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CLINICAL RESEARCH
Atrial fibrillation

Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: a systematic review and meta-analysis

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Aims Non-vitamin K antagonist oral anticoagulants (NOACs) are effective and safe alternatives compared with vitamin K antagonists (VKAs) for thromboembolic prevention in atrial fibrillation (AF), while antiplatelets are no longer recommended. However, to which extent NOAC introduction and guideline updates have increased OAC use in AF, is unclear. Therefore, worldwide trends in real-life prescribing of OACs, NOACs, VKAs, and antiplatelet monotherapy in AF patients were investigated.

Methods and results Using PubMed and Embase, observational nationwide cohort studies on annual prevalent and/or incident OAC use in non-selected AF patients since 2010 were included. A meta-analysis of single proportions was performed. Twenty-one studies were included assessing prevalent and incident use among 9 758 637 and 197 483 OAC-eligible AF patients, respectively. Worldwide prevalence and incidence of OAC users increased from 0.42 [95% confidence interval (CI) 0.22–0.65] and 0.43 (95% CI 0.37–0.49) in 2010 to 0.78 (95% CI 0.77–0.78) and 0.75 (95% CI 0.74–0.76) in 2018, respectively. Prevalent and incident NOAC users increased globally from 0 in 2010 to 0.45 (95% CI 0.45–0.46) and 0.68 (95% CI 0.67–0.69) in 2018, respectively, whereas prevalent and incident VKA use decreased from 0.42 (95% CI 0.22–0.65) and 0.42 (95% CI 0.36–0.49) in 2010 to 0.32 (95% CI 0.32–0.32) and 0.06 (95% CI 0.06–0.07) in 2018, respectively. Prevalent antiplatelet monotherapy use decreased from 0.37 (95% CI 0.32–0.42) in 2010 to 0.09 (95% CI 0.09–0.10) in 2018.

Conclusion The proportion of OAC users worldwide almost doubled following NOAC introduction. As one-quarter of OAC-eligible AF subjects were not anticoagulated and 9% were only treated with antiplatelets in 2018, there is still room for improvement.

Keywords Atrial fibrillation • Anticoagulant • Non-vitamin K antagonist oral anticoagulant • Vitamin K antagonist • Antiplatelet • Trends • Meta-analysis

Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia worldwide, is associated with a fivefold increased risk of stroke.[1] For decades, vitamin K antagonists (VKAs) were the first choice oral antithrombotic treatment, reducing the risk of stroke by 64% and the risk of death by 22%.[2] However, VKAs have disadvantages, such as a slow onset of action, narrow therapeutic window requiring frequent International Normalized Ratio (INR) monitoring, and multiple drug–food interactions.[3] Consequently, considerable VKA underuse has been reported in AF patients at high thromboembolic risk.[4] As an alternative to VKAs, low-dose aspirin was frequently used, although antiplatelets are inferior to oral anticoagulants (OACs) for thromboprophylaxis in AF.[2,5]

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What's new?

- The worldwide proportion of oral anticoagulant (OAC) users among all OAC-eligible patients with atrial fibrillation (AF) almost doubled from 42% in 2010 to 78% in 2018.
- The proportion of newly-diagnosed eligible AF patients starting OACs increased from 43% to 75% over this time period.
- By 2017, prevalent non-vitamin K antagonist oral anticoagulant (NOAC) users surpassed vitamin K antagonist (VKAs) users worldwide, whereas incident NOAC users already exceeded VKA users in 2014.
- However, as one-quarter of OAC-eligible AF patients were not anticoagulated in 2018 and 9% were treated with antiplatelet monotherapy, opportunities to further reduce morbidity and mortality risks among AF patients are still present.

