Thrombosis Research 178 (2019) 101–109

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Dose reduction of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: A Danish nationwide cohort study

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ARTICLE INFO

Keywords:
Atrial fibrillation
NOAC
Dose reduction
Apixaban
Dabigatran
Rivaroxaban

ABSTRACT

Introduction: To investigate the patterns of dose reduction of non-vitamin K antagonist oral anticoagulants (NOAC) in patients with atrial fibrillation (AF).

Materials and methods: Using Danish nationwide registries, we identified all non-valvular AF patients initiated on standard-dose NOAC during 2011–2017 who were followed until dose reduction. The absolute risk of dose reduction was presented as cumulative incidence both overall and according to baseline characteristics. Moreover, to assess baseline comorbidities related to dose reduction, adjusted Cox regression models were used. In subgroup analysis, we investigated dose reduction following acute myocardial infarction and/or percutaneous coronary intervention (MI/PCI), chronic kidney disease (CKD), turned 80 years, intracranial hemorrhage, peripheral bleeding, ischemic stroke, cancer, bone fracture, and antiplatelet treatment start.

Results: Of 24,489 patients included, 12.2% experienced dose reduction during the study period. Dabigatran treatment, higher age at inclusion, high CHA_2DS_2-VASc score, and high HAS-BLED score were related to higher risk of dose reduction. Baseline ischemic heart disease (IHD), heart failure, cancer, CKD, chronic obstructive pulmonale disease (COPD), and hypertension were independent predictors of dose reduction.

In subgroup analysis with six-month follow-up, MI/PCI, CKD, intracranial hemorrhage, peripheral bleeding, and antiplatelet treatment therapy were strongly associated with dose reduction.

Conclusions: Dose reduction of NOACs was observed in 12.2% of AF patients during 2011–2017 and was associated with dabigatran treatment, advanced age at baseline, high CHA_2DS_2-VASc score, and high HAS-BLED score. Among comorbidities, IHD, heart failure, cancer, CKD, COPD, and hypertension predicted dose reduction independently. During six-month follow-up, MI/PCI showed the strongest association with dose reduction.

1. Introduction

For stroke prophylaxis in patients with atrial fibrillation (AF), the usage of non-vitamin K antagonist oral anticoagulants (NOAC) has been increasing rapidly since 2011 [1]. In Denmark, four NOACs including apixaban (*Eliquis*, *Bristol-Myers Squibb-Pfizer*; *New York City*, *USA*), dabigatran (*Pradaxa*, *Boehringer Ingelheim*; *Ingelheim*, *Germany*), edoxaban (*Lixiana*, *Daiichi Sankyo*; *Tokyo*, *Japan*), and rivaroxaban (*Xarelto*, *Bayer*; *Leverkusen*, *Germany*) are available. For each of them, two treatment doses are approved in AF patients, so-called standard-dose and reduced-dose. Using an appropriate dose is crucial to ensure optimal thromboembolic prevention and avoidance of drug-related adverse events in AF patients [2–4]. Current drug labels for dose adjustment of NOACs include the following criteria: age, body weight, renal function, and concomitant treatment with P-glycoprotein inhibitors [5–7]. However, since NOACs are relatively new drugs, knowledge about their proper dosages in different clinical settings is still lacking, let alone comprehensive recommendations for specific patient populations.

Globally, several studies [1,8,9] have examined the initiation patterns of NOACs in clinical practice, but no data are available on how

Abbreviations: AF, atrial fibrillation; ATC, The international Anatomical Therapeutic Chemical system; B.I., Boehringer Ingelheim; B.M.S., Bristol-Myers Squibb; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonale disease; DVT, deep vein thrombosis; ICD, The International Classification of Diseases; ICH, intracranial hemorrhage; IHD, ischemic heart disease; MI, acute myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulants; NSAID, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PE, pulmonale emboli; SD, standard deviations

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https://doi.org/10.1016/j.thromres.2019.04.007
Received 12 November 2018; Received in revised form 25 February 2019; Accepted 7 April 2019
Available online 09 April 2019
0049-3848/

dose adjustment of NOACs is conducted after treatment initiation. To address this knowledge gap, this study aimed to investigate the contemporary patterns of and the factors associated with dose reduction of NOACs in AF patients.

2. Material and methods

2.1. Data sources

In Denmark, every resident is provided with a unique registration number, which permits cross-linking data from national administrative registries at an individual level. In our study we employed three of Danish nationwide registries. First, The Danish National Patient Registry contains information about all somatic hospitalizations and outpatient clinic visits since 1977, including in-hospital diagnostic and interventional procedures. Each patient contact is recorded with one primary and, when relevant, one or more secondary diagnoses according to the International Classification of Diseases (ICD). Second, The Danish National Prescription Registry holds information on all prescription drugs sold in Danish community pharmacies since 1994, e.g. expedition date, strength and number of tablets dispensed. The drugs are classified according to the international Anatomical Therapeutic Chemical (ATC) system. Third, The Danish Civil Registration System provides information on all Danish residents since 1968, e.g. sex, date of birth, and vital status.

2.2. Study population

We identified all Danish patients with AF who had initiated their first oral anticoagulant (OAC) treatment between 22 August 2011 and 31 March 2017. To have a more representative population and to avoid competing treatment indications, we excluded patients aged < 30 years and > 100 years, patients with valvular heart disease, patients who had undergone hip or knee alloplastic surgery within 5 weeks prior to OAC treatment initiation, and patients with venous thromboembolism within 6 months prior to OAC treatment initiation. Furthermore, patients initiated on warfarin, NOAC in reduced-dose treatment, and edoxaban (due to the small number) were also excluded. (See *Appendix A* for ICD and ATC codes).

2.3. NOAC treatment

All claimed NOAC prescriptions and the related dosages were extracted from The National Prescription Registry. Standard-doses of NOACs were defined as apixaban 5 mg twice daily, dabigatran 150 mg twice daily, or rivaroxaban 20 mg once daily, while reduced-doses as apixaban 2.5 mg twice daily, dabigatran 110 mg twice daily, or rivaroxaban 15 mg once daily.

