Effect of oral anticoagulants in atrial fibrillation patients with polypharmacy: a meta-analysis

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Abstract

Aims: The aim of the present meta-analysis was to evaluate the effectiveness and safety of non–vitamin K antagonist oral anticoagulants (NOACs) vs. vitamin K antagonists (VKAs) in atrial fibrillation (AF) patients with polypharmacy. Methods and results: Randomized controlled trials or observational studies reporting the data about the NOACs and VKAs therapy among AF patients with polypharmacy were included. The search was performed in the PubMed and Embase databases up to November 2022. There were no differences in the rates of SSE but increased risk of all-cause death and major bleeding between moderate polypharmacy and severe polypharmacy versus no-polypharmacy patients. The use of NOACs compared with VKAs was significantly associated with reduced risks of stroke or systemic embolism (SSE) in AF patients with moderate polypharmacy (hazard ratios [HRs], 0.77 [95% confidence intervals [CIs], 0.69–0.86]) and severe polypharmacy (HR, 0.76 [95% CI, 0.69–0.82]) and there was no significant difference in major bleeding (moderate polypharmacy: HR, 0.87 [95% CI, 0.74–1.01]; severe polypharmacy: HR, 0.91 [95% CI, 0.79–1.06]) between the two groups. There were no differences in the rates of ischemic stroke, all-cause death, and gastrointestinal bleeding but reduced risk of any bleeding between the NOACs and VKAs users. Compared with VKAs, the risk of intracranial hemorrhage was reduced in patients with moderate polypharmacy but not in patients with severe polypharmacy in NOACs users. Conclusion: In patients with AF and polypharmacy, NOACs showed advantages over VKAs in SSE and bleeding, and non-inferiority in major bleeding, ischemic stroke, all-cause death, intracranial hemorrhage, and gastrointestinal bleeding.

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Abstract

Aims: The aim of the present meta-analysis was to evaluate the effectiveness and safety of non–vitamin K antagonist oral anticoagulants (NOACs) vs. vitamin K antagonists (VKAs) in atrial fibrillation (AF) patients with polypharmacy.

Methods and results: Randomized controlled trials or observational studies reporting the data about the NOACs and VKAs therapy among AF patients with polypharmacy were included. The search was performed in the PubMed and Embase databases up to November 2022. A total of 12 studies involving 767,093 AF patients were included. There were no differences in the rates of SSE but increased risk of all-cause death and major bleeding between moderate polypharmacy and severe polypharmacy versus no-polypharmacy patients. For the primary outcomes, the use of NOACs compared with VKAs was significantly associated with reduced risks of stroke or systemic embolism (SSE) in AF patients with moderate polypharmacy (hazard ratios [HRs], 0.77 [95% confidence intervals [CIs], 0.69–0.86]) and severe polypharmacy (HR, 0.76 [95% CI, 0.69–0.82]) and there was no significant difference in major bleeding (moderate polypharmacy: HR, 0.87 [95% CI, 0.74–1.01]; severe polypharmacy: HR, 0.91 [95% CI, 0.79–1.06]) between the two groups. In secondary outcomes, there were no differences in the rates of ischemic stroke, all-cause death, and gastrointestinal bleeding but reduced risk of any bleeding between the NOACs and VKAs users. Compared with VKAs, the risk of intracranial hemorrhage was reduced in patients with moderate polypharmacy but not in patients with severe polypharmacy in NOACs users.

Conclusion: In patients with AF and polypharmacy, NOACs showed advantages over VKAs in SSE and bleeding, and non-inferiority in major bleeding, ischemic stroke, all-cause death, intracranial hemorrhage, and gastrointestinal bleeding.

Keywords: Atrial fibrillation; non-vitamin K oral antagonists; vitamin K antagonists; polypharmacy; meta-analysis.

Introduction

Atrial fibrillation (AF) is an age-related cardiac arrhythmia, and the elderly aged between 65-85 have occupied nearly 70% of AF patients[1, 2]. Elderly AF patients are often accompanied by a huge comorbidity burden and polypharmacy use. Polypharmacy refers to the situation in which an individual uses multiple drugs at the same time, but there is no international consensus on the threshold and measurement methods of drug use[3].

