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Original article

Non-vitamin K antagonist oral anticoagulants with amiodarone, P-glycoprotein inhibitors, or polypharmacy in patients with atrial fibrillation: Systematic review and meta-analysis

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ABSTRACT

Background: Amiodarone, which inhibits CYP2C9 and P-glycoprotein, is commonly prescribed with non-vitamin K antagonist oral anticoagulants (NOACs) and polypharmacy in high-risk atrial fibrillation (AF) patients. We studied efficacy and safety of NOACs in AF patients receiving amiodarone, P-glycoprotein inhibitor, or polypharmacy.

Methods: After a systematic database search (Medline, EMBASE, CENTRAL, SCOPUS, and Web of Science), four phase-III randomized trials comparing NOACs and warfarin in "with/without amiodarone," "with/without P-glycoprotein inhibitors," or "with/without multiple (≥5, polypharmacy) concomitant drugs" subgroups were included. The outcomes were pooled using a random-effects model to determine the relative risks (RRs) for stroke/systemic thromboembolism (SSTE), major bleeding (MB), intracranial hemorrhage (ICH), and all-cause mortality.

Results: Among patients taking amiodarone, superiority of NOACs over warfarin in non-amiodarone users disappeared in terms of SSTE ($p = 0.11$), MB ($p = 0.95$), ICH ($p = 0.26$), and mortality ($p = 0.32$). No safety benefit (MB) of NOACs compared to warfarin was shown in patients taking P-glycoprotein inhibitors ($p = 0.47$), but SSTE prevention was still superior with NOACs compared to warfarin in the same patient group [RR = 0.78 (0.61–0.99), $p = 0.04$, $I^2 = 11\%$]. In AF patients with polypharmacy, NOACs showed a lower risk of SSTE [RR = 0.82 (0.71–0.96), $p = 0.01$, $I^2 = 0\%$] and mortality [RR = 0.91 (0.83–0.99), $p = 0.04$, $I^2 = 0\%$], but not MB ($p = 0.81$) compared to warfarin.

Conclusions: NOACs were equivalent to warfarin among AF patients with concomitant amiodarone use in terms of efficacy, safety, and mortality. There was no safety benefit of NOACs over warfarin in patients using polypharmacy or P-glycoprotein inhibitors.

Systematic review registration: The protocol of this meta-analysis was registered on PROSPERO under CRD42018104808 (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42018104808).

Introduction

Atrial fibrillation (AF) patients who need to take anticoagulants often have many comorbidities, and concomitant multiple medications, including amiodarone, are becoming more prevalent for these patients in guideline-driven practice [1]. Although complicated due to its side effects, amiodarone is a potent and frequently used anti-arrhythmic drug that can be prescribed for AF patients with significant structural heart disease [2]. However, amiodarone has drug interactions related to multiple metabolizing enzymes. All four non-vitamin K antagonist oral anticoagulants (NOACs), dabigatran, rivaroxaban, apixaban, and edoxaban act as substrates for the gastrointestinal lumen-located efflux transporter permeability-glycoprotein (P-glycoprotein), or

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are metabolized by cytochrome P450 to varying degrees [3]. In addition, some P-glycoprotein inhibitors, such as amiodarone, dronedarone, verapamil, and quinidine, are broadly used with NOACs in managing AF. Administration of NOACs with P-glycoprotein inhibitors can increase the plasma concentrations and potentiate the anticoagulating effects or bleeding side effects of these drugs [3,4]. However, there has been no investigation into whether standard-dose NOACs are appropriate among AF patients with these concomitant interacting drugs, especially P-glycoprotein inhibitors including amiodarone [3]. There are no pooled analyses despite published clinical trials that have reported these outcomes among NOAC-treated AF patients with these concomitant drugs. With this background, we aimed to understand the outcomes of NOAC therapy among AF patients and to assess their relative benefits compared to dose-adjusted warfarin for these subgroups ["with/without amiodarone," "with/without P-glycoprotein inhibitors," and "with polypharmacy (≥5) or with fewer (<5) concomitant drugs"]. Important secondary outcomes, including mortality and intracranial hemorrhage (ICH), were also investigated to help clinicians better understand the full implications of NOACs for these subgroups.