The algorithm we employed to determine the duration of NOAC treatment has been described in detail in previous study [10]. Briefly, the date of redeemed prescriptions, the number and the strength of tablets were used to estimate periods of having tablets available for patients, which we considered as treatment periods. Discontinuation was defined as an interruption ≥30 days between two consecutive treatment periods.

2.4. Outcome

All study patients were followed from the date of their first prescription fill of NOACs and until dose reduction (outcome of interest), discontinuation of initiated treatment, switch to another OAC agent, death, emigration, or 30 June 2017; whichever came first.

2.5. Comorbidities and concomitant medication

Concomitant pharmacotherapy was defined as redeemed prescriptions within 180 days preceding the date of inclusion, while ICD codes from previous hospital contacts prior to the study start were used to identify comorbidities (see *Appendix A*). Based on comorbidities and pharmacotherapy, CHA_2DS_2-VASc score and HAS-BLED score were calculated and used to quantify their risks of thromboembolism and bleeding at baseline, respectively (see *Appendix B*).

2.6. Statistical analysis

Baseline characteristics were presented as means with standard deviations (SD) for continuous variables and as frequencies and proportions for categorical variables. The Kruskal-Wallis test and the χ^2 test were used to assess differences in the distribution of baseline characteristics in different patient groups for continuous and categorical variables, respectively.

Absolute risk of dose reduction was presented as cumulative incidence over time of follow-up, while death, treatment discontinuation, and switch of OAC regarded as competing risks. Moreover, we performed stratification based on the treatment regimen (apixaban, dabigatran, and rivaroxaban), the age at inclusion (age groups 30–64 years, 65–69 years, 70–74 years, 75–79 years, and 80–100 years), CHA_2DS_2-VASc score (low-intermediate (0–1) and high (≥2)) and HAS-BLED score (low-intermediate (0–2) and high (≥3)) estimated at baseline. Finally, to calculate the risk of dose reduction associated with baseline age ≥ 65 years, male sex, and baseline comorbidities listed in Table 1, a multivariable analysis with Cox proportional-hazards model was conducted, where a hazard ratio was determined for each of the covariates. The analysis was, then, repeated separately for the subsets of patients who initiated apixaban, dabigatran, and rivaroxaban, respectively.

As supplementary analyses, we identified subgroups of our study cohort experiencing the following events during follow-up (see *Appendix A* for definition) — aged/turned 80 years, the first diagnosis of chronic kidney disease (CKD), intracranial hemorrhage (ICH), peripheral bleeding, ischemic stroke, acute myocardial infarction (MI) and/or percutaneous coronary intervention (PCI), bone fracture, the first cancer diagnosis, and treatment start of concomitant antiplatelets (estimated by using the same algorithm as that for NOACs). In the subgroup analyses, the cumulative incidence of dose reduction was determined over a follow-up of 6 months from the event date. Stratification was done on basis of NOAC type.

Data management and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.3.2 (R Development Core Team).

3. Results

The study population comprised 24,489 patients with AF (Fig. 1); of whom 8326 (34.0%) received apixaban, 8113 (33.1%) dabigatran and 8050 (32.9%) rivaroxaban. Baseline characteristics overall and according to NOAC treatment regimens are shown in Table 1. Users of dabigatran were characterized by younger age and lower CHA_2DS_2-VASc and HAS-BLED scores, whereas patients treated with apixaban generally had more comorbidities and higher CHA_2DS_2-VASc and HAS-BLED scores.

3.1. Main analysis

Absolute risks of NOAC dose reduction for the study cohort are presented graphically in Fig. 2. The follow-up period was up to 70.0 months (median 10.9 and interquartile range 4.0–23.7) and dose reduction was observed in 12.2% (95% confidence interval (CI): 11.5–12.9) of the study patients. Stratified by NOAC type, we found that a significantly larger proportion of dabigatran users were reduced in treatment dose, than those initiated with apixaban and rivaroxaban.

Fig. 3 illustrates cumulative incidences of dose reduction according to the age at inclusion. Higher age seemed to predict a greater risk of

Table 1
Baseline characteristics of the overall study cohort and individual treatment groups.
Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; RAS inhibitor, renin angiotensin inhibitor.