Since 2010, non-vitamin K antagonist oral anticoagulants (NOACs) are approved for stroke prevention in AF and have shown to be efficacious and safe alternatives to VKAs.[6] Following the 2016 European Society of Cardiology (ESC) AF guidelines, NOACs are preferred over VKAs, given their fixed dosing regimen without need for INR monitoring, fast onset of action, less known interactions, and lower intracranial bleeding risk.[7] Conversely, antiplatelets are no longer recommended for stroke prevention in AF. Moreover, since the 2010 ESC AF guidelines, the CHA_2DS_2-VASc instead of $CHADS_2$ score is recommended to assess a patient's thromboembolic risk, which has increased OAC eligibility.[5,8]

However, it is unclear to which extent the introduction of NOACs and updated guideline recommendations have increased the worldwide use of OACs in AF patients indicated for anticoagulation. Moreover, given the various approval dates and reimbursement criteria of NOACs, differences in the uptake of (N)OACs between countries are expected. Therefore, we aimed to investigate worldwide trends in the proportion of users of OACs, NOACs, VKAs, and antiplatelet monotherapy among OAC-eligible AF patients since 2010 by meta-analysis of nationwide results.

Methods

Search strategy

An extensive search strategy was performed in PubMed and Embase (Supplementary material online, *Table S1* for the detailed search strategy including all used search terms, MeSH/Emtree terms, and Boolean operators). Records were identified up to 1 March 2021. No restriction on publication date or language was used. Additionally, articles were identified by screening the reference list of studies.

Study selection

After study deduplication, records were screened on title and abstract, followed by full-text assessment for eligibility by two independent reviewers (M.G. and C.S.) blinded to each other's decisions. To resolve discrepancies, there was a consensus meeting with a senior researcher (L.L.). Studies were included if they investigated the prevalent and/or incident use of OACs (NOACs or VKAs), NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban), VKAs (warfarin, acenocoumarol, or phenprocoumon), and/or antiplatelet monotherapy (e.g. aspirin) among non-selected AF patients eligible for anticoagulation in a specific country per total calendar year from 2010 up to 2020. Patients were considered as eligible for (N)OAC treatment if they had non-valvular AF (absence of a mechanical prosthetic heart valve or moderate to severe mitral stenosis) and were at moderate to high thromboembolic risk (CHA_2DS_2-VASc score $\geq$1 in men, $\geq$2 in women), in line with international guideline recommendations.[3,9,10] Studies reporting AF-related OAC use before 2010 were not considered, given the non-commercialization of NOACs before this year and use of the $CHADS_2$ instead of the CHA_2DS_2-VASc score to assess OAC eligibility. Only results from observational nationwide healthcare claims databases and large population-based cohort studies were included to investigate trends in real-life prescribing of OACs, whereas randomized controlled trials, reviews, meta-analyses, case reports, editorials, or conference proceedings were not considered. In the full-text assessment, studies specifically including AF patients with a certain comorbidity (e.g. renal dysfunction, dementia, or high age), outcome (e.g. stroke or bleeding) or intervention (e.g. cardioversion, ablation, or percutaneous coronary intervention) were excluded, since the respective comorbidity, outcome, or intervention may have influenced eligibility and prescription rates. Similarly, studies including only hospitalized AF patients (e.g. in the emergency department, geriatric ward, or cardiology department) were also not considered, given that local prescribing habits of a smaller number of physicians may not be generalizable to the nationwide prescribing of a specific country, and given that the hospitalization itself may alter OAC prescription rates at discharge. Furthermore, studies only including OAC-treated AF subjects (exclusion of non-anticoagulated subjects or subjects with antiplatelet monotherapy) were not considered, as the aim was to investigate the proportion of OAC-treated patients among all OAC-eligible AF subjects. Moreover, if OACs were used for indications other than non-valvular AF (e.g. venous thromboembolism), studies were excluded if no separate data in AF patients were reported. Lastly, in case of duplicate cohorts (e.g. studies based on the same healthcare database), results of the study with the most person-years of follow-up were retained for the respective overlapping years.

Data extraction

Data of the study methodology (setting, design, and data source), patient characteristics (number, age, and CHA_2DS_2-VASc score), and outcome (annual prevalent and/or incident use) were extracted from the original publications and supplemental materials by two reviewers (M.G. and C.S.) independently and discrepancies were resolved by consensus. If studies reported the annual use per CHA_2DS_2-VASc score category, only data from AF patients with a CHA_2DS_2-VASc score $\geq$1 were extracted. If relevant data were missing from the original publications, they were requested by directly contacting the corresponding author by e-mail. However, lack of a timely response within 3 months necessitated exclusion of these studies.