Methods

This systematic review and meta-analysis was performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [5] and commonly used reporting guidelines (Supplementary Table 1: PRISMA checklist). The protocol of this meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under identification number CRD42018104808.

Literature search and search strategy

Two investigators (IS Kim and HJ Kim) independently performed comprehensive online literature searches of the following databases: Medline, EMBASE, the Cochrane Library (CENTRAL), SCOPUS, and Web of Science. Articles were searched from the database inception without language restrictions, and the search was started on January 8, 2018 and updated on July 22, 2018. The search strategy was discussed with IS Kim, HN Pak, and a methodological expert, HJ Kim. The detailed strategy is presented in Supplementary Table 2. Reference lists of published meta-analyses were also reviewed.

Study selection

Two independent investigators screened the title and abstract of each identified article and then reviewed the full text of each article according to the inclusion and exclusion criteria. Those included were studies of patients with non-valvular AF (aged ≥18 years and followed for more than 1 year) given either NOACs or warfarin anticoagulation therapy that reported the efficacy and safety outcomes according to the concomitant use of amiodarone, P-glycoprotein inhibitors, and polypharmacy (≥5 concomitant drugs). The detailed criteria are presented in Table 1. Any disagreements or uncertainties between the two reviewers were resolved by consensus, and the final decision was made following a discussion with the senior reviewer (HN Pak).

Data extraction

Two independent investigators extracted trial-level data from the publications of the main clinical trials, supplementary appendices, or reported subgroup data. Extracted data included the study characteristics and available baseline characteristics of the participants from each included clinical trial. Potential dose-dependent differences in the efficacy and safety outcomes of NOACs compared to warfarin, analyzed by subgroups according to the concomitant use of amiodarone, P-glycoprotein inhibitors, and polypharmacy, were the main focus of this meta-analysis.

Table 1
Inclusion and exclusion criteria for eligible study.

Inclusion criteria
The inclusion criteria for study eligibility were as follows:
(1) Participants
– Patients with non-valvular AF aged ≥18 years with indications for anticoagulation according to published guidelines [31] for preventing SSTE.
– Follow-up duration more than 1 year.
(2) Intervention
– Patients in the intervention group received any of the following NOACs: dabigatran, rivaroxaban, apixaban, or edoxaban.
(3) Control
– Patients in the control group received a vitamin K antagonist (i.e. warfarin).
(4) Outcomes: Reported outcomes for AF patients according to subgroups: (i) patients who received, or who did not receive amiodarone at randomization (with or without amiodarone); (ii) patients who received, or who did not receive P-glycoprotein inhibitors at randomization (with or without P-glycoprotein inhibitors); (iii) patients who took multiple (≥5)[a] or fewer (<5) concomitant medications at baseline (with polypharmacy or with fewer concomitant medications). Alternatively, subgroup results for these patients who were allocated to NOACs or warfarin were included
– The primary efficacy outcome was the number of patients with SSTE event.
– The primary safety outcome was the number of patients with major bleeding, mainly defined using the ISTH [32] criteria. However, some trial-specific definitions[b] were also adopted.
– The secondary outcomes were the number of patients with ICH and all-cause mortality, if reported data were available.
(5) Study design
– Phase III RCTs and reported data by subgroups (with or without amiodarone; with polypharmacy or with fewer concomitant medications) comparing any NOAC with warfarin as described above.
– Published in a peer-reviewed journal.
– If two or more studies originated from the same author or center, we determined whether the participants were duplicated across by studies by discussion between two authors (IS Kim and HJ Kim). If the participants had been duplicated, we included only the article that presented data according to these subgroups.
Exclusion criteria
The exclusion criteria were as follows:
(1) No eligible comparators, such as studies in which patients were treated with anti-platelet medication as an intervention, or as a control group.
– Studies for ximelagatran as an interventional comparator, because it was withdrawn from the market due to its unacceptable hepatic toxicity [33].
(2) Studies reporting less than 1 year of follow-up data.
(3) Studies with level V evidence, such as case reports, letters to the editor, and review articles.
(4) Studies with non-human subjects.

