FATAL ORAL ANTICOAGULANT RELATED INTRACRANIAL HEMORRHAGE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction

- **Intracranial hemorrhage (ICH)** is the most feared complication in patients treated with oral anticoagulants due to non-valvular atrial fibrillation (NVAF) [1].
- **Non-vitamin K oral anticoagulants (NOACs)** reduce the risk of ICH compared to **vitamin K antagonists (VKAs)** [2].

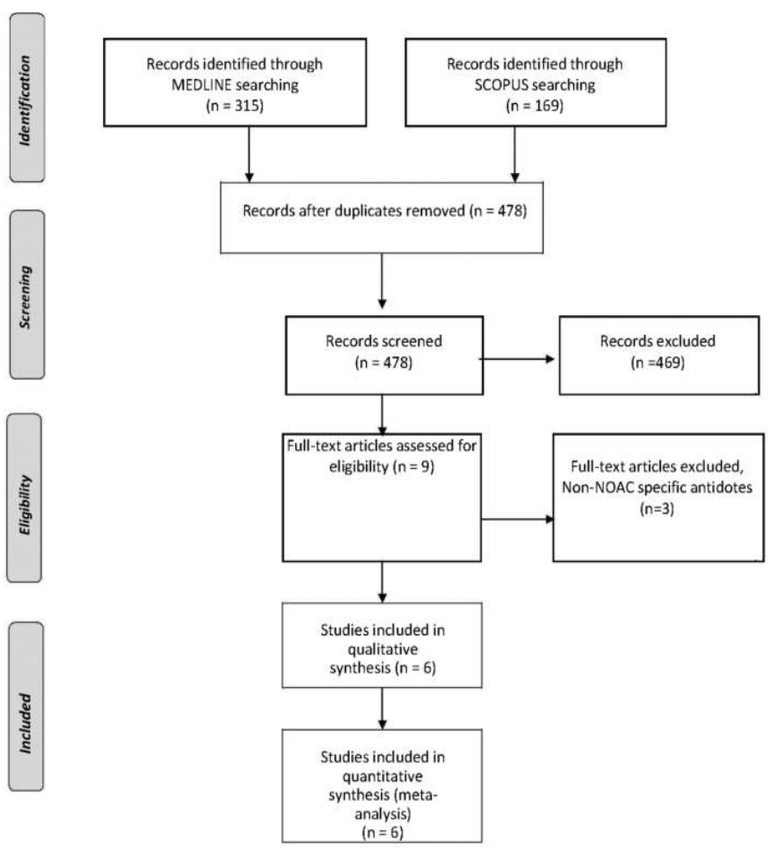
Methods

- We performed a **systematic review and meta-analysis** to evaluate the risk of fatal NOAC-related ICH compared to VKA-related ICH.
- We calculated the corresponding **risk ratios (RRs)** in each included study to express the relative risk of fatal ICH among all patients receiving oral anticoagulation with either NOACs or VKAs.
- We additionally evaluated the mortality rates in NOAC-related ICH in patients treated with and without NOAC-specific reversal agents (idarucizumab or andexanet alpha).
- **Case fatality** was evaluated at 30-90 days following symptom onset.

Results

- Our literature search identified **6 eligible studies** (4 RCTs and 2 open-label trials of NOAC-specific reversal agents; Figure 1 & Table).

Figure 1. Flow chart presenting the selection of eligible studies



Results

Table. Overview of included studies

Study Name	Agent	RCT	Total Patients (n)	Time of evaluation
ARISTOTLE [3]	Apixaban (2.5mg/ 5mg)	yes	9088	30 days
	Warfarin		9052	
ENGAGE AF-TIMI 48 [4]	Edoxaban (30mg)	yes	7002	30 days
	Edoxaban (60mg)		7012	
	Warfarin		7012	
RE-LY [5]	Dabigatran (110mg)	yes	6015	30 days
	Dabigatran (150mg)		6076	
	Warfarin		6022	
ROCKET AF [6]	Rivaroxaban (15mg/ 20mg)	yes	7111	90 days
	Warfarin		7125	
ANNEXA-4 [7]	factor Xa inhibitors antidote	no	67	30 days
RE-VERSE AD [8]	Idarucizumab	no	503	30 days

- In pairwise analyses **NOACs were found to have lower risk of fatal ICH compared to VKAs** (RR=0.46, 95%CI: 0.36-0.58) with no heterogeneity (I^2=0%) across included RCTs (Figure 2A).
- **However, the case fatality rate was similar in NOAC-related and VKA-related ICH** (RR=1.00, 95%CI: 0.84-1.19) with no evidence of heterogeneity (I^2=0%; Figure 2B).
- In the indirect analysis **case fatality rate of NOAC-related ICH in patients treated with specific reversal agents was lower compared to the rest** (17%, 95%CI: 11%-24% vs. 41%, 95%CI: 34-49%; p<0.001; Figure 3).