	Overall	API	DAB	RIV	*p*-Value
N (%)	24,489 (100.0)	8326 (34.0)	8113 (33.1)	8050 (32.9)	
Sex = M (%)	14,372 (58.7)	4812 (57.8)	5114 (63.0)	4446 (55.2)	< 0.001
Duration of AF in years (SD)	1.59 (3.97)	1.51 (3.94)	1.64 (3.98)	1.62 (3.99)	0.075
Age					
Mean (SD)	69.14 (9.82)	70.53 (9.65)	65.68 (8.42)	71.18 (10.35)	< 0.001
< 65 (%)	6710 (27.4)	1873 (22.5)	3011 (37.1)	1826 (22.7)	< 0.001
≥65 (%)	17,779 (72.6)	6453 (77.5)	5102 (62.9)	6224 (77.3)	< 0.001
CHADSVASC score					
Mean (SD)	2.61 (1.53)	2.83 (1.58)	2.22 (1.41)	2.77 (1.53)	< 0.001
0 (%)	1770 (7.2)	477 (5.7)	854 (10.5)	439 (5.5)	< 0.001
1 (%)	4304 (17.6)	1249 (15.0)	1779 (21.9)	1276 (15.9)	< 0.001
≥2 (%)	18,415 (75.2)	6600 (79.3)	5480 (67.5)	6335 (78.7)	< 0.001
HASBLED score (%)					
Mean (SD)	2.04 (1.19)	2.17 (1.22)	1.86 (1.17)	2.09 (1.16)	< 0.001
0–1 (%)	8441 (34.5)	2609 (31.3)	3223 (39.7)	2609 (32.4)	< 0.001
2 (%)	7505 (30.6)	2444 (29.4)	2524 (31.1)	2537 (31.5)	0.006
≥3 (%)	8543 (34.9)	3273 (39.3)	2366 (29.2)	2904 (36.1)	< 0.001
Comorbidities (%)					
Ischemic stroke/thromboembolism	3587 (14.6)	1423 (17.1)	998 (12.3)	1166 (14.5)	< 0.001
Ischemic heart disease	4200 (17.2)	1509 (18.1)	1350 (16.6)	1341 (16.7)	0.015
Peripheral artery disease	521 (2.1)	200 (2.4)	143 (1.8)	178 (2.2)	0.014
Heart failure	3094 (12.6)	1152 (13.8)	959 (11.8)	983 (12.2)	< 0.001
Cancer	3112 (12.7)	1168 (14.0)	830 (10.2)	1114 (13.8)	< 0.001
Chronic kidney disease	446 (1.8)	220 (2.6)	107 (1.3)	119 (1.5)	< 0.001
Liver disease	296 (1.2)	120 (1.4)	87 (1.1)	89 (1.1)	0.056
Bleeding	2405 (9.8)	960 (11.5)	680 (8.4)	765 (9.5)	< 0.001
COPD	2217 (9.1)	852 (10.2)	536 (6.6)	829 (10.3)	< 0.001
Hypertension	13,961 (57.0)	4919 (59.1)	4412 (54.4)	4630 (57.5)	< 0.001
Diabetes mellitus	2933 (12.0)	1142 (13.7)	883 (10.9)	908 (11.3)	< 0.001
Co-medications within 180 days (%)					
ADP receptor inhibitor[a]	2187 (8.9)	868 (10.4)	532 (6.6)	787 (9.8)	< 0.001
Acetylsalicylic acid	7608 (31.1)	2498 (30.0)	2623 (32.3)	2487 (30.9)	0.005
Dipyridamol	449 (1.8)	156 (1.9)	138 (1.7)	155 (1.9)	0.537
NSAID	3709 (15.1)	1220 (14.7)	1300 (16.0)	1189 (14.8)	0.026
Antiadrenergic	315 (1.3)	117 (1.4)	107 (1.3)	91 (1.1)	0.281
Loop diuretics	2791 (11.4)	1055 (12.7)	794 (9.8)	942 (11.7)	< 0.001
Non-loop diuretics	7246 (29.6)	2447 (29.4)	2349 (29.0)	2450 (30.4)	0.106
Vasodilators	24,489 (100.0)	8326 (100.0)	8113 (100.0)	8050 (100.0)	NA
Beta-blocker	8504 (34.7)	2787 (33.5)	2958 (36.5)	2759 (34.3)	< 0.001
Calcium channel blocker	5951 (24.3)	2059 (24.7)	1888 (23.3)	2004 (24.9)	0.029
RAS inhibitor	9949 (40.6)	3518 (42.3)	3250 (40.1)	3181 (39.5)	0.001
Digoxin	1001 (4.1)	315 (3.8)	351 (4.3)	335 (4.2)	0.196
Amiodaron	137 (0.6)	45 (0.5)	47 (0.6)	45 (0.6)	0.946

[a] ADP receptor inhibitor includes clopidogrel, ticagrelor and prasugrel.

dose reduction both overall and when NOACs examined separately. Noticeably, after about 4 years of follow-up the occurrence of dose reduction in the age group 75–79 years exceeded that in the age group 80–100 years (Fig. 3A). The cross-over was caused by the disproportion between users of different NOACs, as this was absent when further stratified by treatment regimen (Fig. 3B–D). Moreover, in comparison with the other two NOACs dabigatran showed a greater association with dose reduction within all the age groups defined at inclusion, particularly among the older individuals (*Appendix C*).

Additionally, both high predicted risks of thromboembolism and bleeding at baseline were associated with higher likelihood of dose reduction (Fig. 4). However, in our study population, 45.5% of the patients with high CHA_2DS_2-VASc score also had high HAS-BLED score (see *Appendix F*).

Lastly, the multivariable analysis assessing the baseline characteristics including comorbidities (see Fig. 5) demonstrated that age ≥ 65 years, ischemic heart disease (IHD), heart failure, cancer, CKD, chronic obstructive pulmonale disease (COPD), and hypertension were independent predictors of NOAC dose reduction, while male sex was related to a lower chance of experiencing dose reduction. When different NOAC patient groups were analyzed separately (see *Appendix G*), similar results were achieved, with the exception of cancer and CKD at baseline that did not predict dose reduction significantly among rivaroxaban users and dabigatran users, respectively.

3.2. Subgroup analysis

Fig. 6 displays absolute risk of NOAC dose reduction over a follow-up of 6 months from event date in subgroups (see *Appendix E* for corresponding cumulative incidence estimates). For all the nine pre-specified events we found an association with dose adjustment exemplified by an initial substantial increase in the cumulative incidence of dose reduction followed by a more modest rise. Nonetheless, this only appeared to be remarkable for CKD, ICH, peripheral bleeding, MI/PCI and antiplatelet treatment start. The largest increase in the absolute risk of dose reduction was observed after MI/PCI (the six-month cumulative incidence: 34.8% (95% CI: 30.1–39.5)).

Furthermore, the subgroup analyses were repeated separately for different NOACs (*Appendix D*, *Fig. D.1–D.9*) and we found similar patterns with initial peak of increase in dose reduction during follow-up after the pre-specified events. When comparing NOACs, the use of apixaban seemed to result in higher risk of dose reduction following