AF, atrial fibrillation; ICH, intracranial hemorrhage; ISTH, International Society on Thrombosis and Hemostasis; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; SSTE, stroke or systemic thromboembolism.
[a] Patients who received ≥5 concomitant medications were defined as subgroup with polypharmacy. Others, <5 concomitant drugs, were defined as subgroup with fewer concomitant medications.
[b] In the RE-LY trial, ISTH criteria plus bleeding events requiring inotropic agents or surgery; in the ROCKET AF trial, ISTH criteria plus bleeding events associated with permanent disability.

Quality assessment

As stated in the inclusion criteria, phase III randomized controlled trials (RCTs) and reported data comparing outcomes

of NOACs and warfarin based on concomitant drugs (with or without amiodarone, P-glycoprotein inhibitors, and/or polypharmacy) in AF patients were included. For trials that were not originally designed to randomize into division by these subgroups, the study validity was assessed using the risk of bias assessment tool for observational studies [6]. Two independent investigators assessed the study validity. The certainty and grade of evidence were assessed across the studies for each outcome following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [7]. Although each study included a relatively large number of participants, fewer than 10 studies were included. Thus, publication bias was not assessed by the funnel plot due to the low power of this test. Instead, to estimate any publication bias, a comprehensive search of trial registries (https://clinicaltrials.gov; and International Clinical Trials Registry Platform Search Portal of World Health Organization: https://apps.who.int/trialsearch) was performed to identify any completed but unpublished trials.

Statistical analyses

The primary efficacy outcome was a stroke or systemic thromboembolism (SSTE) and the primary safety outcome was major bleeding. If reported data were available, the secondary outcomes were all-cause mortality and ICH. Definitions of major bleeding are given in Table 1. Definitions for all other outcomes were consistent across the included trials. In the primary analysis, the total number of events for each outcome was estimated as the number of patients with that event. Each outcome was calculated as a risk ratio (RR) with a corresponding 95% confidence interval. When necessary, the numbers of patients for the outcome events were calculated based on the reported event rate for each outcome, follow-up duration, and sample size. The outcome of each NOAC based on a standard-dose regimen was analyzed according to the subgroup (with or without amiodarone, P-glycoprotein inhibitors, and/or polypharmacy at enrollment) to identify the efficacy and safety outcomes for each subgroup.

Extracted data were combined with a random-effects model with the effect size presented as the ratio of the risks for each outcome in the NOAC-treated group relative to the warfarin-treated group. The total effect size was estimated by the inverse-variance weighted method. If the designs of the included studies were significantly heterogeneous, the cause of the heterogeneity was sought [5]. This assumption was also investigated by I^2-statistics, visual examination of the forest plot to check whether confidence intervals overlapped across the studies, and the Cochran's Q-test [5]. All statistical analyses were performed using RevMan software version 5.3 (Cochrane Collaboration 2014, Nordic Cochrane Center, Copenhagen, Denmark). Two-tailed p-values <0.05 were considered significant.

A sensitivity analysis for each pooled analysis (Supplementary Appendices) was performed including only studies with a median center-based time in therapeutic range (TTR) $\geq$66%. The rationale for this analysis was that the cut-off level differentiates the efficacy and safety of warfarin from dual antiplatelet therapy [8].

Results

Baseline characteristics of the included studies

Of the 19,238 studies identified in a systematic literature search, 6147 duplicates were removed, and the titles and abstracts of the remaining 13,091 records were screened based on the inclusion criteria. In the screening process, 13,043 records were excluded, and 48 full-text articles were reviewed and assessed for eligibility. Of those, 44 were excluded. Finally, four phase III RCTs that met the predefined criteria were identified, and 6 post hoc studies that reported data according to the use of concomitant amiodarone, P-glycoprotein inhibitors, or polypharmacy were included in this study (Fig. 1) [4,9–14]. The study characteristics and detailed patient characteristics are given in Table 2 and Supplementary Table 3. The standard-dose NOAC regimens were combined and in the resulting pooled analyses are referred to as "standard-dose" NOAC regimens.