In patients with AF, oral anticoagulation is necessary to prevent thrombotic events. Current evidence has indicated that the non–vitamin K antagonist oral anticoagulants (NOACs) served as a safer and more effective alternative to warfarin for nonvalvular AF patients, featured fewer drug-food interactions, and rapid

onset of action[4-7]. However, when encountering polypharmacy, a critical treatment issue is presented. In this setting, anticoagulated patients with polypharmacy frequently exhibit an unexpected dose-response relationship to oral anticoagulant (OAC) therapy, in which polypharmacy has been demonstrated to be a risk factor for both anticoagulation-related events such as bleeding and thromboembolism[8-10].

Despite guideline recommendations [ESC, APHRS][11, 12], only approximately 50% of elderly AF patients received OAC therapy[1]. On the one hand, owing to the multiple comorbidities and polypharmacy, these patients take the risks of pill burden, drug-drug interaction, non-adherence, and adverse drug events[13]. On the other hand, the bleeding risk associated with advanced age makes the use of anticoagulants more cautious[14]. In this context, the exploration of safe and effective OAC treatments for AF patients with polypharmacy is necessary.

Several post-hoc analyses of randomized controlled trials (RCTs) in patients with AF polypharmacy have been conducted. For example, Focks et al. conducted a post-hoc analysis of the ARISTOTLE trial and showed that apixaban was more effective than warfarin and was at least just as safe[9]. Numerous real-world studies, such as the ARISTOPHANES study have demonstrated that the effectiveness and safety profiles are more favorable for NOACs vs warfarin[15].

We therefore performed this comprehensive systematic review and meta-analysis via high-quality studies to determine the effectiveness and safety of NOACs versus Vitamin K antagonists (VKAs) in AF patients with polypharmacy. The aims of this meta-analysis were as follows: (1) comparing the risks of stroke, death, and bleeding in AF patients with and without polypharmacy; (2) assessing the efficacy and safety outcomes of NOACs versus VKAs in patients with AF and polypharmacy; (3) assessing the effects of NOACs versus VKAs in AF patients with and without polypharmacy.

Methods

We conducted this meta-analysis based on the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2) criteria. The results were presented according to the preferred reporting items for the systematic review and meta-analysis (PRISMA) 2020 statement. Ethical approval was not required, as this study only included articles of published data in the public domain.

Literature search

Two reviewers performed the literature search, systematically searching the PubMed and Embase databases sources until November 2022 for studies exploring the effect of NOACs in AF patients with polypharmacy. The following search terms were used: (1) “atrial fibrillation”, (2) “dabigatran” OR “rivaroxaban” OR “apixaban” OR “edoxaban” OR “non-vitamin K antagonist oral anticoagulant” OR “direct oral anticoagulant” OR “novel oral anticoagulant” OR “NOAC” OR “DOAC”, (3) “polypharmacy” OR “polymedication”, (4) “Vitamin K antagonists” OR “VKA” OR “warfarin” OR “dicoumarol” OR “acenocoumarol” OR “coumadin”. The above four categories of search terms were combined using the Boolean operator “and”. The detailed search strategies are shown in **Supplemental Table I** . In addition, the reference lists of the retrieved articles and prior reviews were manually checked for additional eligible studies. We applied no restrictions on the language of publication.

Inclusion and exclusion criteria

RCTs, post-hoc analyses, or observational (prospective or retrospective cohort) studies focusing on AF patients with polypharmacy who received VKAs or NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) were all enrolled. Included studies need to report quantitative estimates of the hazard ratios (HRs) and 95% confidence intervals (CIs) for clinical outcomes among patients.

Criteria for exclusion were as follows: (1) certain publication types (e.g., reviews, comments, case reports, case series, letters, editorials, and meeting abstracts); (2) data was unable to obtain or insufficient; (3) studies did not report the relevant outcomes or classification of polypharmacy. If there were overlapping data among two or more studies, we included the one with the largest sample size.