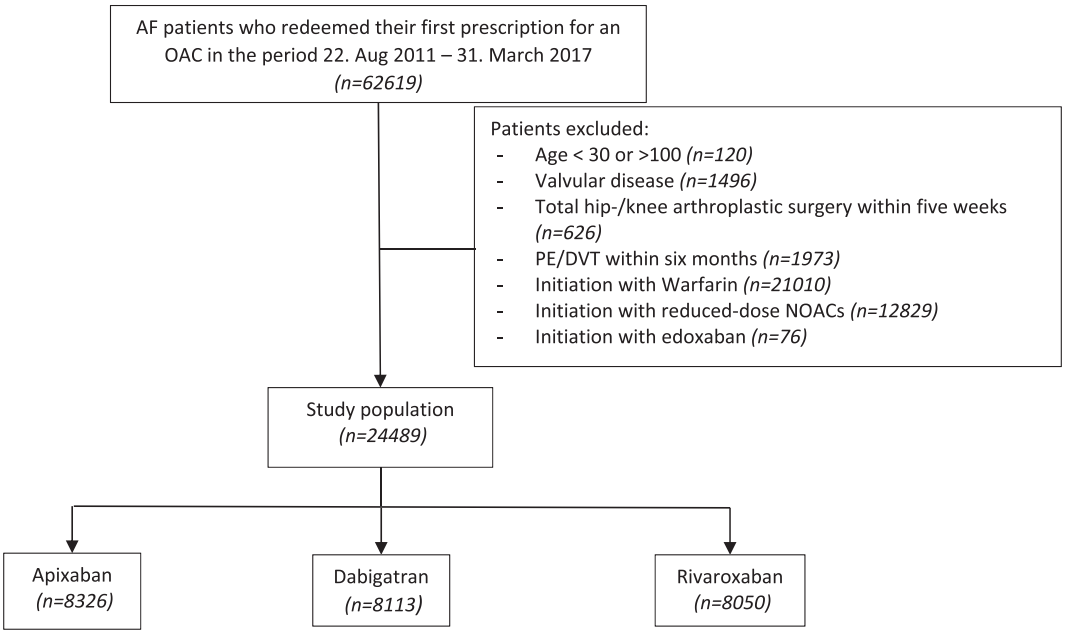

Fig. 1. Flowchart for patient selection proces.
Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulant; PE, pulmonale emboli; DVT, deep vein thrombosis; NOAC, non-vitamin K antagonist oral anticoagulants.

cancer and ICH and in lower risk following MI/PCI, whereas the use of rivaroxaban appeared to be associated with greater tendency of dose reduction after CKD. However, the wide confidence intervals did not allow for strong conclusion for these differences. Conversely, a considerably greater increase in dose reduction following the event of being aged 80 years was observed in dabigatran users, compared with the users of apixaban and rivaroxaban.

4. Discussion

Our study has four principal findings. Firstly, 12.2% of the study cohort were reduced in their NOAC dose within 70.0 months from treatment initiation. Secondly, high CHA_2DS_2-VASc score, high HAS-BLED score, and high age at baseline were associated with an increased risk of dose reduction, as well as being in treatment with dabigatran compared with apixaban and rivaroxaban. Multivariable analysis indicated age ≥ 65 years, female sex, IHD, heart failure, cancer, CKD, COPD, and hypertension as being independent predictors of NOAC dose reduction. Especially age ≥ 65 years at baseline increased the risk of dose reduction by at least 2 times, irrespective of NOAC type. Finally, all the nine pre-specified events demonstrated an association with dose reduction indicated by an initial peak of increase in dose adjustment immediately after the events, even though this pattern was most remarkable for CKD, ICH, peripheral bleeding, MI/PCI, and antiplatelet treatment start.

4.1. Baseline factors associated with dose reduction

In our study, dabigatran-treated patients were more likely to be reduced in treatment dose, even after adjustment for the age at

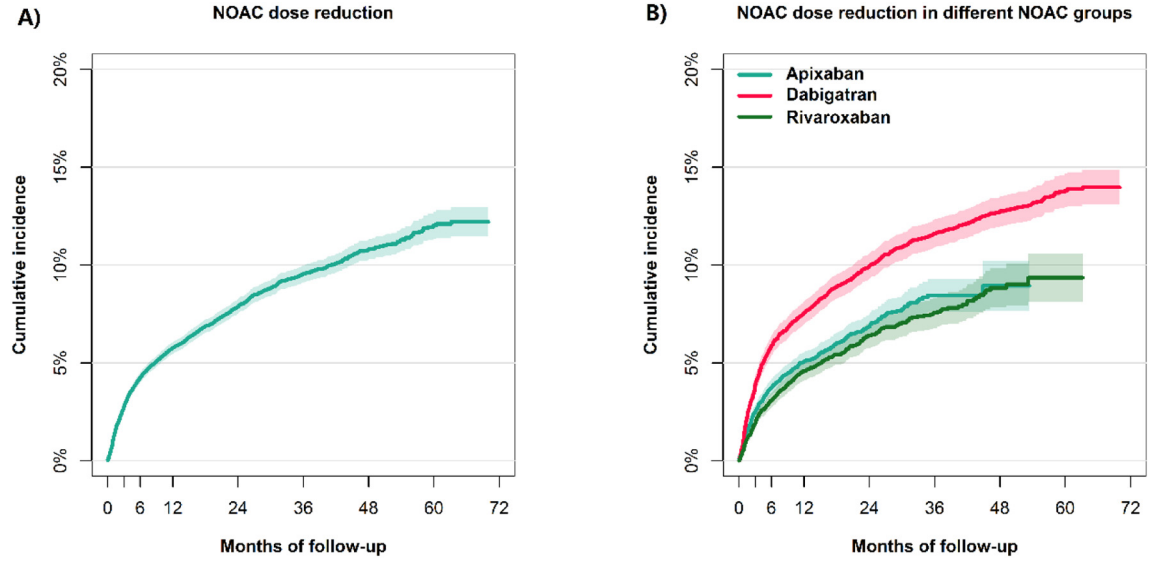

Fig. 2. Cumulative incidence of NOAC dose reduction over time of follow-up in the overall study cohort and in various treatment groups.
A) The overall study cohort; B) different treatment group: apixaban, dabigatran, and rivaroxaban.

