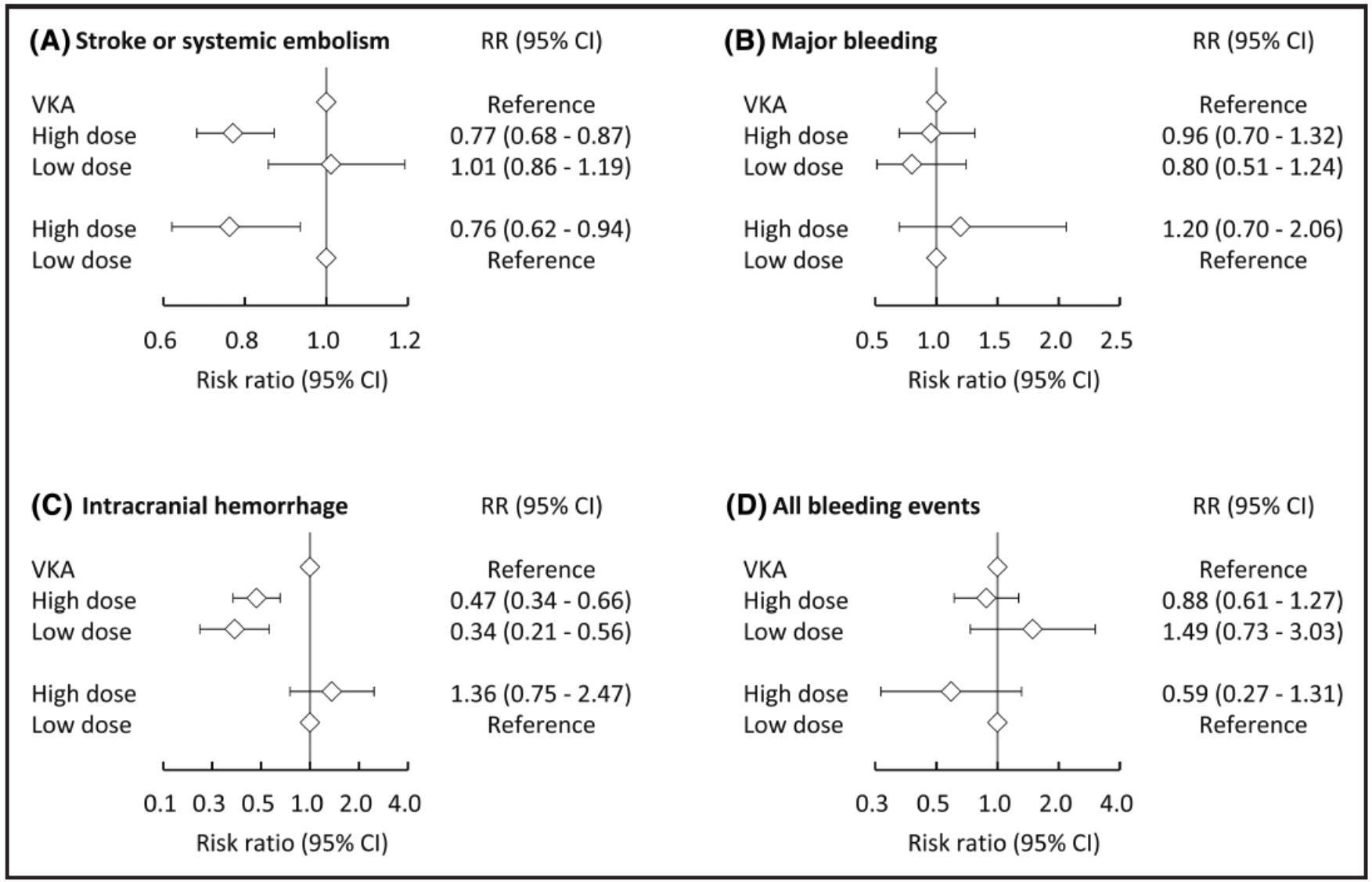
Results: safety

- There were no statistically significant differences in major bleeding between each DOAC and VKA.
- There was a trend toward lower major bleeding risk with apixaban (RR, 0.64 [95% CI, 0.35–1.17]) and edoxaban (RR, 0.74 [95% CI, 0.51–1.07]).
- Dabigatran (RR, 0.41 [95% CI, 0.28–0.61]), apixaban (RR, 0.34 [95% CI, 0.20–0.57]), and edoxaban (RR, 0.36 [95% CI, 0.26–0.49]) had significantly lower ICH risks than VKA and rivaroxaban.
- Apixaban had significantly lower risks for all bleeding events than VKA (RR, 0.73 [95% CI, 0.62– 0.88]).


(A) Stroke or systemic embolism
RR (95% CI)
VKA
Reference
Dabigatran
0.76 (0.58 - 1.01)
Rivaroxaban
0.76 (0.54 - 1.06)
Apixaban
0.75 (0.55 - 1.03)
Edoxaban
0.97 (0.76 - 1.23)
Dabigatran
Reference
Rivaroxaban
0.99 (0.64 - 1.53)
Apixaban
0.99 (0.65 - 1.50)
Edoxaban
1.26 (0.88 - 1.82)
Rivaroxaban
Reference
Apixaban
0.99 (0.63 - 1.57)
Edoxaban
1.28 (0.85 - 1.92)
Apixaban
Reference
Edoxaban
1.28 (0.87 - 1.90)
0.5 1.0 1.5 2.0
Risk ratio (95% CI)
(B) Major bleeding