Clinical Outcomes

To assess the efficacy and safety of NOACs versus VKAs in patients with AF and polypharmacy, we divided the included clinical outcomes into primary outcomes (stroke or systemic embolism, major bleeding) and secondary outcomes (ischemic stroke, all-cause death, any bleeding, intracranial bleeding, gastrointestinal bleeding).

Study selection and data abstraction

The titles and abstracts of the studies acquired from the electronic databases were examined separately by two reviewers. Subsequently, we selected the eligible studies after the full-text screenings based on the pre-defined inclusion criteria. Conflicts were settled by the conversation between the two reviewers or communication with the relevant authors. The following data of the included studies were abstracted: study characteristics (first author, year of publication, study design), study population, and baseline characteristics (study period, demographic, sample size, age, female ratio, definition of polypharmacy, follow-up period), effectiveness and safety outcomes, confounders, and outcome data (sample size and the number of events between groups, adjusted HRs).

Study quality assessment

We assessed the quality of post-hoc analysis RCTs or observational cohorts by using the Newcastle-Ottawa Scale (NOS) tool. This tool had three domains with a total of nine points: the selection of cohorts (0-4 points), the comparability of cohorts (0-2 points), and the assessment of the outcome (0-3 points). In this meta-analysis, the NOS of [?]6 and <6 points were moderate-to-high quality and low quality, respectively.

Statistical analysis

The statistical analyses were conducted using the Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark; https://community.cochrane.org/). In this study, significant heterogeneity was indicated by a P-value of < 0.10 in the Cochrane Q test or an I^2 value of $> 50\%$, which led to the use of random-effects models and the exploration of a potential source of heterogeneity. When these tests were negative for heterogeneity, fixed-effects models were chosen to calculate pooled HRs through the inverse-variance method. In the pooled analysis, the adjusted HRs and 95% CIs were converted to the natural logarithms (Ln [HR]) and their corresponding standard errors (Ln [upper CI]-Ln [lower CI])/3.92), which were pooled by a DerSimonian and Laird random-effects model with an inverse variance method.

Results

The flow chart of literature retrieval is presented in **Figure 1** . Through searching the PubMed, Embase databases, and prior reviews, our initial search yielded 206 articles, from which a total of 42 duplicate articles were removed. After screening the records, we excluded 77 certain articles such as reviews. By reviewing the title and abstract, 19 remaining studies were potentially available, and further assessed under the full-text screenings. According to the pre-defined inclusion and exclusion criteria, we subsequently excluded 7 studies because (1) article is a meta-analysis (n=1)[16]; (2) studies did not report the relevant outcomes (n=3)[17-19]; (3) studies did not report the classification of polypharmacy (n=3) [20-22]. Finally, a total of 12 studies were included in our meta-analysis[8-10, 15, 23-30].

Study Characteristics and Quality

The baseline characteristics of the included studies are illustrated in**Table 1** . Among the 9 included observational studies, 3 were from the UK[29], Germany[8], and Japan [30], the other 6 were derived from nationwide or health insurance claims databases in the United States[15, 23-27]. Of the 3 included post-hoc analyses of RCTs[9, 10, 28], all were multicenter large-scale randomized clinical trials. The mean age of patients ranged from 60.1 to 83.0 years, and the sample size was from 1,558 to 188,863. Across studies, the study populations in the NOACs group were administrated with dabigatran, apixaban, rivaroxaban, and edoxaban. **Supplementary Table II** shows the clinical outcomes of the included articles and the adjustment for confounding

factors of the outcomes. Risk of bias evaluation was performed, shown in **Supplementary Table III** . All the studies had a NOS of [?]6 points suggesting moderate-to-high quality.