NOAC effects in amiodarone-treated AF patients

In amiodarone-treated AF patients (11%, 3107 in NOAC, 3078 in warfarin), NOACs showed similar rates of SSTE ($p = 0.11$), major bleeding ($p = 0.95$), ICH ($p = 0.26$), and all-cause mortality ($p = 0.32$) compared to warfarin (Fig. 2 and Supplementary Fig. 1). In contrast, in AF patients who were not taking amiodarone, NOACs showed a consistently better efficacy and safety for SSTE prevention [RR 0.83 (0.75–0.91), $p < 0.001$, $I^2 = 13\%$], major bleeding [RR 0.83 (0.70–0.98), $p = 0.03$, $I^2 = 78\%$], and ICH [RR 0.50 (0.41–0.61), $p < 0.001$, $I^2 = 7\%$] compared to warfarin. All-cause mortality was also lower in the NOAC group without amiodarone [compared to patients given warfarin RR 0.92 (0.86–0.98), $p = 0.007$, $I^2 = 0\%$] (Fig. 2 and Supplementary Fig. 1).

NOACs with P-glycoprotein inhibitors

Among the patients on P-glycoprotein inhibitors (21%, 6137 in NOAC, 6080 in warfarin), NOACs showed an equivalent safety for major bleeding compared to warfarin ($p = 0.47$, Fig. 3 and Supplementary Fig. 2). Even for ICH, NOACs showed comparable

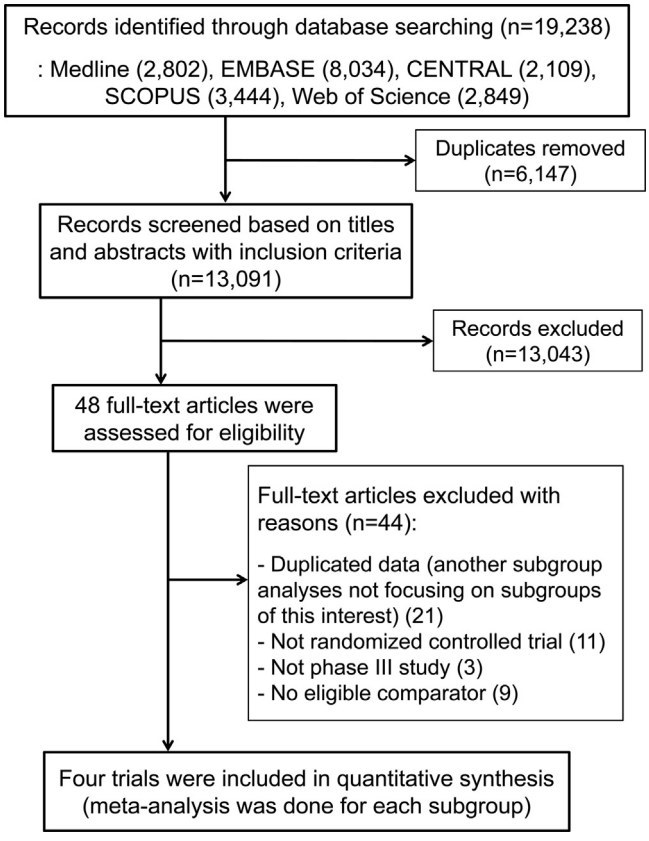

Fig. 1. Study flow diagram of the literature search and selection process of the included studies.

Table 2
Characteristics of included studies.