Quality assessment

The risk of bias of studies included in the meta-analysis was assessed by two independent reviewers (M.G. and C.S.) using the 'QUALSYST' tool from the 'Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields'.[11] Each study was scored on 14 items based on the study quality and outcome levels depending on the

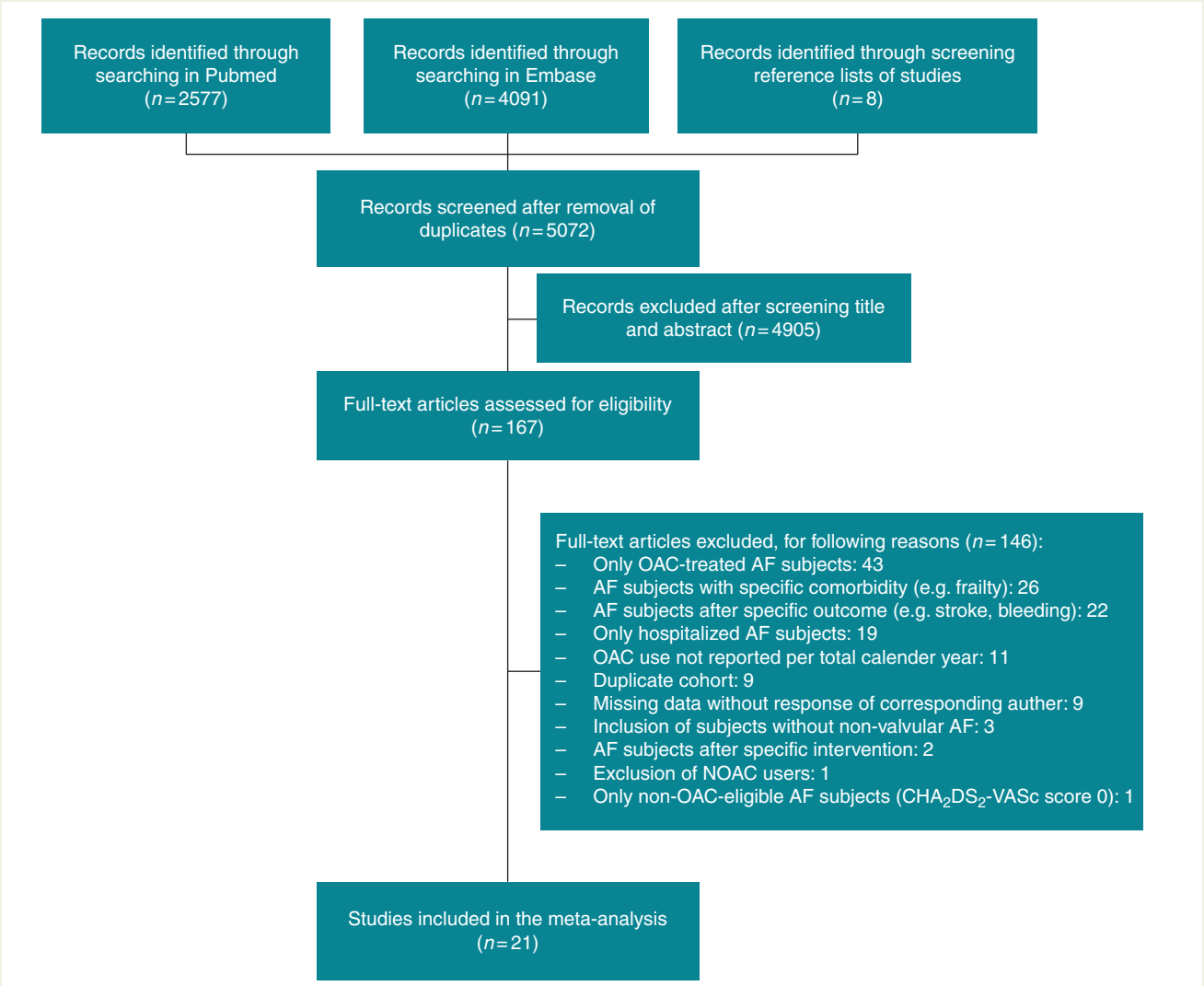

Figure 1 PRISMA flow diagram. AF, atrial fibrillation; OAC, oral anticoagulant.

degree to which the specific criteria were met or reported. For each study, a percentage was calculated by dividing the total score obtained across rated items by the total possible score. Studies were included if they scored ≥75%.