Polypharmacy definition

There was a slight variation in the definition of polypharmacy used across the studies included in our meta-analysis. We defined polypharmacy as a discrete definition. When dividing the boundaries of non-polypharmacy, moderate polypharmacy, and severe polypharmacy, the threshold used by the study author was used. Specifically, 5 studies [10, 15, 23-25] included articles defined moderate polypharmacy as the use of 5-9 drugs, 3 studies [8, 28, 30] included articles defined moderate polypharmacy use as the use of 5-8 drugs, and 2 studies [9, 29] included articles defined moderate polypharmacy use as 6-8 drug use, and 1 article[27] defined moderate polydrug use as 4-8 drug use. Correspondingly, 6 articles [8, 9, 27-30] defined severe polypharmacy as the use of [?]9 drugs, and 6 articles [10, 15, 23-26] defined severe polypharmacy as the use of [?]10 drugs. It should be noted that the article by Martinez et al. [26] defines polypharmacy as the use of 5 or more drugs and explores the grouping of 10 or more drugs in the secondary analysis. Therefore, we did not classify its data into the moderate polypharmacy group but used its secondary analysis data as the severe polypharmacy group. Detailed classification information is shown in **Table 1** .

Association between polypharmacy and outcomes in AF patients

We synthesized the results of the included 3 post-hoc analyses RCTs [9, 10, 28] and 2 observational studies [8, 30] reporting outcomes in AF patients receiving oral anticoagulation with and without polypharmacy.

As shown in **Figure 2** and **Supplementary Figure I** , there were no differences in the rates of SSE between moderate polypharmacy (HR, 1.07 [95% CI, 0.95–1.21]) and severe polypharmacy (HR, 1.14 [95% CI, 0.89–1.47]) versus no-polypharmacy patients. Moderate polypharmacy was associated with an increased risk of all-cause death (HR, 1.34 [95% CI, 1.25–1.44]) and major bleeding (HR, 1.23 [95% CI, 1.10–1.37]) compared with no-polypharmacy AF patients. Risk of all-cause death (HR, 1.66 [95% CI, 1.29–2.31]) and major bleeding (HR, 1.56 [95% CI, 1.25–1.93]) were significantly increased in severe polypharmacy patients. In addition, the risk of intracranial hemorrhage was not statistically different in moderate polypharmacy (HR, 1.17 [95% CI, 0.81–1.70]), but was increased in severe polypharmacy (HR, 1.27 [95% CI, 1.02–1.58]), compared with non-polypharmacy patients.

Effect of NOACs versus VKAsin patients with AF and polypharmacy

Primary outcomes

As shown in **Figure 3** , the use of NOACs compared with VKAs was significantly associated with reduced risks of SSE in AF patients with moderate polypharmacy (HR, 0.77 [95% CI, 0.69–0.86]) and severe polypharmacy (HR, 0.76 [95% CI, 0.69–0.82]). As presented in**Figure 4** , there was no significant difference in major bleeding (moderate polypharmacy: HR, 0.87 [95% CI, 0.74–1.01]; severe polypharmacy: HR, 0.91 [95% CI, 0.79–1.06]) between the two groups.

Secondary outcomes

As shown in **Supplementary Figure II-VI** , there was no significant difference in ischemic stroke (moderate polypharmacy: HR, 0.92 [95% CI, 0.80–1.08]; severe polypharmacy: HR, 0.90 [95% CI, 0.73–1.12]), all-cause death (moderate polypharmacy: HR, 1.02 [95% CI, 0.83–1.26]; severe polypharmacy: HR, 1.00 [95% CI, 0.75–1.33]), and gastrointestinal bleeding (moderate polypharmacy: HR, 1.09 [95% CI, 0.94–1.26]; severe polypharmacy: HR, 1.14 [95% CI, 0.94–1.39]) between the NOACs and VKAs users. The use of NOACs was associated with a reduced risk of any bleeding in AF patients with moderate polypharmacy (HR, 0.85 [95% CI, 0.72–1.00]) and severe polypharmacy (HR, 0.83 [95% CI, 0.72–0.95]). On the contrary, compared with VKAs, the risk of intracranial hemorrhage was reduced in patients with moderate polypharmacy (HR, 0.67 [95% CI, 0.46–0.98]) but not in patients with severe polypharmacy (HR, 0.68 [95% CI, 0.42–1.10]) in NOACs users.