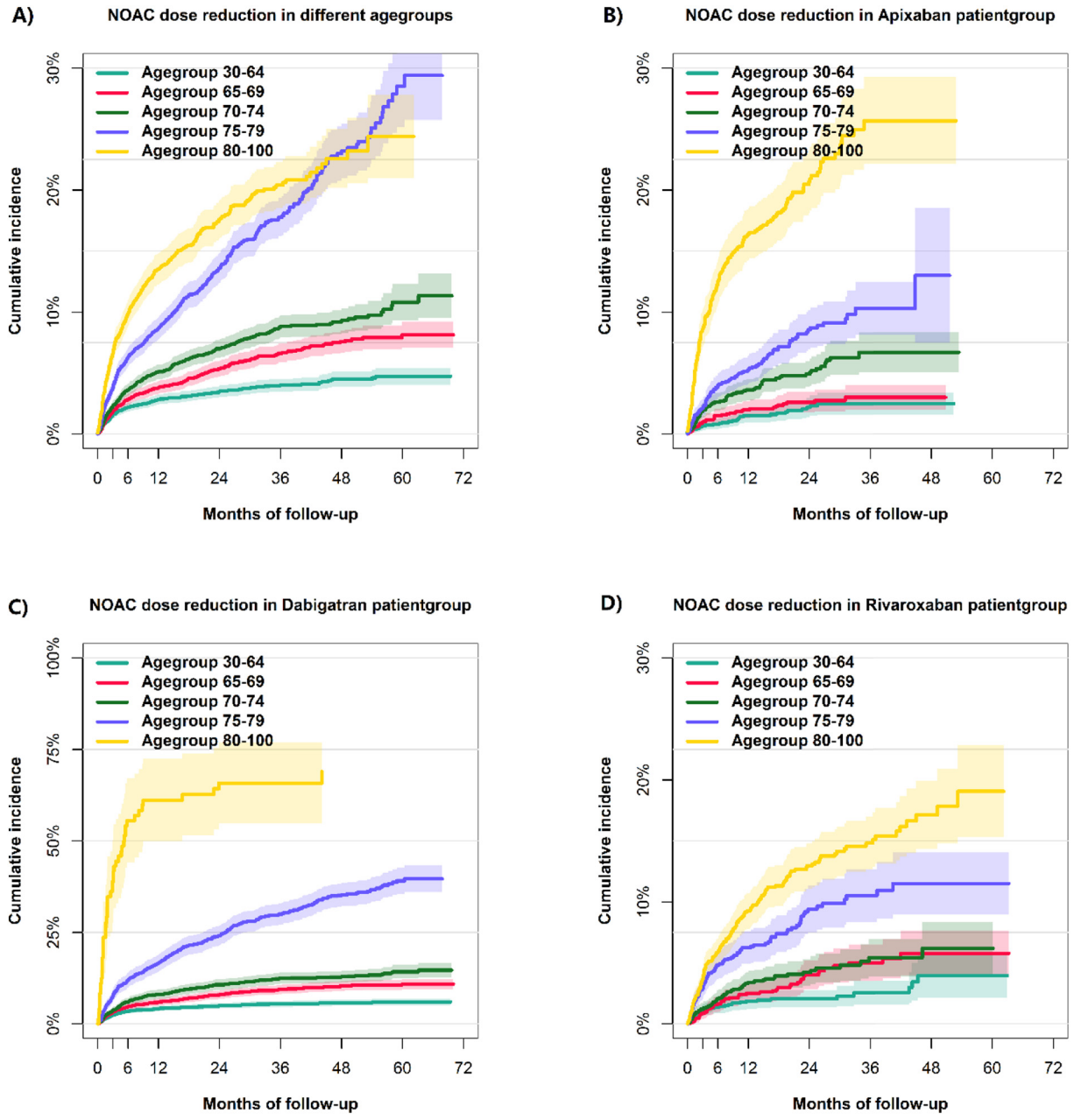

Fig. 3. Cumulative incidence of NOAC dose reduction according to age groups defined at baseline.
A) The overall study cohort; B) apixaban-treated study patients; C) dabigatran-treated study patients; D) rivaroxaban-treated study patients.

baseline. However, the difference in dose reduction between dabigatran and other NOACs was more pronounced among patients in the older age groups. Thus, this may partly account for the overall higher probability of dose reduction detected in dabigatran users. Besides, both doses of dabigatran have been tested in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial [3] with random allocation of the patients, while only small amount of patients received reduced-dose treatment in large clinical trials of apixaban and rivaroxaban [2,4]. Hence, our results may presumably reflect general conservatism in conducting dose reduction of apixaban and rivaroxaban among clinicians.

Moreover, both high predicted risks of thromboembolism and bleeding at baseline seemed to increase the absolute risk of dose reduction. Correspondingly, we found some components of the scores such as old age, female sex, IHD, heart failure, CKD, and hypertension to be independently associated with dose reduction.

4.2. Events associated with dose reduction

Our analysis also examined nine pre-specified events that all showed to be associated with dose reduction. Among these, MI/PCI was related to the largest increase in cumulative incidence during follow-up. According to European guidelines [11,12], the reduced-dose of NOACs combined with antiplatelet therapy are recommended in non-valvular AF-patients following MI/PCI to reduce the risk of major bleeding [13,14]. Nevertheless, we only found 34.8% patients to be reduced in NOAC dose during a follow-up of 6 months after MI/PCI. This discrepancy may have several explanations. First, the current recommendations for anticoagulation in AF patients after MI/PCI were not fully clarified until 2013 [15]. Thus, the calendar time in which the event happened might impact the clinical decision making on NOAC dose adjustment. Second, possibly not all patients were initiated on antiplatelet therapy post-discharge. In our study, we did not examine