Figure 2. Forest plots on the risk of fatal intracranial hemorrhage in the (A) whole study population and (B) patients with intracranial hemorrhage from available randomized controlled trials comparing non-vitamin K oral anticoagulants to warfarin in patients with atrial fibrillation.

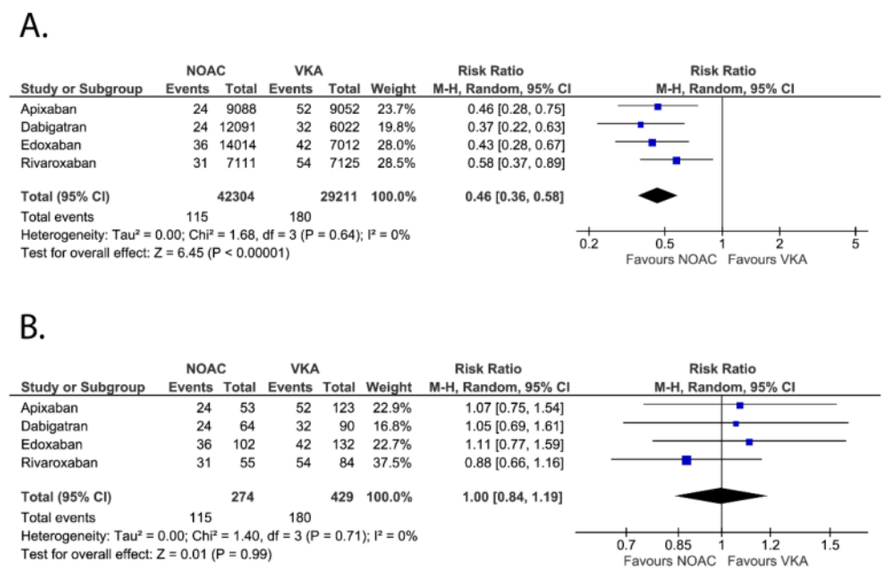
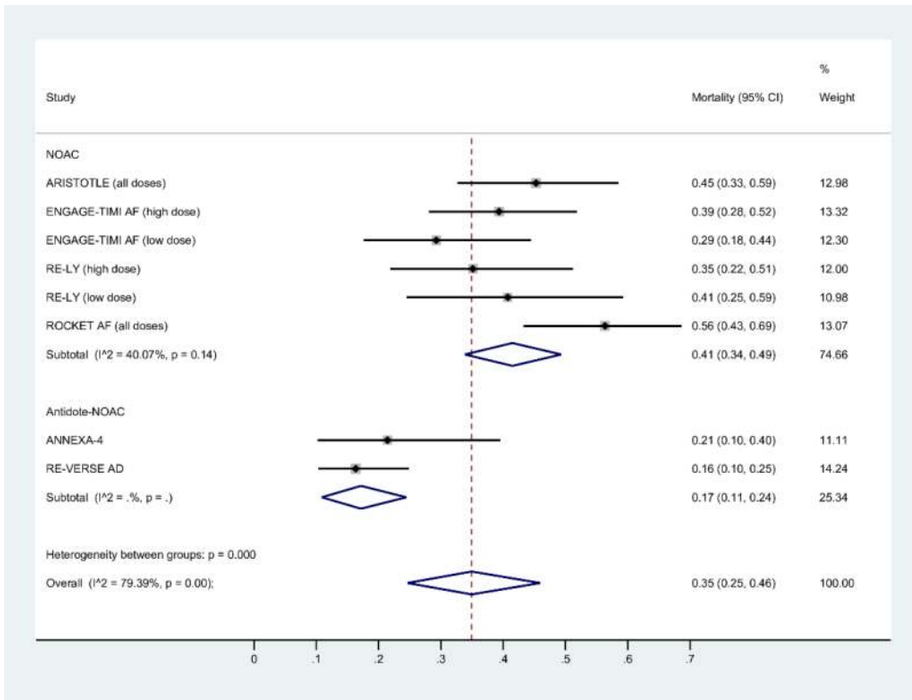


Figure 3. Forest plot on the incidence rates of fatal intracranial hemorrhage in the subgroups of patients with intracranial hemorrhage related to the use of non-vitamin K oral anticoagulants stratified by the use of specific antidote reversal agents.



Conclusion

- ✓ NOACs halve the risk of fatal ICH in NVAF patients compared to VKAs.
- ✓ Indirect comparisons indicate that NOAC-specific reversal agents may be associated with lower case fatality rate in NOAC-related ICH.

References

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