Sensitivity analysis

As presented in **Table 2** , we re-analyzed all outcomes using fixed-effects models, with subgroup analyses based on study design. For the primary outcomes of SSE and major bleeding, the results of the fixed-effects model and subgroup analyses were similar to the random-effects model analyses described above. However, fixed-effects models for major bleeding outcomes showed an advantage in using NOACs in both moderate and severe polypharmacy patients. In the sensitivity analysis, the corresponding HR values were not changed substantially after excluding one study at a time.

Publication Bias

For the primary outcomes, there were no potential publication biases by inspecting the funnel plots (**Supplementary Figure XIV**). For the secondary outcomes, there were no publication biases inspected by the funnel plots (**Supplementary FigureXV**).

Effects of NOACs versus VKAsin AF patients with and without polypharmacy

We synthesized the results of the included 3 post-hoc RCTs [9, 10, 28] and 8 retrospective [15, 23-27, 29, 30] studies that reported the effects of NOACs versus VKAs in AF patients with and without polypharmacy. As shown in **Table 3** , all primary and secondary outcomes of NOACs and VKAs had comparably similar rates between AF patients with and without polypharmacy (all $P>0.05$;**Supplementary Figure VII-XIII**). There were also no publication biases inspected by the funnel plots for all primary and secondary outcomes (**Supplementary Figure XVI- XVII**).

Discussion

The main findings of our meta-analysis can be summarized as follows: 1) There were no differences in the rates of SSE between polypharmacy and no-polypharmacy AF patients, while moderate and severe polypharmacy was associated with an increased risk of all-cause death and major bleeding compared with no-polypharmacy AF patients. 2) For the primary outcomes, NOACs were associated with a significant reduction in SSE but with no significant difference in the risk of major bleeding compared with VKAs in AF patients with moderate polypharmacy and severe polypharmacy. 3) For the secondary outcomes, NOACs were associated with a reduction in any bleeding but with no significant difference in the risk of ischemic stroke, all-cause death, and gastrointestinal bleeding compared with VKAs in AF patients with moderate polypharmacy and severe polypharmacy. Compared with VKAs, the risk of intracranial hemorrhage was reduced in patients with moderate polypharmacy but not in patients with severe polypharmacy in NOACs users. 4) Similar rates of primary and secondary outcomes (NOACs versus warfarin) were observed between AF patients with and without polypharmacy.

Polypharmacy is common in the elderly population who is often accompanied by AF [1, 2]. Although polypharmacy has been shown to be associated with adverse clinical outcomes, the evidence for an association between polypharmacy and adverse outcomes in AF patients receiving maintenance oral anticoagulants is sparse and mixed. The meta-analysis by Harskamp et al [16] enrolled two high-quality post-hoc analyses of RCTs showed that the frequencies of bleeding events and mortality, but not of SSE, were increased with the increasing number of concomitant drugs. Our study yielded the same results after including more high-quality retrospective studies and post-hoc analyses of RCTs, which was more statistically significant. Of note, this increased risk of adverse outcomes should be placed in the context of the association between comorbidities present at baseline. Since subjects with severe polypharmacy are older and sicker, often with multiple comorbidities and frailty, the observed associations between polypharmacy, bleeding events, and all-cause death need to be tightly controlled for potential confounding factors. Since most of the included articles were extensively adjusted for covariates, our conclusions show an increased risk of adverse outcomes with greater confidence. However, Focks et al [9] focused only on the number of concomitant medications as a marker of comorbidities or frailty and poor outcomes, without extensive adjustment for baseline levels. The inclusion of data from this study partly explains the high heterogeneity of our pooled results.

Regardless, our results show that polypharmacy is associated with poor clinical outcomes in AF patients receiving oral anticoagulant maintenance therapy, suggesting that clinicians should minimize the risk of bleed-

ing during the treatment of such patients, including during discontinued concomitant antiplatelet therapy as appropriate.