RR (95% CI)
VKA
Reference
Dabigatran
1.10 (0.72 - 1.67)
Rivaroxaban
1.21 (0.73 - 2.00)
Apixaban
0.64 (0.35 - 1.17)
Edoxaban
0.74 (0.51 - 1.07)
Dabigatran
Reference
Rivaroxaban
1.10 (0.57 - 2.13)
Apixaban
0.58 (0.28 - 1.21)
Edoxaban
0.67 (0.38 - 1.18)
Rivaroxaban
Reference
Apixaban
0.53 (0.24 - 1.17)
Edoxaban
0.61 (0.33 - 1.15)
Apixaban
Reference
Edoxaban
1.15 (0.57 - 2.34)
0.0 0.5 1.0 1.5 2.0 2.5
Risk ratio (95% CI)
(C) Intracranial hemorrhage
RR (95% CI)
VKA
Reference
Dabigatran
0.41 (0.28 - 0.61)
Rivaroxaban
0.80 (0.50 - 1.28)
Apixaban
0.34 (0.20 - 0.57)
Edoxaban
0.36 (0.26 - 0.49)
Dabigatran
Reference
Rivaroxaban
1.95 (1.06 - 3.59)
Apixaban
0.83 (0.43 - 1.59)
Edoxaban
0.87 (0.52 - 1.44)
Rivaroxaban
Reference
Apixaban
0.43 (0.21 - 0.86)
Edoxaban
0.45 (0.25 - 0.79)
Apixaban
Reference
Edoxaban
1.05 (0.57 - 1.94)
0.0 1.0 2.0 3.0 4.0
Risk ratio (95% CI)
(D) All bleeding events
RR (95% CI)
VKA
Reference
Rivaroxaban
1.19 (0.99 - 1.43)
Apixaban
0.73 (0.62 - 0.88)
Rivaroxaban
Reference
Apixaban
0.62 (0.48 - 0.79)
0.4 0.6 0.8 1.0 1.2 1.4 1.6
Risk ratio (95% CI)