Statistical analysis

A meta-analysis of single proportions was performed using a random effects model and the inverse variance weighting method in R (R version 4.0.3 with RStudio version 1.3.1073). Effect measures were calculated and reported as the annual proportions of prevalent or incident users of OACs, NOACs, VKAs, or antiplatelet monotherapy with 95% confidence intervals (CIs), categorized by continent and year. Results were visually presented in forest plots and time series plots. Heterogeneity was tested using the I^2-statistic based on a restricted maximum-likelihood estimator. The risk of publication bias was assessed through funnel plot asymmetry and Peter's regression test. A two-sided *P*-value of <0.05 was considered statistically significant. This work was performed according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Supplementary material online, *Table S5*). The protocol of this meta-analysis was registered on PROSPERO (International Prospective Register of Systematic Reviews) (number CRD42021247570).[12]

Results

Study selection and characteristics

Five thousand and seventy-two unique records were identified (*Figure 1*). After title and abstract screening, 167 articles were selected. Twelve studies had missing data, of which only three authors[13–15] replied to our request to provide these results. Finally, 21 were included in the meta-analysis: 11 European,[16–26] 3 Northern American,[13,27,28] 4 Asian,[15,29–31] 1 Oceanian,[14] 1 Southern American,[32] and 1 study with worldwide and Northern American data.[33] A total of 9 758 637 and 197 483 AF patients were included to determine the annual prevalent and incident

Table 1 Characteristics of included studies

Author (year)	Country	Study design	Data source and study cohort	*n*	Mean/median age [years ± SD; (IQR)]	Mean/median CHA_2DS_2-VASc score [± SD; (IQR)]	Outcome
Europe							
Maura *et al.* (2019)[16]	France	Obs. retrosp. nationwide cohort study	French national health insurance system database and French hospital discharge database (SNIIRAM-PMSI)	2011: 853 440; 2016: 1 098 657	NR	NR	Prevalent use: 2011 and 2016 (OAC, VKA, NOAC, AP)
Schwill *et al.* (2018)[17]	Germany	Obs. retrosp. multicentre cohort study	Continuous-morbidity-registration-Epidemiologic-Network (CONTENT) database	2011: 1887; 2014: 1838	2011: Group A 79 [71–86], Group C 75 [68–81]; 2014: Group B 77 [70–83], Group C 78 [71–84] (NR for overall cohort per year)	Score ≥2: 2011: Group A 87.3%, Group C 81.6%; 2014: Group B 84.8%, Group C 83.8% (NR for overall cohort per year)	Prevalent use: 2011 and 2014 (OAC, VKA, NOAC, AP)
Hohnloser *et al.* (2019)[18]	Germany	Obs. retrosp. nationwide cohort study	Claims-based database from the Institute for Applied Health Research, Berlin	2011: 85 224; 2012: 92 708; 2013: 94 998; 2014: 102 786; 2015: 109 427; 2016: 116 118	No therapy: 73.8 ± 12.7; NOAC: 75.0 ± 10.2; VKA: 75.2 ± 8.8; Antiplatelet: 77.7 ± 10.0 (Data NR per year)	No therapy: 3.5 ± 1.8; NOAC: 3.9 ± 1.7; VKA: 3.9 ± 1.5; Antiplatelet: 4.4 ± 1.6 (Data NR per year)	Prevalent use: 2011–16 (OAC, VKA, NOAC, AP)
Maggioni *et al.* (2020)[19]	Italy	Obs. retrosp. multicentre cohort study	Ricerca e Salute (ReS) database	2012: 47 116; 2013: 47 945; 2014: 47 472; 2015: 51 497	2012: 77 ± 11; 2013: 77 ± 11; 2014: 78 ± 11; 2015: 78 ± 11	NR	Prevalent use: 2012–15 (OAC, VKA, NOAC, AP)
Loikas *et al.* (2017)[20]	Sweden	Obs. retrosp. multicentre cohort study	Stockholm regional healthcare data warehouse (Vårdanalysdatabasen); inclusion if CHA_2DS_2-VASc ≥1	2011: 39 259; 2015: 45 093	2011: men 72.5 ± 14.4: women 79.1 ± 13.3; 2015: men 71.3 ± 13.4: women 77.5 ± 12.0	2011: men 3.0 ± 1.9: women 4.5 ± 1.8; 2015: men 3.0 ± 1.8: women 4.4 ± 1.7	Prevalent use: 2011 and 2015 (OAC, VKA, NOAC, AP)
Mochalina *et al.* (2017)[21]	Sweden	Obs. retrosp. multicentre cohort study	Skåne Healthcare Register	2011: 3700; 2012: 3907; 2013: 3893	2011: 77 ± 11; 2012: 77 ± 11; 2013: 77 ± 11	NR	Incident use: 2011–13 (OAC, VKA, NOAC, AP)
Forslund *et al.* (2018)[22]	Sweden	Obs. retrosp. multicentre cohort study	Stockholm regional healthcare data warehouse (Vårdanalysdatabasen)	2012: 41 008; 2017: 49 510	2012: 74.6 ± 12.5; 2017: 75.0 ± 11.9	2012: 3.62 ± 1.9; 2017: 3.66 ± 1.9	Prevalent use: 2012 and 2017 (OAC, VKA, NOAC)
Holt *et al.* (2012)[23]	UK	Obs. retrosp. multicentre cohort study	QResearch database; inclusion if CHA_2DS_2-VASc ≥2	2010: 50 547	2010: 80.0 [71.0–87.0] (NR per OAC type)	NR	Prevalent use: 2010 (OAC, VKA, AP)

