Thrombosis and Haemostasis
International Journal for Vascular Biology and Medicine

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3
2018

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Reprint from Thromb Haemost 2018; 118: 526–538 | ISSN 0340-6245 | E 3185

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Effectiveness and Safety of Non–Vitamin K Oral Anticoagulants in Comparison to Phenprocoumon: Data from 61,000 Patients with Atrial Fibrillation

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Thromb Haemost 2018;118:526–538.

Abstract

All pivotal trials have evaluated non–vitamin K oral antagonists (NOACs) against warfarin. However, in some regions of the world, phenprocoumon is the most widely used vitamin K antagonist (VKA). There is little evidence documenting effectiveness and safety of NOACs compared with phenprocoumon in atrial fibrillation (AF). A retrospective cohort study using a German claims database was conducted to assess effectiveness (stroke, systemic embolism [SE]) and safety (bleeding leading to hospitalization) during therapy with NOACs and phenprocoumon in 61,205 AF patients. Hazard ratios (HRs) for effectiveness and safety outcomes were derived from Cox proportional hazard models, adjusting for baseline characteristics. Propensity score matching was performed as a sensitivity analysis. As a prespecified subgroup analysis, the effects of reduced NOAC dosing were compared with phenprocoumon. A total of 61,205 patients were identified in whom phenprocoumon ($n = 23{,}823$, 38.9%), apixaban ($n = 10{,}117$, 16.5%), dabigatran ($n = 5{,}122$, 8.4%), or rivaroxaban ($n = 22{,}143$, 36.2%) was initiated. After adjusting for baseline confounders, all three NOACs tested had significantly lower risks of stroke/SE compared with phenprocoumon (apixaban—HR: 0.77, 95% CI: 0.66–0.90; dabigatran—HR: 0.74, 95% CI: 0.60–0.91; rivaroxaban—HR: 0.86, 95% CI: 0.76–0.97). Apixaban (HR: 0.58, 95% CI: 0.49–0.69) and dabigatran (HR: 0.64, 95% CI: 0.50–0.80) were associated with lower bleeding risks than phenprocoumon, whereas the risk was similar for rivaroxaban and phenprocoumon. All three NOACs showed reduced risk of intracranial bleeding compared with phenprocoumon. Reduced doses of NOACs were predominantly used in patients with advanced age and comorbidities with generally similar effectiveness and safety benefits compared with phenprocumon as standard-dose NOACs.

Keywords

- atrial fibrillation
- stroke prevention
- anticoagulation
- non–vitamin K oral anticoagulants
- phenprocoumon

received
October 20, 2017
accepted after revision
November 20, 2017

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DOI https://doi.org/10.1160/TH17-10-0733.
ISSN 0340-6245.

Introduction

Atrial fibrillation (AF) patients with stroke risk factors need oral anticoagulation therapy to prevent stroke and systemic embolism. Since 2009, four non–vitamin K oral antagonists (NOACs) have been approved for stroke prevention in AF. All four NOACs were tested in pivotal trials against warfarin and were found to be at least as effective and probably safer than treatment with VKA.[1–4] As in some regions of the world phenprocoumon is the predominant VKA in clinical practice, comparative data for NOACs versus this VKA are warranted. We have previously reported that NOACs are associated with better safety profiles compared with phenprocoumon.[5] In addition, as patients in daily practice tend to be older and have more comorbidities including renal disease than in the pivotal trials, reduced dose NOAC regimens are much more commonly used in real world than in the pivotal trials. As only limited experience is available from the trials, evidence on effectiveness and safety of reduced NOAC dosing regimens must be obtained from real-world datasets. In this observational cohort study, we compare the effectiveness of standard and reduced dose NOAC regimens versus phenprocoumon in preventing stroke, systemic embolism, and death in a large cohort of patients with AF.

Methods

Study Design and Data Source

This retrospective observational study is based on the Institute for Applied Health Research (formerly Health Risk Institute, Berlin) database which is an anonymized healthcare claims database with longitudinal data from approximately 6.7 million Germans insured in one of approximately 70 German statutory health insurances.[6] As a postauthorization effectiveness and safety study (PAES/PASS), the study is registered at the European Medicines Agency (http://www.encepp.eu/encepp/viewResource.htm?id=22064). In brief, the database includes demographic information, information on outpatient healthcare services and data related to hospital treatment, including admission and discharge dates, diagnoses, operations and interventions (OPS codes) as well as prescription and dispensation of reimbursed medications, remedies and aids. All diagnoses in the database were coded according to the German modification of the 10th revision of the International Classification of Diseases (ICD-10 GM). Patient-level data can be arrayed chronologically to provide a detailed longitudinal profile of all medical and pharmacy services used by each insured member.

All patient identifiers were either fully encrypted or removed from the database which is therefore compliant with the German data protection regulations. As no patient contact was made and patient information was deidentified, Institutional Review Board approval was not required.

Study Population

Patients who had a first-time prescription claim for a NOAC (apixaban, dabigatran or rivaroxaban) or phenprocoumon between 1 January 2013 and 31 December 2015 were eligible for the study. Patients who had taken any of the above-mentioned anticoagulants within the previous 12 months were excluded to establish an anticoagulation-naïve cohort. The date of the first prescription was defined as the index date and the first prescription as the index medication. Several inclusion and exclusion criteria were applied to focus on patients treated for stroke prevention in AF. All patients were required to have at least one outpatient verified, primary or secondary hospital discharge diagnosis of AF in the previous or same quarter of the index date. Patients with valvular AF, deep vein thrombosis, haemodialysis, pregnancy, with anticoagulation therapy for any other indication during the 12 months prior to or on index date as well as patients who were prescribed more than one OAC agent on the index date were excluded. In addition, patients who were not continuously insured for at least 1 year prior to the index date were excluded. A consort diagram showing patient selection is presented in ►**Fig. 1**.

Study Endpoints

The primary effectiveness outcome was the composite of stroke (ischaemic or haemorrhagic) and systemic embolism (SE). The primary safety outcome was major bleeding. Secondary effectiveness outcomes were the occurrence of stroke, ischaemic stroke, haemorrhagic stroke, and death from any cause. Other safety outcomes were intracranial bleeding, gastrointestinal bleeding and any bleeding.

All events were considered that occurred during treatment, that is from onset of treatment until the end of continuous enrolment, study end (31 March 2016) or discontinuation of treatment, or switching to another anticoagulant. A maximum of a 30-day gap in days of drug supply was allowed when defining treatment discontinuation.

Stroke/SE was defined as a hospitalization with an ICD-10-GM hospital discharge diagnosis of cerebral infarction, intracerebral haemorrhage, uncertain type of stroke not specified as haemorrhage or ischaemic, and arterial embolism or arterial thrombosis. Ischaemic stroke outcome was defined according to the hospital discharge diagnosis of cerebral infarction and haemorrhagic stroke using the hospital discharge diagnosis of intracerebral haemorrhage. Major bleeding consisted of a hospital admission with an ICD-10-GM hospital discharge diagnosis. Intracranial bleeding was defined as a hospitalization with an ICD-10-GM hospital discharge diagnosis of intracerebral haemorrhage, subarachnoid haemorrhage, subdural haemorrhage or traumatic epidural haemorrhage. Gastrointestinal bleeding was defined as bleeding with localization in the gastrointestinal tract and documented ICD-10-GM hospital discharge diagnosis. Any bleeding was defined using prespecified primary or secondary ICD-10-GM hospital discharge diagnoses at any time. Further details about the outcome definitions are provided in the ►**Supplementary Appendix** (►**Tables S1** and **S2**).