Before the advent of NOACs, VKAs had been the first choice for anticoagulation in AF patients. As research progresses, 4 landmark RCTs confirm that NOACs are superior to warfarin in the AF population [4-7]. The current guidelines only recommend the use of NOACs as first-line anticoagulants in general population AF patients, but specifically for those patients with polypharmacy, their safety and efficacy remain to be verified. Our results show that NOACs are non-inferior to VKAs in AF patients with polypharmacy and are even superior to VKAs in some efficacy and safety outcomes, such as SSE and any bleeding. The intuitive effect of polypharmacy is an increase in drug-drug interactions, which may lead to a decrease in the efficacy of given drugs or an increase in the level of toxicity. While NOACs can target a single coagulation factor such as factor Xa and factor IIa, the anticoagulant effect is independent of antithrombin, has a rapid onset of oral administration, and has less interaction with food and drugs [31]. This property of NOACs gives them an advantage in a polypharmacy population with an increased risk of drug interactions.

Existing evidence suggests that NOACs may interact pharmacokinetically with strong Cytochrome P450 (CYP3A4) and P-glycoprotein (P-gp) inhibitor or inducer, thereby affecting their absorption, distribution, or clearance levels [32]. Even though many of the drugs used in AF patients are P-gp or CYP3A4 inhibitors (e.g., verapamil, amiodarone, and rifampicin), guidelines recommend avoiding or very cautiously combining NOACs with them [33]. Unfortunately, our study did not focus on this issue, but related studies have shown that the advantages of NOACs in terms of efficacy or safety are not affected in patients using the above-mentioned combined inhibitors [10, 16].

Another effect of polypharmacy is a decrease in drug adherence. A systematic review by Claxton et al. [34]showed that drug adherence decreased with increasing frequency of dosing, with adherence of 79% for once-daily medication and only 51% for four-times-daily medication. This result may be due to a patient's loss of trust in medical care or drug intolerance. In any case, decreased drug adherence in patients with AF is associated with an increased risk of thromboembolic and bleeding events. There has been no consensus on whether NOAC or warfarin drug adherence is higher. There is a view that warfarin requires frequent monitoring and dose adjustment, which has been shown to be associated with higher adherence [35]. Other studies have shown that NOACs (especially rivaroxaban and dabigatran) have higher adherence in AF patients [26, 28, 36]. The latter may partly explain the demonstrated advantages of NOACs over VKAs in terms of efficacy and safety. Unfortunately, many relevant retrospective studies based on claims databases, because frequent dose changes of warfarin make assessment difficult, did not further assess adherence to both oral anticoagulants.

Limitation

Our meta-analysis has several limitations. First, the thresholds for defining polypharmacy status differed in each study, and subjects with different baseline characteristics may have significant bias despite statistical adjustments. Second, the included studies only assessed the extent of patients' polypharmacy at baseline and were unable to adjust drug use for subsequent prescription changes. Fortunately, the burden of co-morbidity in polypharmacy populations is often chronic, and the number of drugs rarely changes significantly. In addition, the study did not take into account non-prescription drugs and health products that patients were taking, which could lead to a potential influence on the results. Third, drug compliance largely determines how patients actually take their medication. Unfortunately, the frequent dose changes of warfarin prevented the study from further evaluating the compliance of the two classes of oral anticoagulants. Finally, due to the limited amount of data, we were unable to perform head-to-head comparisons among NOACs, and more studies in the future may reveal which NOACs would be more suitable for this population.

Conclusion

This meta-analysis finds no differences in the rates of SSE but increased risk of all-cause death and major bleeding between moderate polypharmacy and severe polypharmacy versus no-polypharmacy patients. In patients with AF and polypharmacy, NOACs showed advantages over VKAs in SSE and any bleeding, and

non-inferiority in major bleeding, ischemic stroke, all-cause death, intracranial hemorrhage, and gastrointestinal bleeding. In addition, all primary and secondary outcomes of NOACs and VKAs were compared at similar rates between AF patients with and without polypharmacy.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: Not required.

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Figure legends

Figure 1: The flow chart of literature retrieval of this meta-analysis

Figure 2. A summary graph of pooled results for associations between polypharmacy and outcomes in AF patients.

AF=atrial fibrillation; SSE=stroke or systemic embolism; CI=confidence interval; IV=inverse of the variance; SE=standard error.

Figure 3. Forest plot for comparing the SSE of NOACs with VAKs in AF patients with polypharmacy.