Results: Low versus high-dose regimens

- High dose regimens (dabigatran 150 twice daily, rivaroxaban 20 mg once a day, edoxaban 60 mg once a day, apixaban 5 mg twice daily) showed superior efficacy in stroke or systemic embolism prevention compared with VKA (RR, 0.77 [95% CI, 0.68–0.87]) and low-dose regimens (dabigatran 110 mg twice daily, rivaroxaban 15 mg once a day, edoxaban 30 mg once a day, apixaban 2.5 mg twice daily)(RR, 0.76 [95% CI, 0.62–0.94]).
- Both high and low-dose regimens had similar major and any bleeding risks to VKA but were associated with significantly lower ICH risks (high-dose regimen versus VKA: RR, 0.47 [95% CI, 0.33–0.66]; low-dose regimen versus VKA: RR, 0.34 [95% CI, 0.21–0.56]).

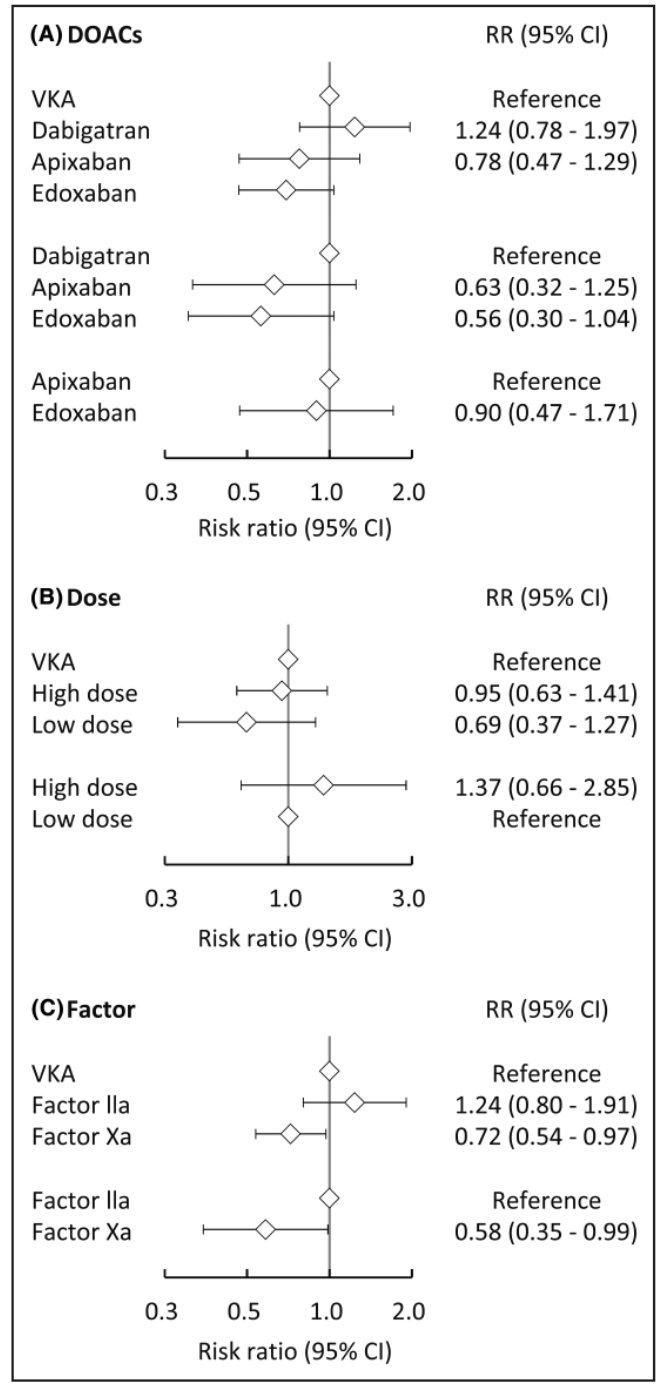

(A) Stroke or systemic embolism
RR (95% CI)
VKA
High dose
Low dose
High dose
Low dose
Reference
0.77 (0.68 - 0.87)
1.01 (0.86 - 1.19)
0.76 (0.62 - 0.94)
Reference
0.6 0.8 1.0 1.2
Risk ratio (95% CI)
(B) Major bleeding
RR (95% CI)
VKA
High dose
Low dose
High dose
Low dose
Reference
0.96 (0.70 - 1.32)
0.80 (0.51 - 1.24)
1.20 (0.70 - 2.06)
Reference
0.5 1.0 1.5 2.0 2.5
Risk ratio (95% CI)
(C) Intracranial hemorrhage
RR (95% CI)
VKA
High dose
Low dose
High dose
Low dose
Reference
0.47 (0.34 - 0.66)
0.34 (0.21 - 0.56)
1.36 (0.75 - 2.47)
Reference
0.1 0.3 0.5 1.0 2.0 4.0
Risk ratio (95% CI)
(D) All bleeding events
RR (95% CI)
VKA
High dose
Low dose
High dose
Low dose
Reference
0.88 (0.61 - 1.27)
1.49 (0.73 - 3.03)
0.59 (0.27 - 1.31)
Reference
0.3 0.5 1.0 2.0 4.0
Risk ratio (95% CI)

Results: factor IIa versus factor Xa inhibitors

- Both factor IIa and Xa inhibitors led to fewer stroke and systemic embolic events than VKA.
- Major bleeding risks did not differ significantly between factor IIa inhibitors, factor Xa inhibitors, and VKA.