Statistical Analysis

Data analysis was performed by the Institute for Applied Health Research, Berlin. Baseline characteristics of the study population were reported as percentages or

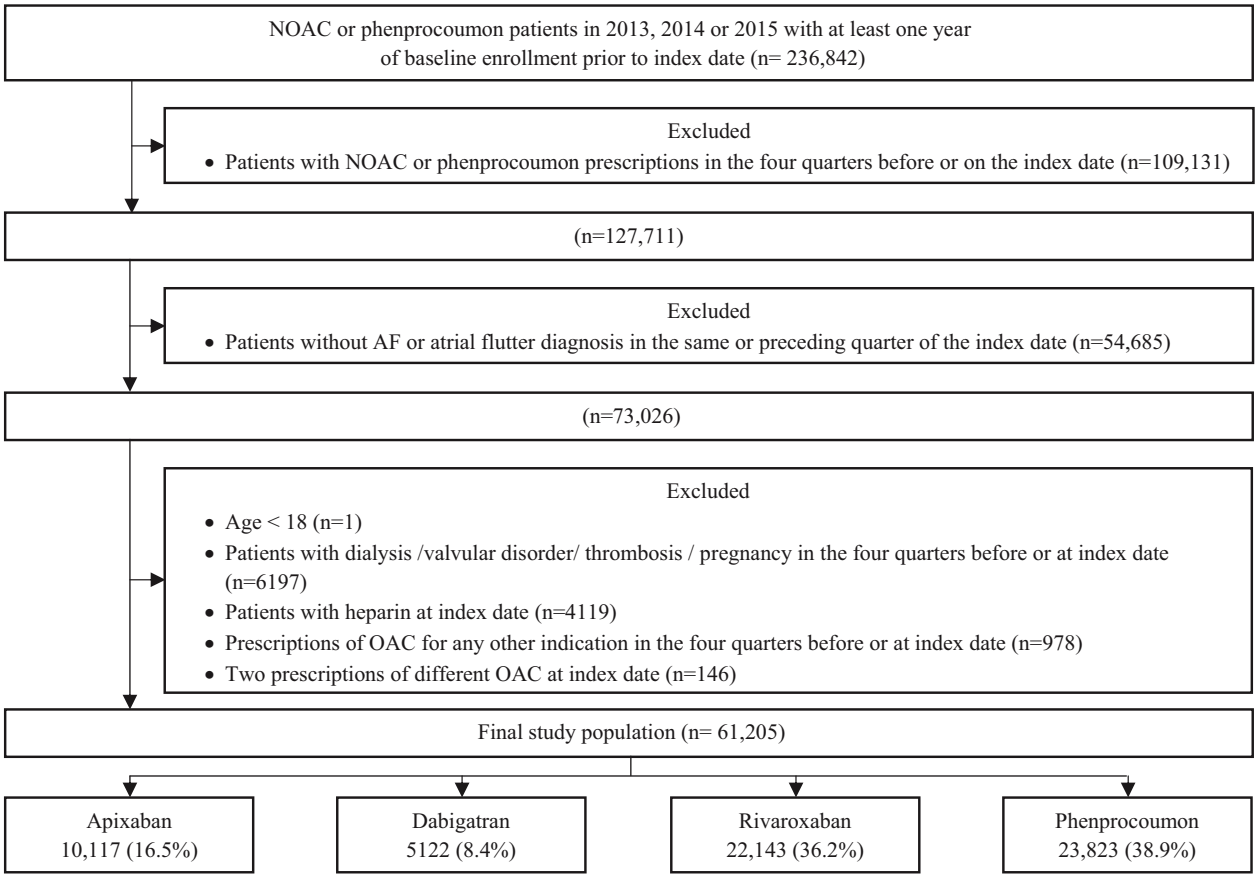

Fig. 1 CONSORT (Consolidated Standards of Reporting trials) diagram of patient selection.

means ± standard deviation (SD). Person-years of follow-up were calculated from the onset of treatment to the occurrence of the first endpoint, the end of continuous enrolment, the end of the study period, or discontinuation of treatment or switching to another OAC, whichever came first. Unadjusted crude rates were calculated as number of events divided by person time and were expressed per 100 person-years. Multiple outcome-specific Cox proportional-hazards regression models were used to estimate treatment effects (apixaban, dabigatran and rivaroxaban using phenprocoumon as reference) on the outcome-specific hazard rates. To avoid confounding, models were adjusted for prespecified baseline demographics and clinical factors. The variables that entered the final models were selected on the basis of background knowledge about the relationship of the variable to treatment and outcome (e.g., age, gender, prior history of ischaemic stroke, or TIA) and by using gradient boosting, an automatic variable selection technique.[7] The proportional hazard assumption was tested on the basis of Schoenfeld residuals and was valid for all outcomes.[8]

As a prespecified subgroup analysis, effectiveness and safety analyses were performed for patients receiving reduced-dose and standard-dose NOAC therapy. The effect modification by dosing regimens on the associations between treatment and outcomes was tested using interaction terms in the Cox proportional-hazards regressions and by comparing hazard rates in the dose-stratified analyses.

Data management and statistical analyses were performed using SAS 9.3 (SAS Institute Inc.) and R 3.1.0. A two-sided p-value < 0.05 was considered statistically significant.

Sensitivity Analyses

Two prespecified sensitivity analyses were performed. First, to assess the robustness of the results utilizing different statistical methods, a propensity score matching (PSM) analysis was performed to estimate treatment effects.[9] For each apixaban, rivaroxaban and dabigatran case, one control patient was selected from the pool of subjects in the phenprocoumon group. Controls were matched 1:1 according to the propensity score without replacement and using nearest-neighbour matching with a 0.1 maximum allowed difference in the propensity scores. Standardized mean differences were used to assess the balance of baseline characteristics after matching. A standardized difference less than 10% indicates a negligible difference in baseline characteristics and balanced matched cohorts.[10] A Cox proportional hazard model was used to compare endpoints in each of the propensity score-matched cohorts.

Second, because in all clinical trials that have evaluated NOACs against therapy with vitamin K antagonists, the average follow-up period ranged from 1.6 to 2.0 years, a sensitivity analysis was performed including only patients starting treatment until 31 March 2015 to allow for a follow-up time of at least 1 year in all patients.