SSE=stroke or systemic embolism; NOACs=non–vitamin K antagonist oral anticoagulants; VKAs=vitamin K antagonists; AF=atrial fibrillation; CI=confidence interval; IV=inverse of the variance; SE=standard error.

Figure 4. Forest plot for comparing the major bleeding of NOACs with VAKs in AF patients with polypharmacy.

NOACs=non–vitamin K antagonist oral anticoagulants; VKAs=vitamin K antagonists; AF=atrial fibrillation; CI=confidence interval; IV=inverse of the variance; SE=standard error.

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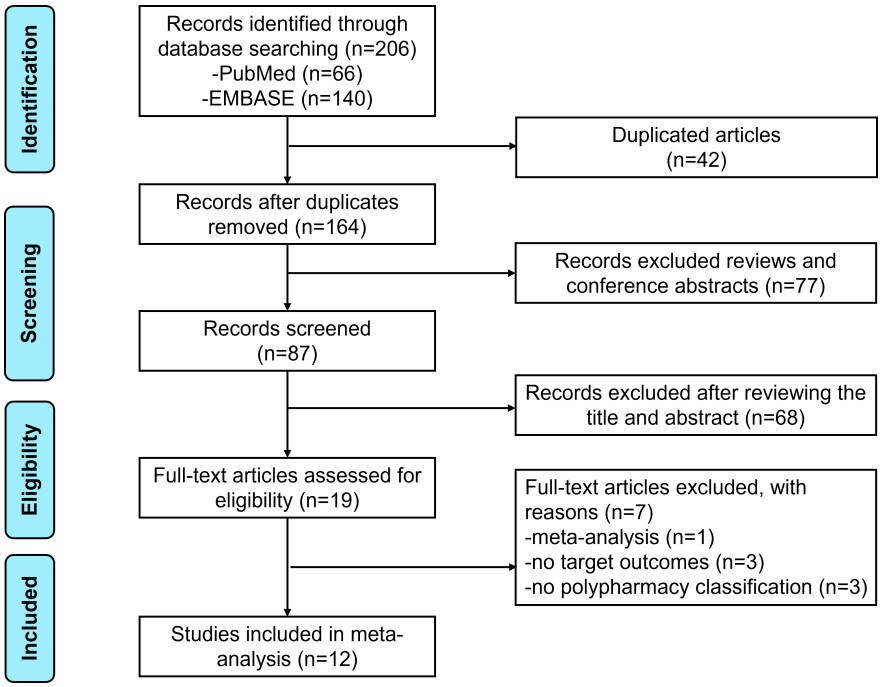