Study	Study design of main trial/Phase	Intervention (*n*)	Control (target INR range) (*n*)	Patients with amiodarone/with P-gp inhibitors, or/with polypharmacy, *n* (%)[a]		Age, *M* ± SD	Female, %	$CHADS_2$, *M* ± SD	PAF, %	Follow-up years (median)
				NOAC	W	NOAC/W	NOAC/W	NOAC/W	NOAC/W	
ARISTOTLE, 2011 [10,14]	RCT/III	Apixaban 5 mg bid (*n* = 8963)	Warfarin (*n* = 8944)	1009 (11%) /1903 (21%) /5696 (62%)	1042 (11%) /1913 (21%) /5562 (61%)	69 ± 10/69 ± 10	35%/35%	2.1 ± 1.1/2.1 ± 1.1	15%/16%	1.8
ENGAGE AF-TIMI48, 2013 [11,13]	RCT/III	Edoxaban 60 mg qd (*n* = 7035)	Warfarin (*n* = 7036)	866 (12%) /1093 (16%) /NR	827 (12%) /1042 (15%) /NR	71 ± 9/71 ± 9	38%/37%	2.8 ± 1.0/2.8 ± 1.0	26%/25%	2.8
RE-LY, 2009 [12]	RCT/III	Dabigatran 150 mg bid (*n* = 6075)	Warfarin (*n* = 6017)	665 (11%) /1827 (30%) /NR	644 (11%) /1855 (31%) /NR	71 ± 9/72 ± 9	36%/37%	2.1 ± 1.1/2.1 ± 1.1	32%/34%	2.0
ROCKET AF, 2011 [9]	RCT/III	Rivaroxaban 20 mg qd (*n* = 7131)	Warfarin (*n* = 7133)	572 (8%) /1314 (18%) /4590 (64%)	572 (8%) /1270 (18%) /4573 (64%)	71 ± 9/71 ± 9	40%/40%	3.5 ± 0.9/3.5 ± 1.0	18%/18%	1.9

AF, atrial fibrillation; ARISTOTLE, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; ENGAGE AF-TIMI48, the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 trial; INR, international normalized ratio; *M*, mean; NOAC, non-vitamin K antagonist oral anticoagulant; NR, not reported; PAF, paroxysmal atrial fibrillation; P-gp, permeability-glycoprotein (P-glycoprotein); RCT, randomized controlled trial; RE-LY, the Randomized Evaluation of Long-Term Anticoagulation Therapy trial; ROCKET AF, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SD, standard deviation; W, warfarin.

[a] Patients who received ≥5 concomitant medications were defined as polypharmacy subgroup. Others, <5 concomitant drugs, were defined as subgroup of fewer concomitant medications.

outcomes to warfarin in patients on P-glycoprotein inhibitors ($p = 0.06$). In contrast, NOACs showed better safety profiles for major bleeding in the AF group not prescribed P-glycoprotein inhibitors [RR 0.84 (0.71–0.98, $p = 0.03$, $I^2 = 77\%$)]. NOACs showed a better efficacy for SSTE prevention than warfarin in those treated [RR 0.78 (0.61–0.99), $p = 0.04$, $I^2 = 11\%$] and not [RR 0.83 (0.74–0.95), $p = 0.005$, $I^2 = 20\%$] with P-glycoprotein inhibitors.

NOACs in AF patients using polypharmacy

Even with polypharmacy (63%, 10,259 in NOAC, 10,112 in warfarin), NOACs were still superior to warfarin in terms of SSTE [RR 0.82 (0.71–0.96), $p = 0.01$, $I^2 = 0\%$] or all-cause mortality [RR 0.91 (0.83–0.99), $p = 0.04$, $I^2 = 0\%$; Fig. 4 and Supplementary Fig. 3]. However, there were no significant benefits for the risks of major bleeding ($p = 0.81$) and ICH ($p = 0.09$) with NOACs compared to warfarin in polypharmacy-treated AF patients (Fig. 4B and C and Supplementary Fig. 3). In AF patients with fewer than 5 concomitant drugs, NOACs showed a better safety for major bleeding [RR 0.59 (0.45–0.76), $p < 0.001$, $I^2 = 41\%$] and ICH [RR 0.48 (0.32–0.74), $p < 0.001$, $I^2 = 0\%$] compared to warfarin.

Risk of bias for the included studies and quality of evidence across the studies

The risk of bias for each study is summarized in Supplementary Fig. 4. The RE-LY trial was an open-label study on warfarin. However, we judged this study to have a low risk for performance bias because the data appeared to be less affected by the clinical outcomes. We assessed the grade of evidence for each outcome across the studies following the GRADE [7] approach described in Supplementary Table 4. To assess for any publication bias, the completed but unpublished trials were identified and are listed in Supplementary Table 5.