Results

Patient Population

The study population comprised 61,205 AF patients initiating phenprocoumon ($n = 23{,}823$, 38.9%), apixaban ($n = 10{,}117$, 16.5%), dabigatran ($n = 5{,}122$, 8.4%) or rivaroxaban ($n = 22{,}143$, 36.2%; ►**Table 1**). Mean follow-up duration was 362 ± 275 days in the phenprocoumon group, 306 ± 239 days in the apixaban group, 339 ± 317 days in the dabigatran group and 340 ± 284 days in the rivaroxaban group.

The distribution of baseline characteristics varied between treatment groups (►**Table 1**). For example, subjects exposed to phenprocoumon or apixaban were older and had more comorbidities compared with dabigatran and rivaroxaban users. The proportion of patients with a history of stroke or SE was higher among patients being newly initiated on apixaban and dabigatran indicating preferential use of these two substances for secondary stroke prevention.

Effectiveness Outcomes

►**Table 2** displays the number of effectiveness outcome events, and the crude and adjusted event rates per 100 person-years according to treatment. There were 1,383 stroke/SE events during follow-up. Of these, 968 were coded as ischaemic strokes. Slightly higher crude event rates of stroke or systemic embolism were observed for apixaban and phenprocoumon. The highest crude event rates of death from all causes were observed for patients on apixaban which, however, comprised the subgroup of patients with the highest mean age, CHA_2DS_2-VASc, HAS-BLED and comorbidity scores (►**Table 1**). ►**Fig. 2** displays the adjusted hazard ratios and corresponding forest plots for each pairwise medication comparison for the main analysis and the sensitivity analyses (propensity score-matched analysis and extended follow-up analysis). After adjusting for baseline confounders, all three NOACs had significantly lower risks of stroke/SE, ischaemic and haemorrhagic stroke, and haemorrhagic stroke alone compared with phenprocoumon. The risk reduction was numerically more pronounced for apixaban and dabigatran users. A similar pattern was observed for the outcome of ischaemic stroke. However, the risk reduction reached statistical significance only for apixaban compared with phenprocoumon (HR: 0.82, 95% CI: 0.68–0.99, $p = 0.036$). Therapy with dabigatran was associated with lower risks of death from any cause compared with phenprocoumon (HR: 0.83, 95% CI: 0.72–0.95, $p = 0.006$). Both apixaban and rivaroxaban users showed similar risk of death from any cause compared with phenprocoumon users.

Safety Outcomes

►**Table 2** displays the number of events, and the crude and adjusted event rates per 100 person-years according to initiated treatment for safety outcomes. A total of 336 patients experienced an intracranial bleeding event. For apixaban and dabigatran, crude event rates of all safety outcomes were lower than that for phenprocoumon and rivaroxaban.

After adjusting for baseline confounders, both apixaban (HR: 0.58, 95% CI: 0.49–0.69, $p < 0.001$) and dabigatran (HR: 0.64, 95% CI: 0.50–0.80, $p < 0.001$) were associated with lower risks of major bleeding than phenprocoumon (►**Fig. 3**). The risk of major bleeding was similar between rivaroxaban and phenprocoumon users. All three NOACs were associated with reduced risk of intracranial bleeding compared with phenprocoumon, with the largest risk reduction observed for apixaban (HR: 0.44, 95% CI: 0.30–0.64, $p < 0.001$) followed by dabigatran (HR: 0.52, 95% CI: 0.33–0.84, $p = 0.007$) and rivaroxaban (HR: 0.68, 95% CI: 0.53–0.88, $p = 0.003$). Apixaban was the only NOAC that showed a reduced risk of gastrointestinal bleeding compared with phenprocoumon (HR: 0.71, 95% CI: 0.60–0.82, $p < 0.001$).

Sensitivity Analyses

Results for the sensitivity analyses are detailed in ►**Figs. 2** and **3**. In all propensity score-matched cohorts, standardized differences in patient characteristics were of less than 10%, indicating a high degree of similarity in the distributions of baseline characteristics (►**Table S3** in the ►**Supplementary Appendix**). Results from PSM analysis were generally consistent with the results of the main analysis using Cox proportional hazard regression models.

In the second sensitivity analysis, the inclusion time was limited from January 2013 to March 2015 yielding an extended follow-up period of at least 1 year in all patients. For apixaban and dabigatran patients, the findings for effectiveness and safety outcomes remained consistent with the main analysis. For patients using rivaroxaban, results of the main analysis regarding stroke-related outcomes yielded no longer significant differences, while results for safety outcomes were consistent with the main analysis.

Subgroup Analysis of Reduced vs. Standard NOAC Doses

Among patients who received apixaban, dabigatran and rivaroxaban, 37% ($n = 3{,}741$), 51% ($n = 2{,}596$) and 28% ($n = 6{,}220$), respectively, initiated treatment at a reduced dose. There were important differences in baseline characteristics of patients receiving reduced and standard NOAC dosing: Patients receiving the reduced dose regimens were older by 9.8 to 11.3 years and had more comorbidities resulting in higher CHA_2DS_2-VASc and modified HAS-BLED scores (►**Table 3** and ►**Table S4** in the ►**Supplementary Appendix**).

►**Figs. 4** and **5** display results for effectiveness and safety outcomes for reduced and standard NOAC doses compared with phenprocoumon. For apixaban, both reduced and standard doses were associated with significant risk reductions in the primary and secondary effectiveness outcomes. Concerning all-cause mortality, the standard dose of apixaban was associated with a lower risk of death compared with phenprocoumon (HR: 0.84, 95% CI: 0.74–0.96), whereas there was no significant difference for the reduced apixaban dose (HR: 1.07, 95% CI: 0.97–1.19). For patients on dabigatran, there were no significant differences in the risk of effectiveness outcomes when treated with 2 × 110 mg compared with patients treated with phenprocoumon, whereas therapy with dabigatran 2 × 150 mg was associated with significantly lower risks of all effectiveness outcomes. For rivaroxaban, effectiveness outcomes compared with phenprocoumon were similar for both doses except the outcome death from any cause. Patients