Continued

Table 1 *Continued*

Author (year)	Country	Study design	Data source and study cohort	*n*	Mean/median age [years ± SD; (IQR)]	Mean/median CHA_2DS_2-VASc score [± SD; (IQR)]	Outcome
Durham *et al.* (2017)[24]	UK	Obs. retrosp. nationwide cohort study	UK Clinical Practice Research Datalink (CPRD)	2010: 5431	OAC: 73.9 ± 10.4; No OAC: 74.6 ± 13.0 (NR per year)	OAC: 3.6 ± 1.7; No OAC: 3.4 ± 1.8 (NR per year)	Incident use: 2010 (OAC) (Duplicate cohort of Bakhai *et al.*[26]: 2011–14: OAC)
Wu *et al.* (2020)[25]	UK	Obs. retrosp. multicentre cohort study	Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) registry; inclusion if CHA_2DS_2-VASc ≥1	2011: 39 022; 2012: 132 779; 2013: 57 637; 2014: 49 230; 2015: 77 883; 2016: 90 862; 2017: 100 221; 2018: 83 262	NR	NR	Prevalent use: 2010–18 (OAC, VKA, NOAC, AP)
Bakhai *et al.* (2021)[26]	UK	Obs. retrosp. nationwide cohort study	UK Clinical Practice Research Datalink (CPRD)	2011: 4866; 2012: 4945; 2013: 4581; 2014: 4046; 2015: 3387	Overall: 76.0 ± 12.6; VKA: 73.0 ± 11.8; NOAC: 72.9 ± 12.1; Aspirin: 74.3 ± 12.3; No OAC/AP: 74.5 ± 16.3 (NR per year)	Overall: 2.3 ± 1.3; VKA: 1.9 ± 1.2; NOAC: 1.9 ± 1.2; Aspirin: 2.0 ± 1.2; No OAC/AP: 2.1 ± 1.3 (NR per year)	Incident use: 2011–15 (OAC, VKA, NOAC, AP)
North America							
Ashburner *et al.* (2017)[13]	USA	Obs. retrosp. multicentre cohort study	Primary Care Practice Based Research Network database	2010: 4920 (747 new); 2011: 5147 (728 new); 2012: 5576 (800 new); 2013: 5853 (804 new); 2014: 6257 (830 new); 2015: 6452 (860 new)	2010: 73.4 ± 12.8; 2011: 73.5 ± 12.7; 2012: 73.7 ± 12.6; 2013: 73.8 ± 12.5; 2014: 74.1 ± 12.5; 2015: 74.2 ± 12.4	2010: 3.41; 2011: 3.47; 2012: 3.74; 2013: 3.78; 2014: 3.83; 2015: 3.82	Incident use: 2010–15 (OAC, VKA, NOAC); prevalent use: 2010–15 (OAC, VKA, NOAC)
Steinberg *et al.* (2017)[33]	USA	Obs. prosp. multicentre cohort study	ORBIT-AF II registry	2014: 1847; 2015: 2138	ORBIT-AF-II: 70.3 [70.1–70.5] (NR per year)	ORBIT-AF-II: score 0: 4.1%, 1: 10.9%; ≥2: 85.0% (NR per year)	Incident use: 2014–15 (OAC, VKA, NOAC, AP)
Nguyen *et al.* (2018)[28]	USA	Obs. retrosp. nationwide cohort study	Truven Health MarketScan Medicare Database; inclusion if CHA_2DS_2-VASc ≥2	2010: 49 961	2010: 77.8 ± 7.5	2010: 3.64 ± 1.4	Incident use: 2010 (OAC, VKA, NOAC)
Maddox *et al.* (2020)[27]	USA	Obs. prosp. nationwide cohort study	National Cardiovascular Data Registry PINNACLE (Practice Innovation and Clinical Excellence); inclusion if CHA_2DS_2-VASc ≥2	2013: 460 489; 2014: 632 994; 2015: 777 207; 2016: 885 792; 2017: 891 475	2013: 66.0 [55.0–76.0]; 2014: 65.0 [52.0–75.0]; 2015: 64.0 [50.0–74.0]; 2016: 63.0 [50.0–74.0]; 2017: 64.0 [49.0–74.0]	NR	Prevalent use: 2013–17 (OAC, VKA, NOAC)