Discussion

Main findings

The focus of this meta-analysis was to evaluate the outcomes for AF patients across all phase III trials that directly compared NOACs with warfarin for concomitant drugs, particularly amiodarone, P-glycoprotein inhibitors, or polypharmacy. Contrary to the superiority of NOACs compared to warfarin in amiodarone non-users, the efficacy and safety were equivalent for NOACs and warfarin in amiodarone users in terms of SSTE prevention, major bleeding, ICH, and mortality among the patients with AF. In AF patients who were taking P-glycoprotein inhibitors or polypharmacy, NOACs did not reduce the major bleeding risk compared to warfarin.

Drug interactions of NOACs

Generally, NOACs have fewer drug interactions with other concomitant drugs, which permits more co-administration with other drugs in NOAC-treated patients than with warfarin. Despite these advantages, excretion or re-secretion over a P-glycoprotein transporter is an important interaction mechanism after absorption of NOACs in the gastrointestinal tract [15]. Therefore, competitive inhibition of P-glycoprotein transporters can increase plasma concentrations of all four NOACs and is also associated with renal clearance [16]. P-glycoprotein inhibitors are also expressed in capillary endothelial cells constituting the blood-brain barrier [17], which may contribute to the lack of the ICH protective effect of NOACs compared to warfarin among AF patients on amiodarone or P-glycoprotein

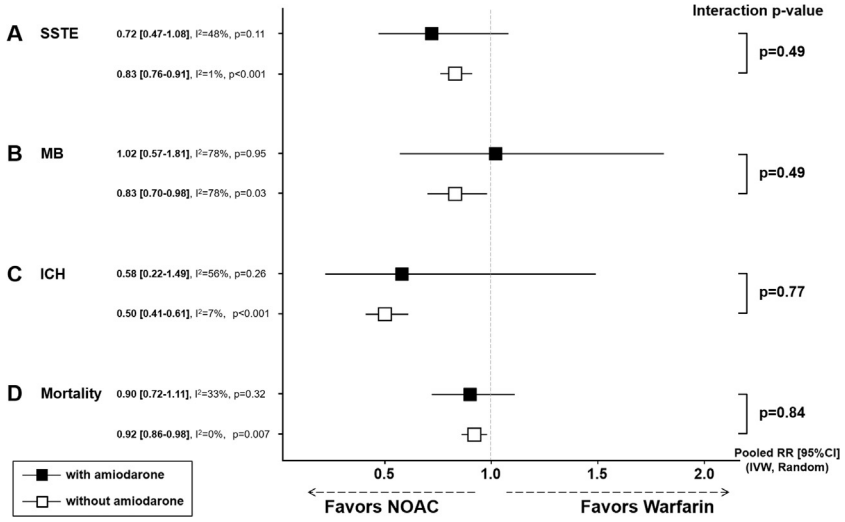

Fig. 2. Forest plot for SSTE, major bleeding, ICH, and all-cause mortality in patients with NOACs versus warfarin, according to amiodarone use. (A) Pooled RR of SSTE for NOACs versus warfarin; (B) pooled RR of major bleeding for NOACs versus warfarin; (C) pooled RR of ICH for NOACs versus warfarin; (D) pooled RR of the all-cause mortality for NOACs versus warfarin. CI, confidence interval; ICH, intracranial hemorrhage; IVW, inverse variance weighted method; MB, major bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; Random, random-effects model; RR, risk ratio; SSTE, stroke or systemic thromboembolism.