Table 1 Baseline characteristics of the study population

Characteristic	Phenprocoumon $n = 23,823$	Any NOAC $n = 37,382$	Apixaban $n = 10,117$	Dabigatran $n = 5,122$	Rivaroxaban $n = 22,143$
Patient demographics					
Age (mean ± SD)	75.2 (9.5)	72.7 (11.7)	74.5 (11.4)	71.7 (11.6)	72.1 (11.8)
Male (%)	53.3	53.8	51.4	55.1	54.7
Medical history					
CHA_2DS_2-VASc score (mean ± SD)	4.0 (1.6)	3.7 (1.8)	4.0 (1.8)	3.7 (1.8)	3.5 (1.8)
Modified HAS-BLED score (mean ± SD)	2.8 (1.1)	2.6 (1.2)	2.8 (1.2)	2.6 (1.2)	2.5 (1.2)
Charlson Comorbidity Index (mean ± SD)	3.4 (2.6)	3.0 (2.6)	3.4 (2.7)	2.9 (2.5)	2.9 (2.5)
Number of hospitalizations (mean ± SD)	1.2 (1.3)	1.3 (1.3)	1.3 (1.3)	1.3 (1.2)	1.2 (1.3)
Hospitalization within 30 d before first dispensation (%)	46.3	61.0	62.3	62.6	60.0
Hospitalization due to stroke/SE within 30 d before first dispensation (%)	3.6	6.9	10.2	11.2	4.4
Comorbidities					
Ischaemic stroke or TIA (%)	11.9	15.0	20.1	21.7	11.2
Myocardial infarction (%)	8.3	5.1	5.7	5.5	4.8
Renal insufficiency (%)	23.6	16.8	21.0	12.3	15.9
Congestive heart failure (%)	39.7	36.7	35.5	30.7	32.5
Coronary heart disease (%)	46.6	36.7	38.3	36.0	36.1
Hypertension (%)	88.2	84.8	87.0	84.4	83.8
Cancer (%)	19.7	18.5	19.8	17.5	18.2
Moderate or severe liver disease (%)	0.6	0.4	0.6	0.2	0.4
Dementia (%)	7.1	8.5	10.8	6.5	7.9
Atherosclerosis (%)	7.5	5.7	6.3	5.3	5.6
Hemiplegia (%)	6.2	9.3	12.9	12.7	6.9
Thyroid dysfunction (%)	28.6	28.5	29.9	27.8	28.0
COPD (%)	29.9	27.5	27.7	26.1	27.8
Diabetes mellitus (%)	37.0	32.3	33.4	30.2	32.2
Obesity (%)	24.9	23.6	22.9	22.4	24.3
Mobility and gait disorders (%)	10.5	11.7	15.4	9.9	10.4
Senility (%)	5.6	6.3	8.9	4.5	5.5
Any bleeding event (%)	8.8	8.0	9.3	7.2	7.6
Concomitant medications					
Antiplatelet drugs (%)	25.3	23.9	26.5	25.1	22.5
ASA (%)	19.3	19.1	21.2	19.3	18.1
NSAIDs (%)	35.4	36.4	35.8	35.5	36.9
β-Blocker (%)	82.2	82.4	81.9	82.3	82.6
Amiodarone (%)	6.5	4.9	5.0	4.1	5.1
Diuretics (%)	54.3	44.8	48.5	41.6	43.9
Antipsychotics (%)	4.4	5.7	7.3	4.7	5.2
Proton-pump inhibitors (%)	43.9	44.1	46.0	44.0	43.6

Abbreviations: ASA, acetylsalicylic acid; CHA2DS2-VASc, congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA, vascular disease, age, sex category, modified; COPD, chronic obstructive pulmonary disease; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly, drugs/alcohol concomitantly; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischaemic attack.

Table 2 Number of effectiveness and safety events, crude event rates and adjusted event rates per 100 person-years according to initiated treatment

Outcome	Phenprocoumon			Apixaban			Dabigatran			Rivaroxaban		
	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate	Events	Crude rate	Adjusted rate
Effectiveness outcomes												
Stroke/SE	597	2.5	2.2	226	2.7	1.7	104	2.2	1.5	456	2.2	1.8
Stroke	510	2.1	1.9	196	2.3	1.4	91	1.9	1.3	396	1.9	1.5
Ischaemic stroke	399	1.7	1.4	165	1.9	1.2	82	1.7	1.2	322	1.6	1.2
Haemorrhagic stroke	119	0.5	0.4	25	0.3	0.2	10	0.2	0.1	78	0.4	0.3
Death from any cause	1595	6.7	4.6	804	9.4	4.4	253	5.2	3.7	1509	7.2	4.6
Safety outcomes												
Major bleeding	692	2.9	2.3	167	2.0	1.4	80	1.7	1.5	568	2.7	2.3
Intracranial bleeding	175	0.7	0.6	35	0.4	0.3	20	0.4	0.3	106	0.5	0.4
Gastrointestinal bleeding	730	3.0	2.4	213	2.5	1.7	123	2.6	2.2	759	3.7	2.9
Any bleeding	2573	11.4	9.8	822	10.0	7.7	393	8.5	7.9	2276	11.5	10.1

treated with reduced dose rivaroxaban had an increased risk of all-cause mortality compared with phenprocoumon (HR: 1.17, 95% CI: 1.07–1.27).

Apixaban given at reduced or standard dose was associated with lower risks of all types of bleeding events compared with phenprocoumon. With respect to dabigatran, both doses were associated with lower risks of major and intracranial bleeding and similar risk of gastrointestinal bleeding. The use of dabigatran 2 × 150 mg led to risk reduction of any bleeding compared with phenprocoumon (HR: 0.70, 95% CI: 0.53–0.93), while the risk of any bleeding was similar between phenprocoumon and dabigatran 2 × 110 mg users. Both reduced and standard doses of rivaroxaban had similar risks of major and any bleeding compared with phenprocoumon. The risk of intracranial bleeding was reduced for both rivaroxaban doses compared with phenprocoumon, whereas the risk of gastrointestinal bleeding was higher for both doses when compared with phenprocoumon.

Discussion

Main Findings

The present study is the first to compare the effectiveness profiles of NOACs to that of phenprocoumon in a real-world setting comprising more than 61,000 patients with AF. There are several important new findings of this study: First, NOACs demonstrated improved effectiveness in preventing stroke over phenprocoumon. Second, improved effectiveness was confirmed in prespecified sensitivity analyses. Third, safety findings confirmed previous observations demonstrating better safety profiles of NOACs versus phenprocoumon. Furthermore, this is the first study comparing reduced and standard NOAC dosing versus phenprocoumon. Importantly, reduced dose NOAC regimens, preferentially used in patients with more advanced age and more comorbidities, displayed similar effectivity and safety benefits relative to phenprocoumon as the standard-dose NOAC regimens.

Stroke Prevention with NOACs versus Phenprocoumon

Several real-world studies have confirmed the effectiveness of NOACs versus warfarin with respect to stroke prevention in AF.[11–14] For instance, in comparison to warfarin, apixaban was associated with lower risk of stroke, whereas dabigatran and rivaroxaban were associated with similar risk of stroke in one of the largest respective studies comprising 125,243 patients.[11] Similarly, Li et al showed in the largest real-world comparison of apixaban versus warfarin that initiation of this NOAC was associated with significant risk reductions in stroke/SE.[12]

Prior to our study, no effectiveness comparisons of NOACs versus phenprocoumon have been published. Phenprocoumon represents the most commonly prescribed VKA in some countries including Germany.[15] Consistent with the pivotal phase 3 trials and above-mentioned real-world data, the present study demonstrates that NOACs are generally more effective than phenprocoumon for the prevention of cardiovascular events in patients with AF. These observations were confirmed in two prespecified sensitivity analyses. Utilizing PSM (instead of Cox proportional hazard analysis) to adjust for baseline confounders, consistent observations were made. This is reassuring and reflects the robustness of the results to the various model assumptions. The extended follow-up analysis revealed similar results for apixaban and dabigatran providing evidence that results are robust irrespective of differences in follow-up time. For rivaroxaban, the results of the main analysis were slightly attenuated when longer follow-up was analysed.