Continued

Table 1 *Continued*

Author (year)	Country	Study design	Data source and study cohort	*n*	Mean/median age [years ± SD; (IQR)]	Mean/median CHA_2DS_2-VASc score [± SD; (IQR)]	Outcome
					(overall, NR for AF patients only)		
Asia							
Yamashita *et al.* (2017)[31]	Japan	Obs. prosp. multicentre cohort study	Fushimi AF Registry	2011: 2617; 2012: 2672; 2013: 2615; 2014: 2451; 2015: 2076	VKA: 74.4 ± 9.1; NOAC: 72.0 ± 10.3; No OAC: 73.1 ± 12.6 (NR per year)	VKA: 3.7 ± 1.6; NOAC: 3.2 ± 1.5; No OAC: 3.1 ± 1.7 (NR per year)	Prevalent use: 2011–15 (OAC, VKA, NOAC, AP)
Lee *et al.* (2017)[29]	South Korea	Obs. retrosp. nationwide cohort study	National Health Insurance Service database of Korea (NHIS)	2010: 9614; 2011: 10 502; 2012: 11 301; 2013: 11 993	NR	2010: 4.18; 2011: 4.26; 2012: 4.34; 2013: 4.42	Prevalent use: 2010–2013 (AP) (Duplicate cohort of Yu *et al.*[15]: 2010–13: OAC, NOAC, VKA)
Lee *et al.* (2017)[30]	South Korea	Obs. retrosp. nationwide cohort study	National Health Insurance Service database of Korea (NHIS); inclusion if CHA_2DS_2-VASc ≥1	2015: 263 783	2015: NOAC: 73.1 ± 9.1; VKA: 71.7 ± 10.3; No OAC: 72.1 ± 11.2; AP: 72.0 ± 10.8 (NR for other years)	2015: NOAC: 4.3 ± 1.5; VKA: 4.0 ± 1.5; No OAC: 3.8 ± 1.5; AP: 3.8 ± 1.5 (NR for the other years)	Prevalent use: 2015 (AP) (Duplicate cohort of Yu *et al.*[15]: 2010–15: OAC, NOAC, VKA)
Yu *et al.* (2020)[15]	South Korea	Obs. retrosp. nationwide cohort study	National Health Insurance Service database of Korea (NHIS); inclusion if CHA_2DS_2-VASc ≥2	2010: 265 547; 2011: 290 948; 2012: 316 610; 2013: 342 756; 2014: 368 253; 2015: 394 265; 2016: 421 986	2010–12: 64.2 ± 14.6; 2013–2014: 64.3 ± 14.7; 2015–2016: 65.1 ± 14.3 (NR per year)	2010–12: 3.04 ± 1.86; 2013–14: 3.05 ± 1.92; 2015–16: 3.10 ± 1.95 (NR per year)	Prevalent use: 2010–16 (OAC, VKA, NOAC)
Oceania							
Bezabhe *et al.* (2020)[14]	Australia	Obs. retrosp. nationwide cohort study	National Prescribing Service (NPS) MedicineWise's dataset, MedicineInsight	2010: 4190; 2011: 4686; 2012: 5158; 2013: 5843; 2014: 6559; 2015: 6847; 2016: 7438; 2017: 8244; 2018: 8179	OAC: 73.4 ± 10.95; No OAC: 70.6 ± 16.27 (NR per year)	OAC: 3.46 ± 1.66; No OAC: 2.79 ± 1.86 (NR per year)	Incident use: 2010–18 (OAC, VKA, NOAC)
South America							
Marcolino *et al.* (2015)[32]	Brazil	Obs. retrosp. multicentre cohort study	Telehealth Network of Minas Gerais (TNMG) database	2011: 4637	2011: 70.3 ± 13.5	NR	Prevalent use: 2011 (OAC, VKA, AP)
Worldwide							
Steinberg *et al.* (2017)[33]	35 countries	Obs. prosp. multicentre cohort study	GARFIELD-AF; inclusion if ≥1 stroke risk factor	2011: 4600; 2012: 6800; 2013: 10 014; 2014: 9780; 2015: 1674	GARFIELD-AF: 69.7 [69.6–69.8] (NR per year)	GARFIELD-AF: score 0: 2.8%, 1: 12.2%; ≥2: 85.0% (NR per year)	Incident use: 2011–15 (OAC, VKA, NOAC, AP)