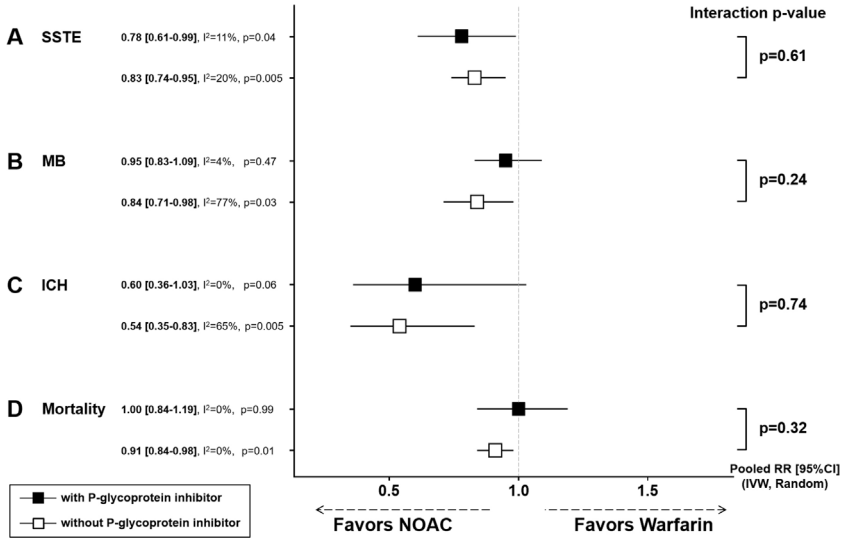

Fig. 3. Forest plot for SSTE, major bleeding, ICH, and all-cause mortality in patients with NOACs versus warfarin, according to the P-glycoprotein inhibitor uses. (A) Pooled RR of SSTE for NOACs versus warfarin; (B) pooled RR of major bleeding for NOACs versus warfarin; (C) pooled RR of ICH for NOACs versus warfarin; (D) pooled RR of all-cause mortality for NOACs versus warfarin. CI, confidence interval; ICH, intracranial hemorrhage; IVW, inverse variance weighted method; MB, major bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; Random, random-effects model; RR, risk ratio; SSTE, stroke or systemic thromboembolism.

inhibitors in this study. A cytochrome P450 (especially CYP3A4)-dependent metabolism is associated with hepatic elimination of apixaban (25%) and rivaroxaban (18%) [3,18]. Inversely, it also means that strong inducers of P-glycoprotein and CYP3A4 (such as carbamazepine and rifampicin) will reduce the plasma concentrations of NOACs; therefore, concomitant use of inducers of P-glycoprotein and CYP3A4 is generally not recommended in NOAC-treated AF patients. Amiodarone is a P-glycoprotein inhibitor that interferes with the metabolism of all four NOACs, consequentially increasing the plasma concentrations and potentiating the anticoagulating effects of NOACs [3]. Although only one phase III RCT was designed around the concomitant use of these P-glycoprotein inhibitors as a dose reduction criterion [19], a dose reduction of other NOACs is primarily recommended according to published criteria regardless of concomitant P-glycoprotein inhibitors [3]. And because most of the amiodarone users or polypharmacy patients have various comorbidities, those worse demographics may diminish NOAC effect. Based on the outcome of this study, these drug interactions should be considered individually when prescribing NOACs with other specific interacting drugs in AF patients, despite fewer drug interactions compared to warfarin.

Trends and risks of polypharmacy

Use of multiple medications is common and a well-known risk factor for frail elderly AF patients with multiple comorbidities [20]. Many AF patients requiring anticoagulation therapy have comorbidities associated with an increasing risk of SSTE that results in a need for multiple medications, and the resulting polypharmacy also involves adverse events with an increasing stroke or bleeding risk. One cross-sectional study found that 42% of