Furthermore, the efficacy of OAC using VKA for stroke prevention is closely related to the quality of international normalized ratio (INR) control, as reflected by time in

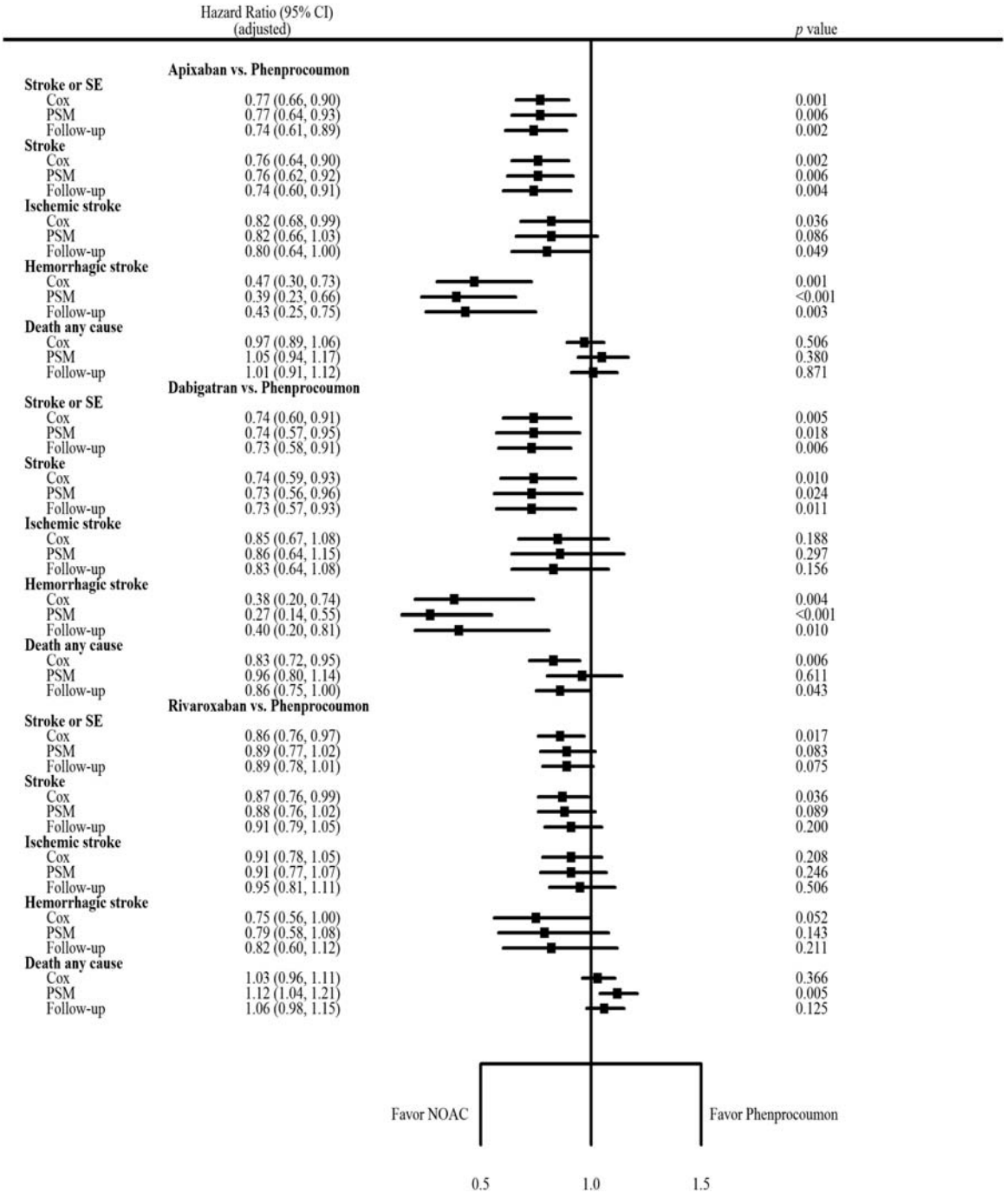

Fig. 2 Adjusted hazard ratios with 95% confidence intervals for effectiveness outcomes (Cox, Cox proportional hazard model; PSM, propensity score matching analysis; follow-up, extended follow-up analysis).

therapeutic range (TTR). Unfortunately, INR measurements were not available in our study. In general, 'real-world' observational studies from Germany utilizing different methodologies and various data sources reported highly variable TTR values, ranging from 56% in a retrospective analysis of clinical data to 75% in a prospective registry of daily care patients.[16–18] However, a systematic selection bias assuming only poor quality treatment of VKA in our study is highly unlikely.

Furthermore, the efficacy and safety of OAC therapy strongly depends on medication adherence and persistence. In general, real-world studies reported highly variable adherence and persistence for all OACs.[19] For example, a recently published study using primary care data from Germany found that 37.1% apixaban, 43.4% rivaroxaban, 49.9% dabigatran and 42.5% VKA patients discontinued their treatment after 1 year follow-up, whereas a study from Sweden found 1-year discontinuation rates between 14.9 and 25.6%.[20,21] Similar evidence was reported by U.S. claim databases.[22,23] Unfortunately, medication adherence and persistence data are lacking in this study. Therefore, benefits of NOACs over phenprocoumon could potentially be related in part to better persistence and adherence.