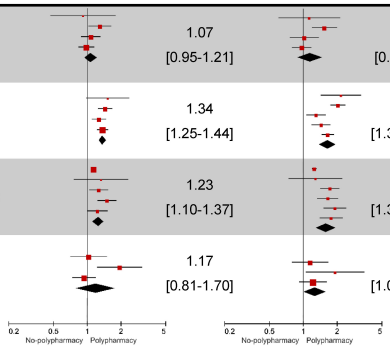
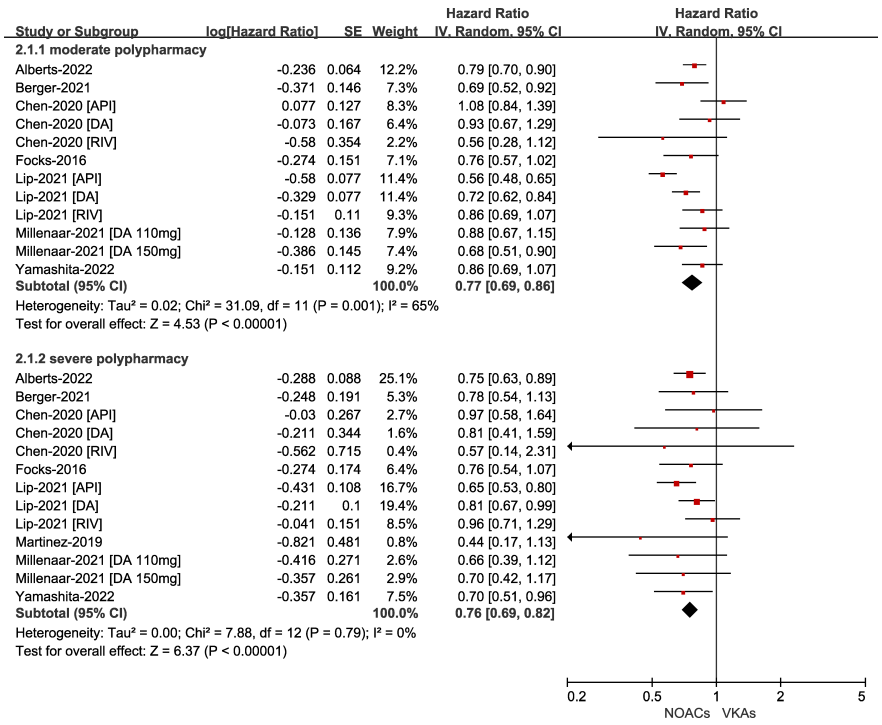
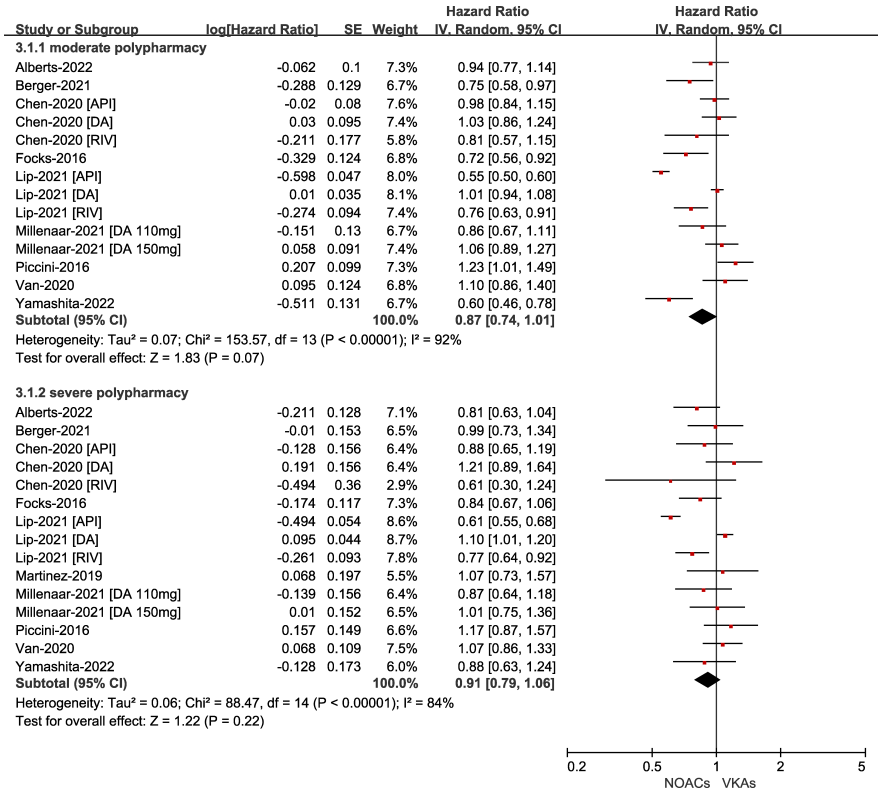


Outcomes	No. of studies	No-polypharmacy	Polypharmacy	Moderate group	Hazard ratio (95%CI)	Severe group	Hazard ratio (95%CI)
SSE	4	24,550	41,345		1.07 [0.95-1.21]		1.14 [0.89-1.47]
All-cause death	5	29,716	54,292		1.34 [1.25-1.44]		1.65 [1.39-1.95]
Major bleeding	6	192,519	230,229		1.23 [1.10-1.37]		1.59 [1.31-1.93]
Intracranial hemorrhage	3	24,230	39,654		1.17 [0.81-1.70]		1.27 [1.02-1.58]







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