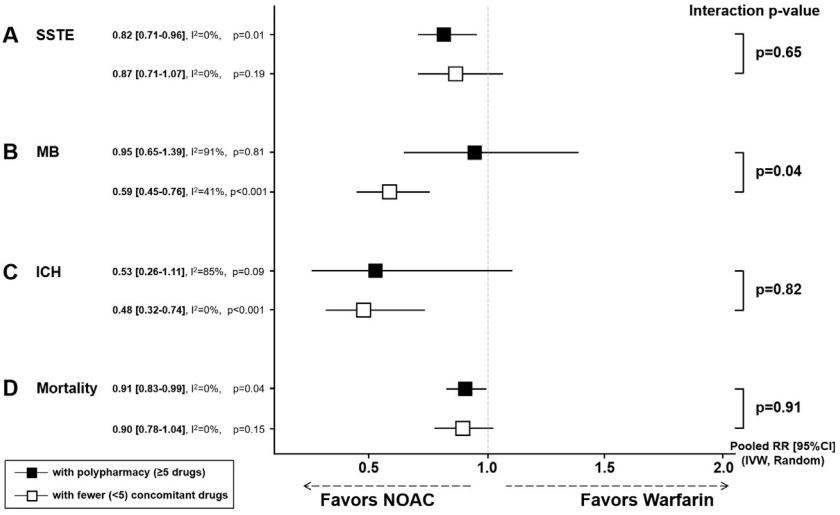

Fig. 4. Forest plot for SSTE, major bleeding, ICH, all-cause mortality in patients with NOACs versus warfarin, according to polypharmacy (≥5 concomitant drugs). (A) Pooled RR of SSTE for NOACs versus warfarin; (B) pooled RR of major bleeding for NOACs versus warfarin; (C) pooled RR of ICH for NOACs versus warfarin; (D) pooled RR of the all-cause mortality for NOACs versus warfarin. CI, confidence interval; ICH, intracranial hemorrhage; IVW, inverse variance weighted method; MB, major bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; Random, random-effects model; RR, risk ratio; SSTE, stroke or systemic thromboembolism.

AF patients are taking concomitant P-glycoprotein-modulating drugs [21]. Drug interactions are one of the accompanying risks and can lower the quality of life or decrease the adherence [22]. Unlike warfarin, which is known to have a narrow therapeutic window with multiple drug interactions and a need for frequent dose adjustments due to its association with increased bleeding events [23], NOACs had fewer drug interactions, with the exception of some medications described above. In this study, NOACs showed better safety profiles with fewer concomitant drugs and still had a better efficacy for SSTE prevention and reduced mortality compared to warfarin among AF patients with polypharmacy. However, the major bleeding risk was equivalent to warfarin in this high-risk population with polypharmacy.

NOAC-related issues in clinical practice

Because AF patients with indications for NOACs have multiple co-morbidities, polypharmacy is common and includes many P-glycoprotein inhibitors. For elderly patients over 75-years-old, NOACs showed an equivalent safety but better efficacy and lower mortality compared to warfarin even in those with a moderately impaired renal function [24]. In patients with a prior stroke history, only low-dose NOACs had a lower risk of major bleeding and all-cause mortality but an equivalent efficacy compared to warfarin [25]. In patients with AF and valvular heart disease (not a valvular AF), the major bleeding risk is higher than that in those without valvular heart disease during anticoagulation [26]. NOACs had an equivalent risk of major bleeding and all-cause mortality, but lower SSTE and ICH risks compared to warfarin [27].

P-glycoprotein is also known to be affected by genetic polymorphisms [28]. Therefore, further studies are needed to determine whether there are any ethnic differences in the drug interactions, especially in Asian populations, which are at a higher risk of bleeding than populations of European descent. However, there is no clear evidence for a reduction in the NOAC doses (except edoxaban [19]) in patients who are taking concomitant P-glycoprotein inhibitors or amiodarone [3].

Limitations

As data on individual patients were not available, the main limitation of this meta-analysis was that it was performed at the study level. Since the meta-analysis was based on phase III RCTs and not real world data, there was no off-label reduced-dosage in this analysis, and only one trial was designed to examine the concomitant use of P-glycoprotein inhibitors as a dose reduction criterion [19]. We need to recognize that off-label inappropriate dosing [29] or non-persistent [30] increased event rates have occurred in recent real-world clinical settings. Despite the potential sources of a selection and comparability bias, the robustness of this pooled analysis was verified through a sensitivity analysis for each pooled analysis (Supplementary Fig. 5), motivated by the limitations in the included original studies (for details, see Statistical analysis section). We included only studies with a median TTR ≥66%, i.e. the ARISTOTLE, ENGAGE AF-TIMI48, and RE-LY trials. We carefully estimated the validities of the included studies according to the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS). This estimate showed moderate reliability and promising feasibility and validity [6]. Finally, a publication bias could have favored the NOAC studies because all of the published trials were sponsored by pharmaceutical companies.

Conclusions

NOACs were equivalent to warfarin among AF patients with concomitant amiodarone use in terms of efficacy, safety, and mortality. There was no safety benefit (major bleeding and ICH) of NOACs over warfarin in the patients using polypharmacy or P-glycoprotein inhibitors.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.12.018.

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