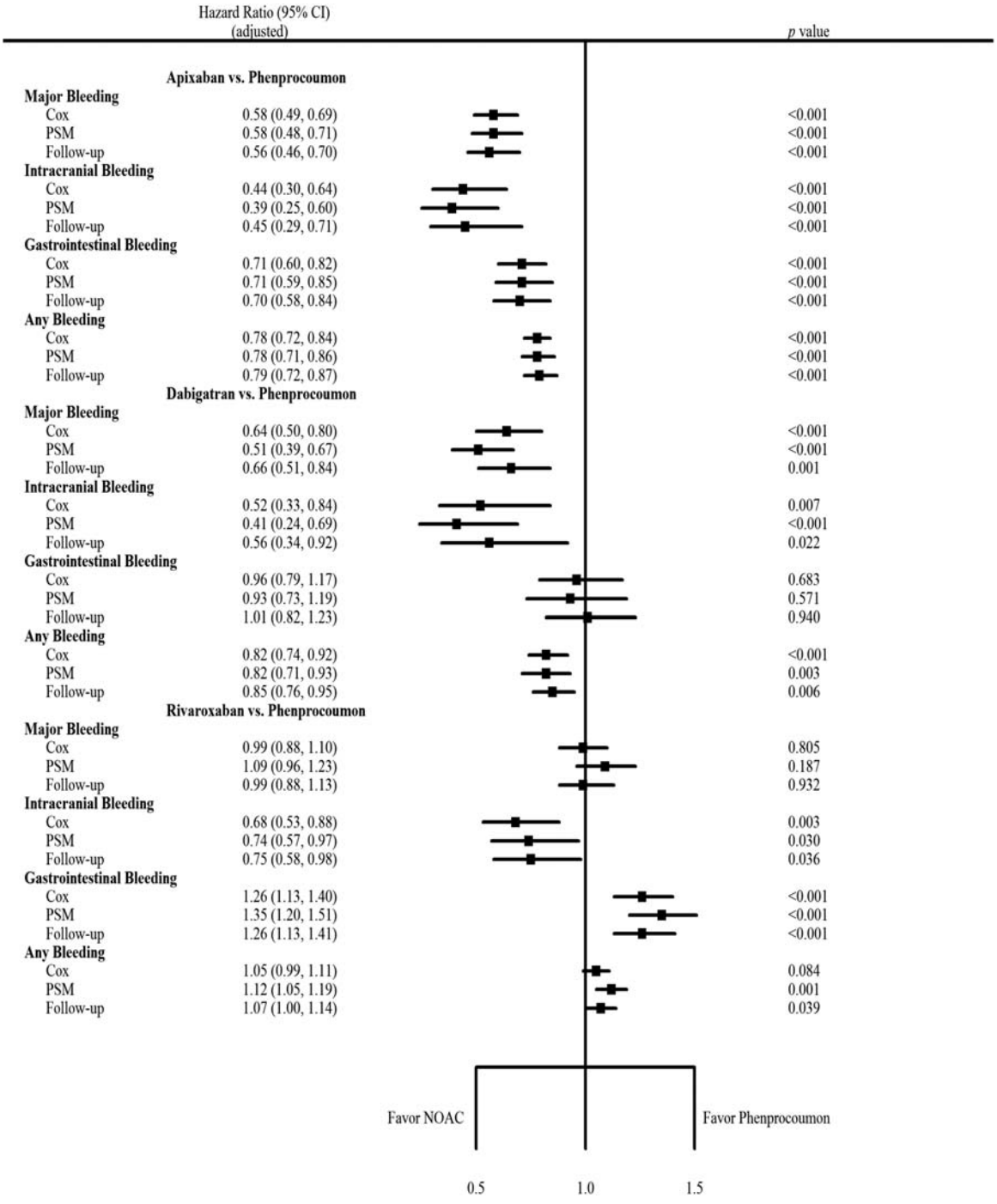

Fig. 3 Adjusted hazard ratios with 95% confidence intervals for safety outcomes (Cox = Cox proportional hazard model; PSM, propensity score matching analysis; follow-up, extended follow-up analysis).

Safety Comparison between NOAC and Phenprocoumon

In the randomized trials comparing NOACs to VKA, the direct oral anticoagulants had generally better safety features than VKA.[1–4] We have recently published the first real-world data comparing safety outcomes for NOACs versus phenprocoumon.[5] These initial observations could be confirmed and extended in the present study. In the overall population, apixaban in particular was associated with a significantly better safety profile than phenprocoumon including a 29% reduction in gastrointestinal bleeding risk. Unlike apixaban, dabigatran carried a similar risk of gastrointestinal bleeding when compared with phenprocoumon. With respect to other safety outcomes, the results for dabigatran were similar to that of apixaban. For rivaroxaban, the observed higher risk of gastrointestinal bleeding along with similar risks of major and any bleeding compared with phenprocoumon is in line with the results of the ROCKET trial.[2]

In the present study, 336 intracranial bleeding events were observed. This large number of events allowed for a robust risk

Table 3 Baseline characteristics of the study population according to NOAC dose

Characteristic	Phenprocoumon	Apixaban		Dabigatran		Rivaroxaban	
	n = 23,823	(5 mg)	(2.5 mg)	(150 mg)	(110 mg)	(20 mg)	(15 mg)
		n = 6,376	*n* = 3,741	n = 2,526	*n* = 2,596	*n* = 15,923	*n* = 6,220
Patient demographics							
Age (mean ± SD)	75.2 (9.5)	70.4 (10.9)	81.6 (8.2)	66.0 (10.7)	77.3 (9.5)	69.3 (11.6)	79.1 (9.0)
Male (%)	53.3	57.6	40.7	63.5	46.9	58.3	45.5
Medical history							
CHA_2DS_2-VASc score (mean ± SD)	4.0 (1.6)	3.5 (1.8)	4.9 (1.5)	2.9 (1.7)	4.4 (1.7)	3.2 (1.7)	4.5 (1.6)
Modified HAS-BLED score (mean ± SD)	2.8 (1.1)	2.5 (1.2)	3.2 (1.1)	2.2 (1.1)	3.0 (1.2)	2.3 (1.1)	3.0 (1.1)
Charlson Comorbidity Index (mean ± SD)	3.4 (2.6)	2.8 (2.5)	4.4 (2.8)	2.2 (2.0)	3.6 (2.7)	2.4 (2.3)	4.0 (2.8)
Number of hospitalizations (mean ± SD)	1.2 (1.3)	1.2 (1.2)	1.6 (1.5)	1.1 (1.1)	1.4 (1.4)	1.2 (1.2)	1.4 (1.4)
Comorbidities							
Ischaemic stroke or TIA (%)	11.9	18.0	23.6	18.6	24.7	9.6	15.4
Myocardial infarction (%)	8.3	4.2	8.2	3.4	7.6	3.8	7.4
Renal insufficiency (%)	23.6	12.6	35.2	5.5	19.0	9.3	32.6
Congestive heart failure (%)	39.7	27.6	49.0	22.0	39.2	27.0	46.6
Coronary heart disease (%)	46.6	32.9	47.4	28.3	43.5	32.1	46.2
Concomitant medications							
Antiplatelet drugs (%)	25.3	20.9	36.1	17.4	32.5	18.7	32.2
ASA (%)	19.3	16.9	28.7	14.1	24.5	15.2	25.6

Abbreviations: ASA, acetylsalicylic acid; CHA2DS2-VASc, congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA, vascular disease, age, sex category, modified; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly, drugs/alcohol concomitantly; TIA, transient ischaemic attack.