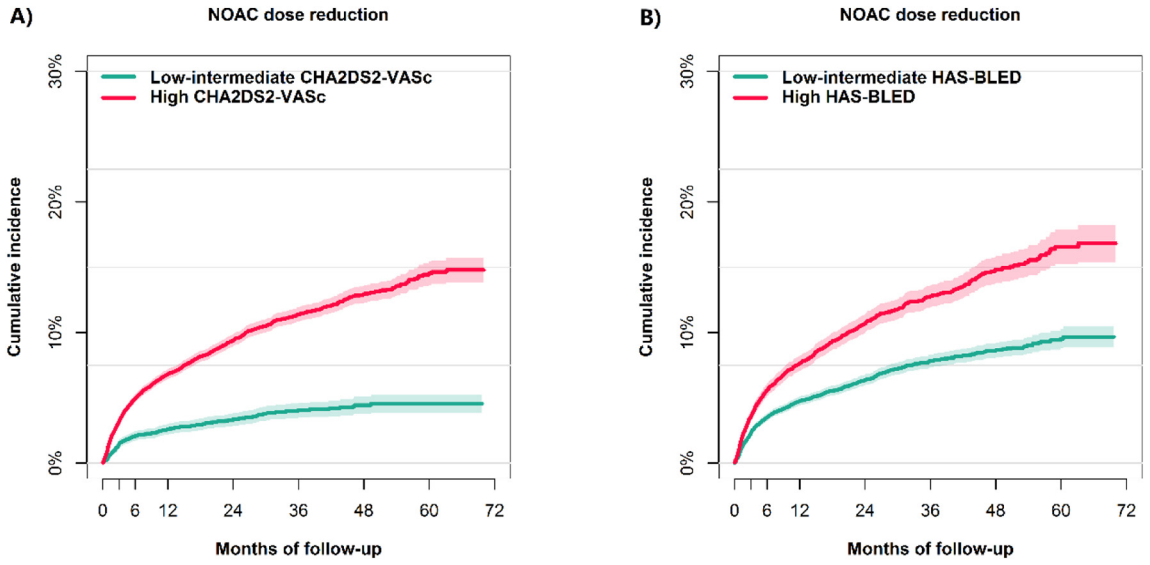

Fig. 4. Cumulative incidence of NOAC dose reduction according to predicted risks of thromboembolism and bleeding at baseline.
A) Study patients with low-intermediate (0–1) versus high (2–9) CHA_2DS_2-VASc score; B) study patients with low-intermediate (0–2) versus high (3–8) HAS-BLED score.

whether AF patients received concomitant antiplatelet after MI/PCI. Instead, the initiation of antiplatelet treatment irrespective of clinical indications was assessed. We observed that it was associated with dose reduction, but to a lesser extent compared with MI/PCI. This is consistent with the fact that guidelines are lacking in other clinical contexts where antiplatelet is added to a well-established NOAC treatment.

With a cut-off age of 80 years as indicated by the drug labels [5,6], our results pointed out an augmented risk of dose reduction following the 80th birthday in AF patients, which was mainly driven by a substantial increase in dose reduction among dabigatran users. This is in line with the European label for dabigatran [6] justifying dose reduction in patients aged ≥80 years, while no dose adjustment based on age is specified for rivaroxaban [7] and other clinical criteria have to be satisfied for qualifying a dose reduction of apixaban [5]. Importantly, dose modification according to age was only observed in 33.2% of dabigatran-treated patients during the 6-month follow-up, despite the clear instructions given in the drug label.

Our study suggests that CKD diagnosis was associated with dose reduction, especially among rivaroxaban users. This could be explained by the fact that rivaroxaban has a higher limit of renal function specified in the criteria for dose reduction than apixaban [5,7], while there is no strict recommendation for dabigatran treatment [6]. Considering that dabigatran is mainly eliminated by renal excretion, treatment discontinuation or switch to another OAC agent would probably be favored in patients with renal failure. Nonetheless, the sample sizes in our study were too small to detect significant differences between various NOACs. The association between CKD and NOAC dose reduction was further supported by our results from the multivariable analysis, where CKD at baseline showed to be a clear predictor of dose reduction. Overall, we found that only 14.5% of patients were reduced

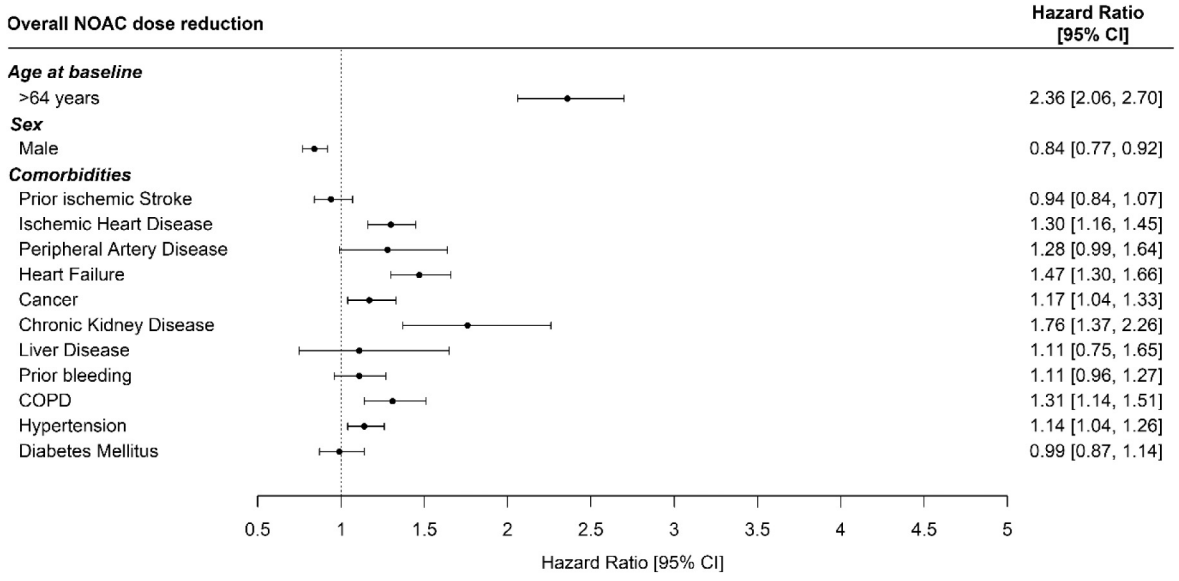

Fig. 5. Hazard ratio for baseline characteristics with respect to NOAC dose reduction.
*Multivariable analysis of baseline covariates as independent predictors of dose reduction; statistical significance is obtained when the 95% confidence interval for hazard ratio does not contain one.
Abbreviation: COPD, chronic obstructive pulmonale disease.