- Both factor IIa and Xa inhibitors led to fewer ICH events than VKA (factor IIa versus VKA: RR, 0.41 [95% CI, 0.23–0.72]; factor Xa versus VKA: RR, 0.43 [95% CI, 0.30–0.63]).

Results: very old patients

- No data about rivaroxaban.
- Dabigatran, apixaban, edoxaban, and VKA had similar major bleeding risks in patients aged ≥80 years, both at high or low-dose regimens.
- Factor Xa inhibitors showed superior safety in terms of major bleeding risk to VKA (RR, 0.72 [95% CI, 0.54–0.97]) and factor IIa inhibitors (RR, 0.58 [95% CI, 0.35–0.99]) in patients aged ≥80 years.
- The risk did not significantly differ between factor IIa inhibitors and VKA (RR, 1.24 [95% CI, 0.80–1.91]).


(A) DOACs
RR (95% CI)
VKA
Reference
Dabigatran
1.24 (0.78 - 1.97)
Apixaban
0.78 (0.47 - 1.29)
Edoxaban
Dabigatran
Reference
Apixaban
0.63 (0.32 - 1.25)
Edoxaban
0.56 (0.30 - 1.04)
Apixaban
Reference
Edoxaban
0.90 (0.47 - 1.71)
0.3
0.5
1.0
2.0
Risk ratio (95% CI)
(B) Dose
RR (95% CI)
VKA
Reference
High dose
0.95 (0.63 - 1.41)
Low dose
0.69 (0.37 - 1.27)
High dose
1.37 (0.66 - 2.85)
Low dose
Reference
0.3
1.0
3.0
Risk ratio (95% CI)
(C) Factor
RR (95% CI)
VKA
Reference
Factor IIa
1.24 (0.80 - 1.91)
Factor Xa
0.72 (0.54 - 0.97)
Factor IIa
Reference
Factor Xa
0.58 (0.35 - 0.99)
0.3
0.5
1.0
2.0
Risk ratio (95% CI)

Conclusions

- In patients aged ≥75 years, using DOACs in AF was associated with lower stroke and systemic embolic event risks and similar bleeding risks to VKA, with a trend toward lower efficacy with edoxaban.
- The use of rivaroxaban was associated with greater risk of ICH compared with other DOACs.
- In older patients, high-dose regimens showed superior efficacy in preventing embolic events without increasing bleeding risk compared with low-dose regimens and VKA.
- Further studies focused on older patients are needed to guide treatment in this high-risk population.