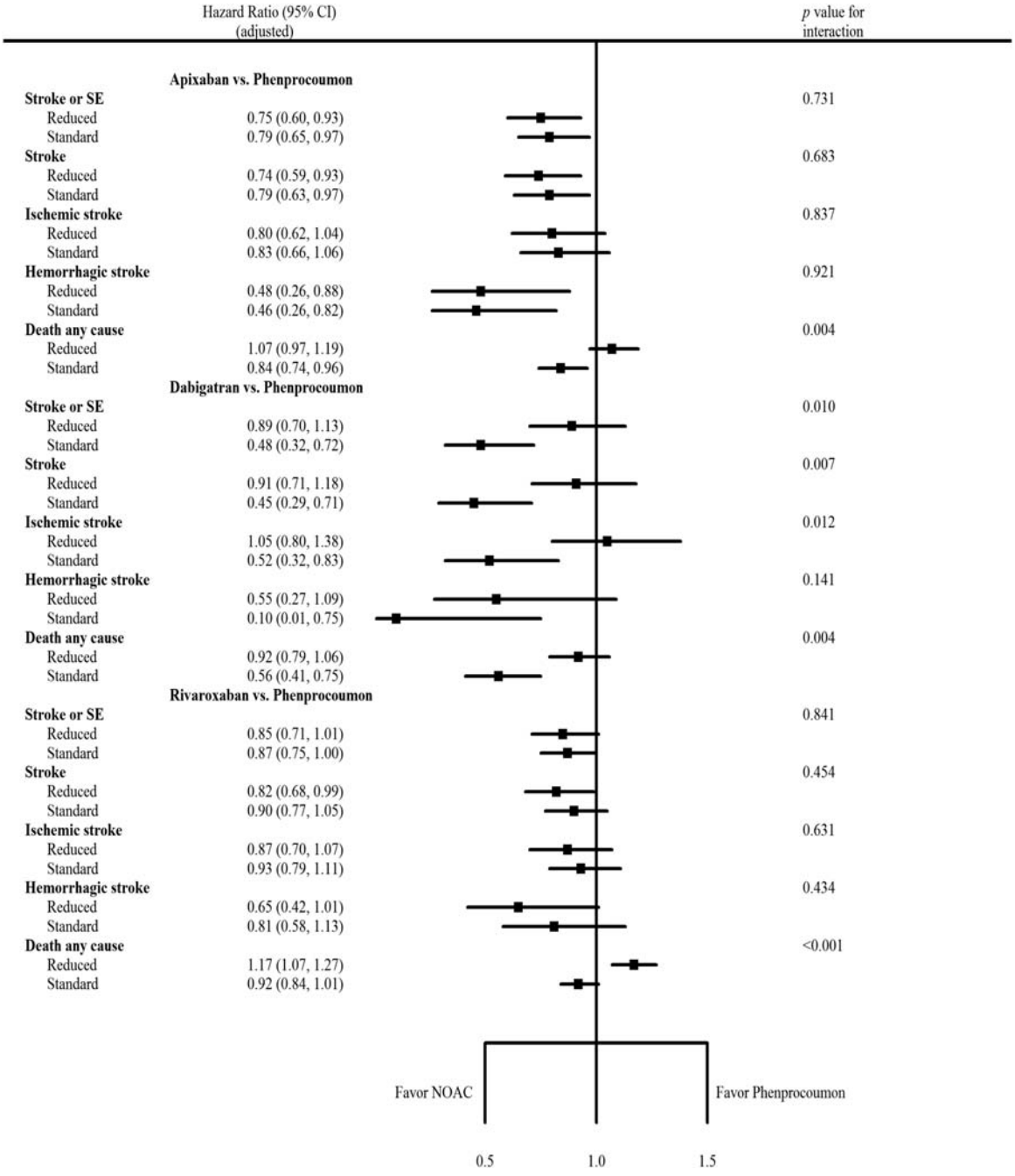

Fig. 4 Adjusted hazard ratios with 95% confidence intervals and p-values for interactions of effectiveness outcomes for the low and standard dose of apixaban, dabigatran, and rivaroxaban compared with phenprocoumon.

assessment of this most feared complication of anticoagulation therapy. After adjusting for baseline confounders, the highest risk reduction was observed for apixaban followed by dabigatran and rivaroxaban.

Our observations are also in agreement with the recently published real-world safety data comparing warfarin to different NOACs.[11,24] For instance, Lip et al,[24] using data from a large U.S. insurance database, found that apixaban and dabigatran were associated with a significantly lower risk for major bleeding than warfarin, whereas rivaroxaban carried a similar risk of major bleeding when compared with warfarin. Similarly, Yao et al[11] showed that all three NOACs were associated with lower intracranial bleeding rates than warfarin, whereas only apixaban was associated with a reduction in gastrointestinal bleeding.

A similar pattern in bleeding rates between different NOACs was also reported in the Dresdner NOAC registry.[25–27] However, because all NOACs were evaluated in separate cohorts and at different time periods and adhering to differences in patient selection criteria and bleeding definitions, the magnitude of the crude event rates reported in the Dresdner NOAC registry was different from those in our study.

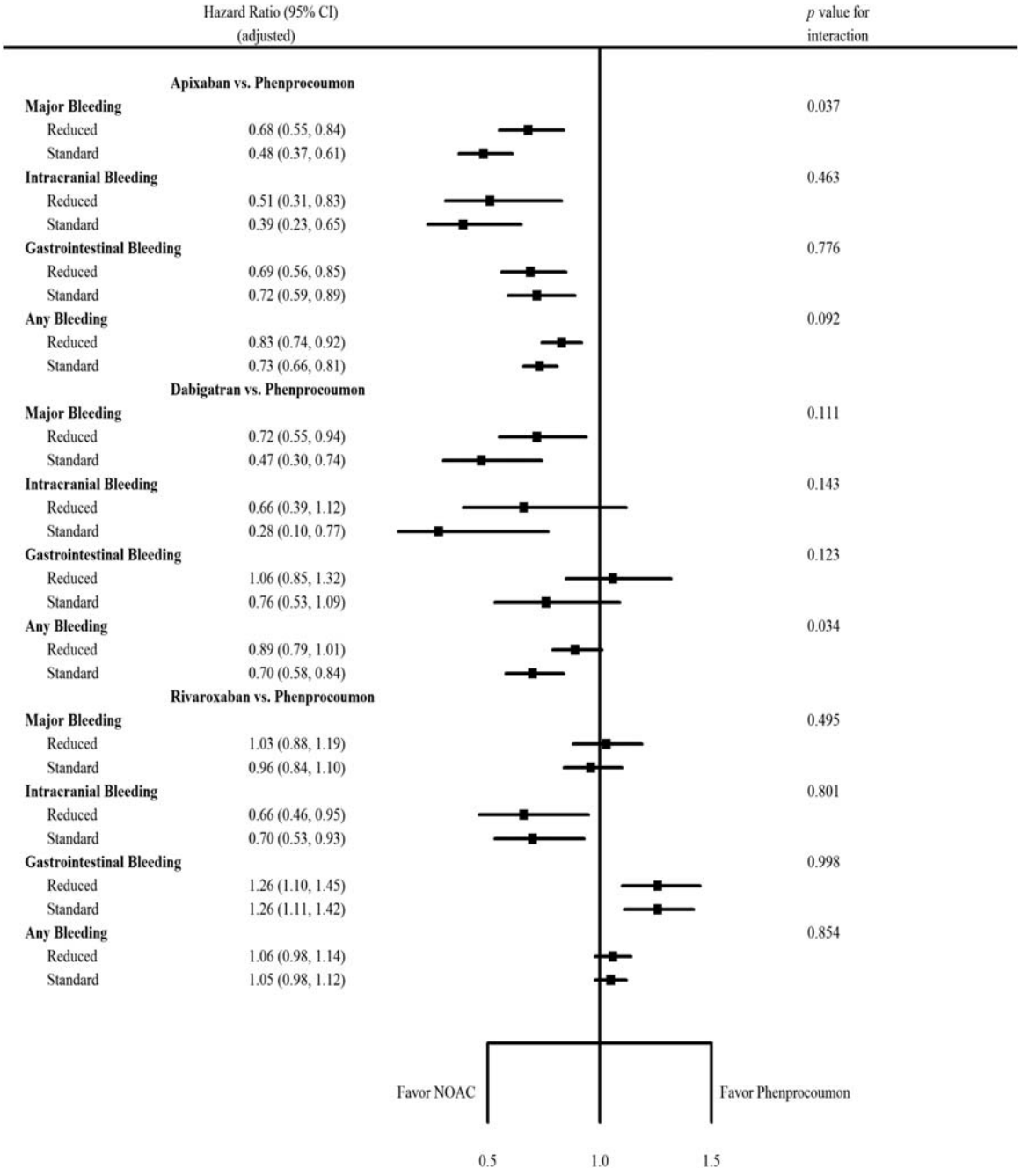

Fig. 5 Adjusted hazard ratios with 95% confidence intervals and p-values for interactions of safety outcomes for the low and standard dose of apixaban, dabigatran, and rivaroxaban compared with phenprocoumon.