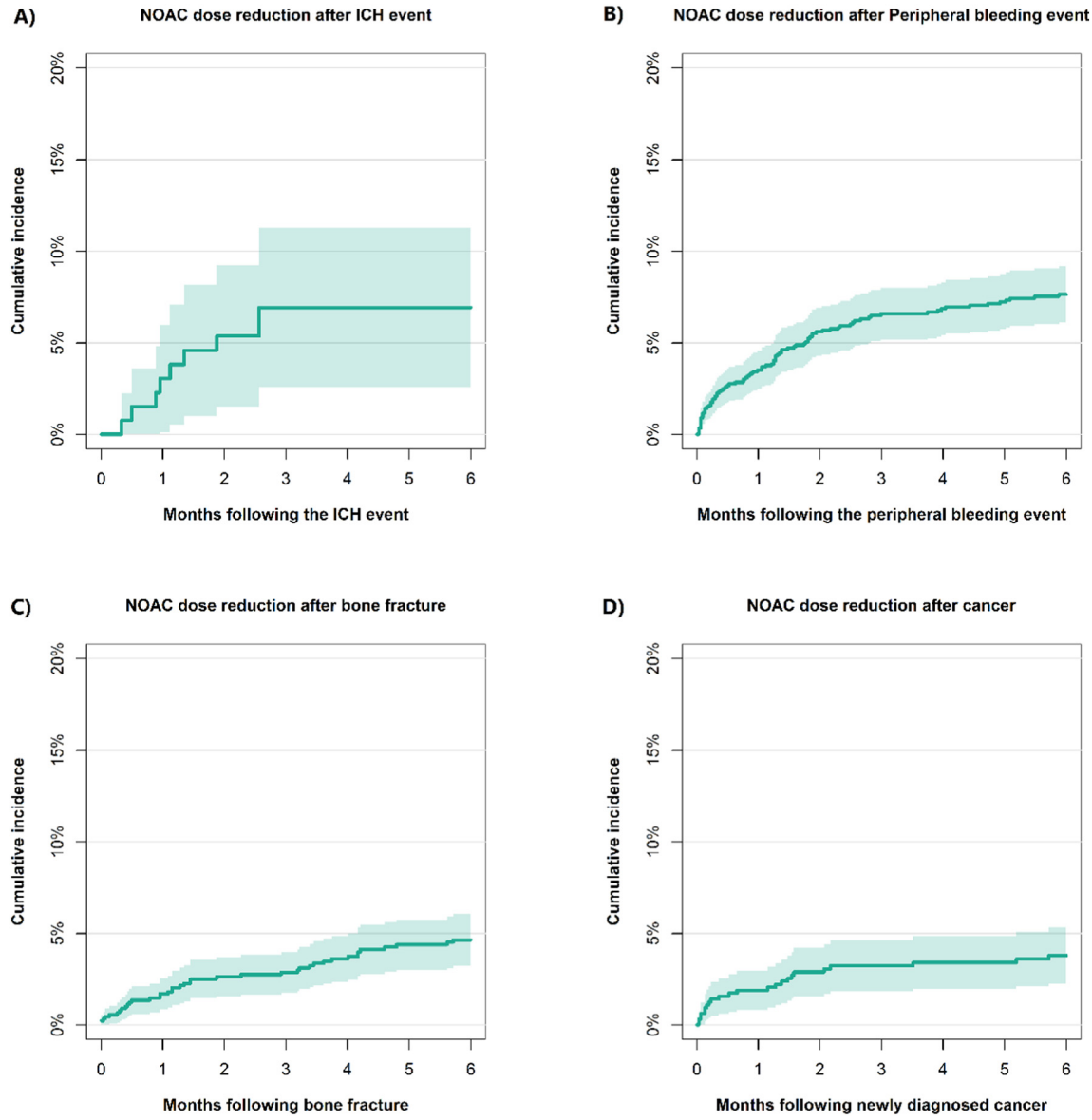

Fig. 6. Cumulative incidence of NOAC dose reduction over six months after the pre-specified events (subgroup analysis).
A) Intracranial hemorrhage (ICH); B) peripheral bleeding; C) bone fracture; D) cancer diagnosis; E) acute myocardial infarction (MI) and/or percutaneous coronary intervention (PCI); F) date of being aged 80 years; G) start date of concomitant antiplatelet treatment; H) diagnosis of chronic kidney disease (CKD); I) ischemic stroke.

in NOAC dose during a follow-up of 6 months after discharge for CKD. However, not all patients diagnosed with CKD would have a renal function lower than the pre-defined limits for dose reduction of NOACs.

Currently, no evidence-based guidelines addressing how the anticoagulation should continue in AF patients who suffered from bleeding complications are available [11,12]. In an analysis of the Dresden NOAC registry, bleeding complications had shown to be the reason for 30% of discontinuations during rivaroxaban treatment [16]. This could explain the low incidences of dose reduction after ICH and peripheral bleeding in our study, where patients possibly ended up with discontinuation or switch of NOAC treatment instead.

A more modest association with dose reduction was observed for ischemic stroke, cancer and bone fracture. According to the current guidelines, no dose adjustment is recommended after an ischemic stroke [11]. The limited association with dose reduction shown in our study could be due to competing causes for stroke such as newly detected carotid artery stenosis, where additional antiplatelet therapy might be relevant [17]. In case of AF patients with malignancies, no specific recommendations for stroke prevention are available [11,12]. The marginal increase in the risk of dose reduction following cancer diagnosis may be related to cancer-related factors such as bleeding [18] or chemotherapy [12]. Also in our multivariable analysis cancer at baseline predicted an increased risk of dose reduction independently. Lastly, we employed hospitalization for bone fracture as possible proxy for fall risk, which is one of the most cited reasons among clinicians for not providing anticoagulation to elderly patients [19]. The relatively small association that we noticed in our study, could be biased by the presence of spontaneous fractures or fractures caused by minor trauma – especially in patients with osteoporosis [20] – which are not associated with NOAC dose reduction.