AF, atrial fibrillation; AP, antiplatelets; CHA_2DS_2-VASc, congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); GARFIELD-AF, The Global Anticoagulant Registry in the Field-Atrial Fibrillation; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; NR, not reported; OAC, oral anticoagulant; Obs., observational; ORBIT-AF, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; Prosp., prospective; Retrosp., retrospective; SD, standard deviation; VKA, vitamin K antagonist.

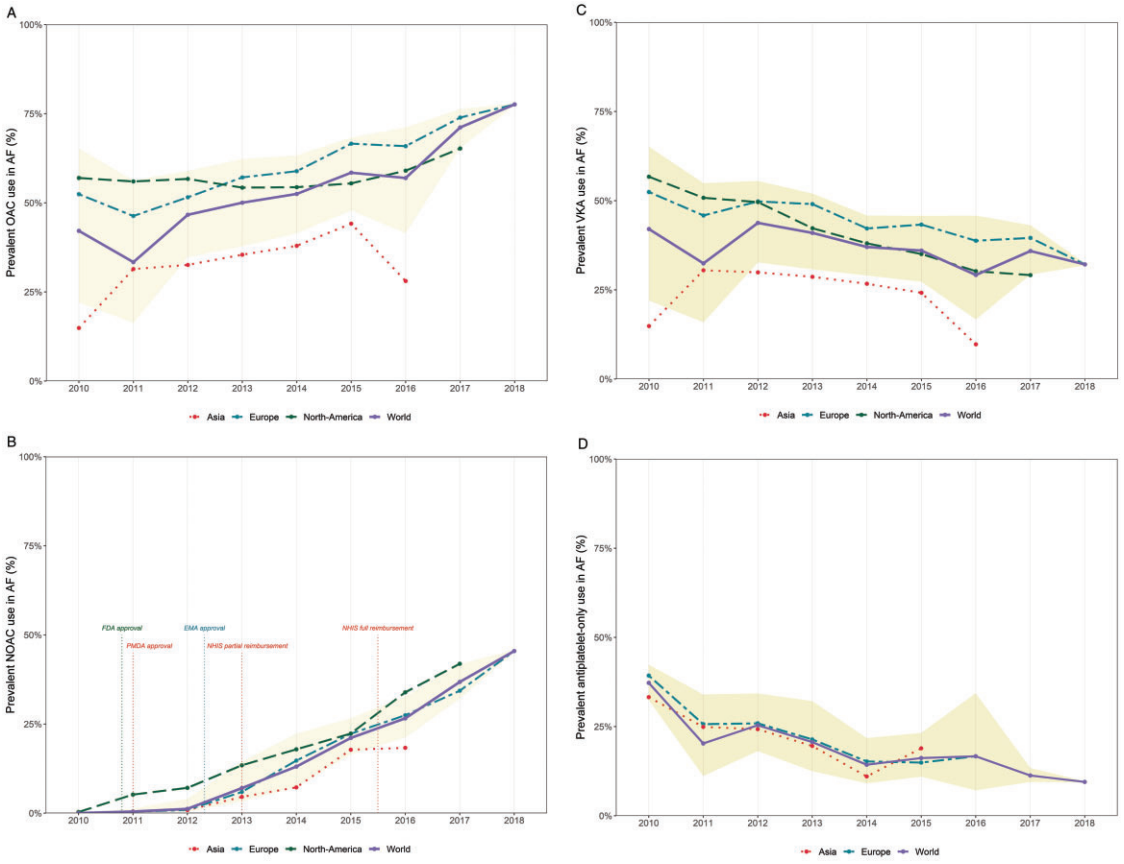

Figure 2 Trends in prevalent use of (*A*) OACs, (*B*) NOACs, (*C*) VKAs, and (*D*) antiplatelet monotherapy in OAC-eligible AF patients from 2010 to 2018, categorized by continent. Yellow band: 95% CI of worldwide meta-analysed proportion per year. (*B*) Approval date of dabigatran by the respective authorities is highlighted. AF, atrial fibrillation; CI, confidence interval; EMA, European Medicine Agency (Europe); FDA, Food and Drug Administration (USA); NHIS, National Health Insurance System (Korea); NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PMDA, Pharmaceuticals and Medical Devices Agency (Japan); VKA, vitamin K antagonist.

OAC use respectively, from 2010 to 2018 (no data for 2019–20). Study characteristics (e.g. study cohort, mean/median age, and CHA_2DS_2-VASc score) are summarized in *Table 1* and Supplementary material online, *Table S2*. All studies scored ≥75% on the 'QUALSYST' tool (Supplementary material online, *Table S3*).

Prevalent use