Concomitant Medical Therapy

In our study, there was a high prevalence of use of drugs known to increase bleeding risk (antiplatelets or NSAIDs) in all treatment groups. The common prescription of NSAIDs might be related to our collective of elderly patients who are at increased risk of experiencing chronic pain and inflammation associated with a wide variety of clinical conditions. The high prevalence of cardiovascular diseases observed among our patients may be responsible for the high rate of antiplatelet therapy. However, a comparably high incidence of concomitant antiplatelet therapy was observed in clinical trials.[2,3] Since the proportion of patients using NSAIDs and antiplatelets was similar for all exposure groups and both medications were controlled for in the statistical analyses, this should not have impacted our results.

Reduced versus Standard NOAC Dosing: Effectiveness and Safety

A high proportion of patients are prescribed NOAC treatment at lower than standard doses.[28] Although there are clear dosing recommendations for each NOAC, clinical patient characteristics may largely be responsible for prescription of reduced NOAC doses. To elucidate this relationship, additional effectiveness and safety data of reduced dose NOAC regimens needs

to be obtained from real-world data. The present study, therefore, provides a unique opportunity to evaluate reasoning, effectiveness, and safety of reduced NOAC dosing.

There were distinct differences in patient characteristics for subjects prescribed reduced versus standard NOAC doses: Patients receiving reduced doses were older by $\geq$ 10 years and suffered from significantly more comorbidities compared with patients receiving the standard dose. Unfortunately, renal function parameters were not available from the database used, but considering the older age, higher incidence of congestive heart failure, coronary disease and other comorbidities, it can be assumed that renal function was more often compromised in subjects receiving reduced dose NOAC therapy.

Importantly, the advantage in stroke prevention compared with phenprocoumon was similar in patients receiving the reduced dose of apixaban (2×2.5 mg), indicating that patients meeting dose reduction criteria derive similar benefits from apixaban treatment over phenprocoumon as patients eligible for the standard dose. Risk of death from any cause was significantly reduced in patients receiving standard-dose apixaban, while being similar to phenprocoumon in patients receiving reduced dose apixaban. This is not surprising given the very advanced age and the multiple comorbidities of these patients making age by itself increasingly important as the main driver of mortality. Our observations are in line with those from a very large real-world study where reduced dose apixaban also had similar benefits as the standard dose regarding stroke and bleeding risk compared with warfarin.[12]

For dabigatran, somewhat different effects of the two doses on thromboembolic and bleeding outcomes were observed, which, however, were consistent with the results of the RE-LY trial.[1] Use of the reduced dabigatran dose was associated with thromboembolic and bleeding risks comparable to that of phenprocoumon, the only exception being the outcomes major and intracranial bleeding (lower risk compared with phenprocoumon). The high dose of dabigatran clearly revealed a favorable benefit–risk profile over phenprocoumon with lower risk of stroke/SE and bleeding outcomes, except for gastrointestinal bleeding which was similar for users of high-dose dabigatran and phenprocoumon. It should be noted, however, that the high-dose dabigatran regimen was used in the youngest patient subgroup with the lowest CHA_2DS_2-VASc, HAS-BLED, and comorbidity scores. These more favorable effectiveness and safety outcomes in younger patients are in line with the findings of the RE-LY trial.[29] Rivaroxaban showed similar effectiveness and safety data for both doses. The only exception was the outcome death from any cause for which use of reduced dose was associated with an increased risk compared with phenprocoumon.

Limitations of the Study

Some limitations of our study need to be considered. All analyses are subject to several limitations which are inherent to any retrospective data analysis. Despite all attempts to adjust for important baseline confounders by applying various statistical methods including PSM, residual bias cannot be entirely excluded. However, the large patient sample size and the consistency of results with previously published real-world studies and clinical trials indicate that our observations are robust. Another concern may be the potential for coding errors inherent to retrospective analysis of claims databases. However, one can expect that residual bias associated with coding errors may be similar for all exposure groups and thus should not meaningfully influence the assessment of our outcomes. The lack of INR measurements and laboratory data on renal function represents another inherent limitation of our study.

Conclusion

Results from this large real-world data analysis demonstrate that NOACs have better effectiveness and safety characteristics than phenprocoumon. Reduced NOAC dosing regimens were prescribed preferentially to patients with advanced age and comorbidities. The reduced dosing regimens of apixaban and rivaroxaban showed a similar effectiveness and safety profile compared with phenprocoumon as the standard-dose regimens.

What is known about this topic?

- All pivotal trials have demonstrated that non–vitamin K antagonist oral anticoagulants (NOACs) are not inferior or superior to warfarin for stroke prevention in nonvalvular atrial fibrillation (NVAF).
- In some regions of the world, phenprocoumon is the most widely used vitamin K antagonist (VKA) in clinical practice.
- There is little evidence documenting the effectiveness and safety of NOACs over phenprocoumon.
- Only limited experience is available from the trials regarding the efficacy and safety of reduced NOAC dosing regimens.

What does this paper add?

- Using multiple Cox regression models and propensity score matching (PSM), the risk of stroke or systemic embolism (SE) and bleedings leading to hospital admission during therapy with NOACs and phenprocoumon was evaluated.
- NOACs demonstrated improved effectiveness in preventing stroke over phenprocoumon.
- Reduced doses of NOACs were predominantly used in patients with advanced age and comorbidities with generally similar effectiveness and safety benefits compared with phenprocoumon as standard-dose NOACs.
- The present study is the first to compare the effectiveness profiles of NOACs to that of phenprocoumon in a real-world setting comprising more than 61,000 patients with AF.
- Furthermore, this is one of the first studies comparing reduced and standard NOAC dosing versus phenprocoumon.

Funding
This study was sponsored by Bristol-Myers Squibb and Pfizer.

Conflict of Interests
Professor Hohnloser has served as a consultant for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo and Jansen. Professor Nabauer has received lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo. Dr. Hohmann has served as a consultant for Pfizer and received grants from Orion Pharma. Dr. Basic is employee of Pfizer Deutschland GmbH. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Addendum
Stefan H. Hohnloser and Edin Basic have conceived the study and developed the protocol, supervised data collection and statistical analyses, and wrote the first draft of the paper.
Drs. Hohmann and Nabauer have critically revised the manuscript.
All authors have had access to the data.

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