Several limitations existed in this study. First, the observational nature made it impossible to prove causality, but only associations. Second, we did not have access to data on some important clinical features such as the internal normalized ratio levels, body weight, blood pressure, renal function, and other potential confounders that could have impact on our results. Third, the sample sizes in subgroup analyses

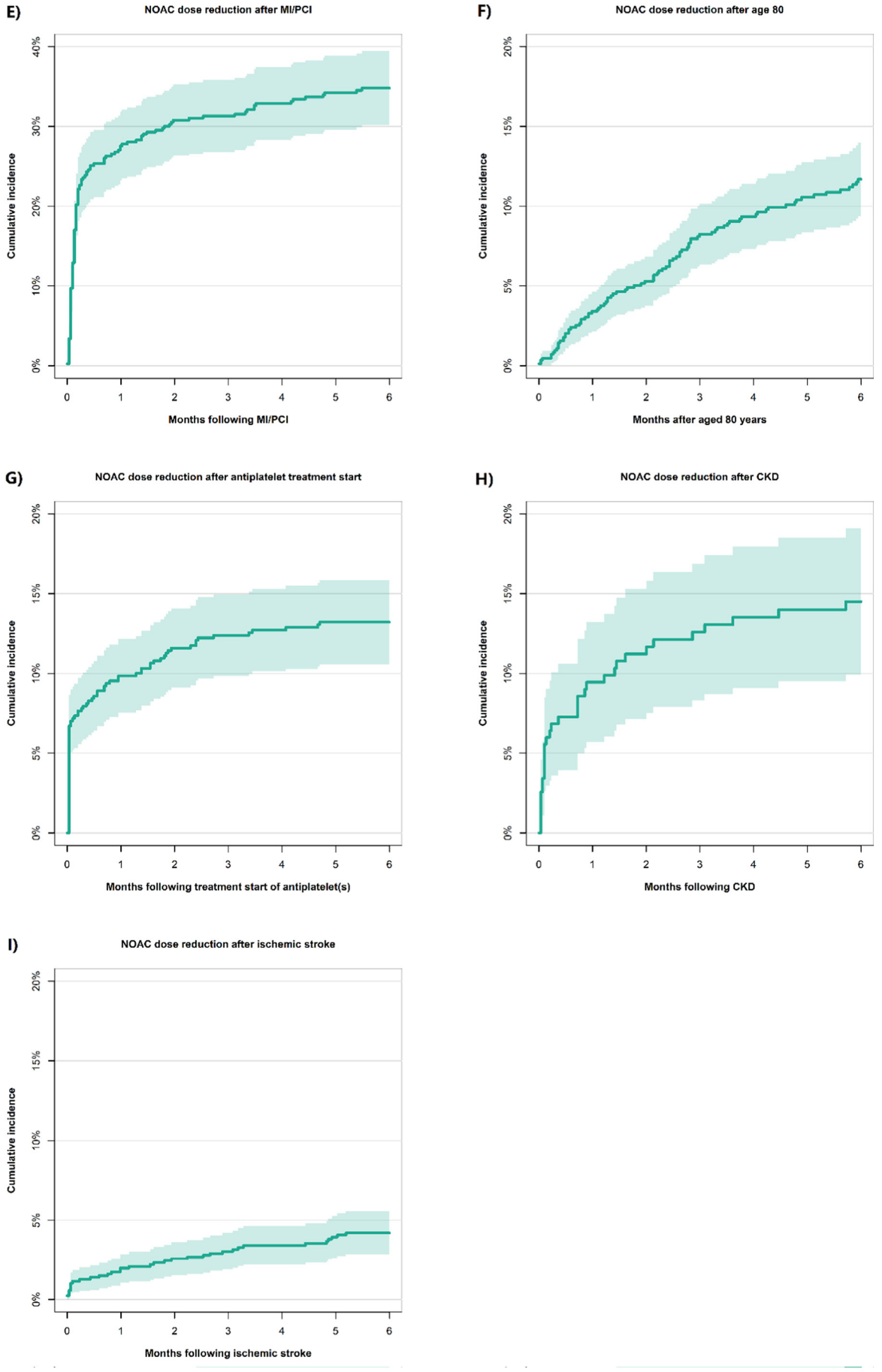

Fig. 6. (*continued*)

were small, which could have led to a greater uncertainty in our results. Fourth, the registries do not contain information about mild adverse reactions or allergies – primarily handled in the primary sector – that might have caused discontinuation of NOAC treatment or switch to another OAC agent, rather than dose reduction. Fifth, information concerning diagnosis in primary care (general practitioner) was not available. Therefore, this study only included patients with hospital contacts for AF before initiating NOAC. It may potentially contribute to selection bias towards sicker patients who are more prone to dose reduction.

5. Conclusions

In conclusion, factors such as high predicted risks of thromboembolism and bleeding, advanced age, and treatment with dabigatran were associated with a predisposition to dose reduction of NOACs in AF patients. Furthermore, baseline IHD, heart failure, cancer, CKD, COPD, and hypertension demonstrated to be independent predictors of dose reduction. Among various events occurred during the study period, the risk of dose reduction was particularly high after MI/PCI. However, NOAC treatment was not dosed appropriately among most AF patients according to the existing guidelines in clinical settings — including age turned 80 years, CKD, MI/PCI, and antiplatelet treatment start. Accordingly, more careful attention should be paid to these specific patient populations in clinical practice. Besides, evidence-based recommendations regarding NOAC dosage are needed to provide practice guidance to clinicians managing AF patients with bleeding complications, malignancy, and increased fall risk. Generally, there is a lack of comparative studies assessing the real-life impact of dose reduction on outcomes.

Funding

This work was supported by an unrestricted grant from Bristol-Myers Squibb [grant numbers CV185-386]. B.M.S. was not involved in the study design or the analysis and interpretation of data.

Conflict of interest

LYX, CAB, CS-P and ANB have nothing to declare. GHG has received research grants from B.M.S., B.I., Pfizer and Bayer. JBO has been speaker for B.M.S., B.I., Bayer and AstraZeneca, served as consultant for B.M.S., B.I., Novartis Healthcare and Novo Nordisk, and received funding for research from B.M.S. and The Capital Region of Denmark, Foundation for Health Research.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.04.007.

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