From 2010 to 2018, the worldwide proportion of eligible AF patients using OACs was 0.50 (95% CI 0.44–0.56), increasing from 0.42 (95% CI 0.22–0.65) in 2010 to 0.78 (95% CI 0.77–0.78) in 2018 (*Figure 2A*, Supplementary material online, *Figure S1* and *Table S4*). The proportion of eligible AF patients using NOACs increased globally from 0.00 (95% CI 0.00–0.00) in 2010 to 0.45 (95% CI 0.45–0.46) in 2018, whereas the proportion of VKA users slightly decreased from 0.42 (95% CI 0.22–0.65) in 2010 to 0.32 (95% CI 0.32–0.32) in 2018 (*Figure 2B and C*, Supplementary material online, *Figures S2 and S3*). Among OAC-eligible AF patients, the worldwide proportion of patients using antiplatelet monotherapy decreased from 0.37 (95% CI 0.32–0.42) in 2010 to 0.09 (95% CI 0.09–0.10) in 2018 (*Figure 2D*, Supplementary material online, *Figure S4*).

Increasing trends were comparable between continents, although the proportion of NOAC users started to increase earlier in North America (from 2011) than Europe and Asia (from 2013), and prevalent (N)OAC use was consistently lower in Asia than North America and Europe (no data from other continents) (Supplementary material online, *Table S4*).

Incident use

The worldwide proportion of newly diagnosed eligible AF patients starting OACs was 0.55 (95% CI 0.49–0.61) from 2010 to 2018, increasing from 0.43 (95% CI 0.37–0.49) in 2010 to 0.75 (95% CI 0.74–0.76) in 2018 (*Figure 3A*, Supplementary material online, *Figure S5* and *Table S4*). Worldwide, the proportion of incident NOAC users increased from 0.00 (95% CI 0.00–0.02) in 2010 to 0.68 (95% CI 0.67–0.69) in 2018, while the proportion of incident VKA users decreased from 0.42 (95% CI 0.36–0.49) in 2010 to 0.06 (95% CI 0.06–0.07) in 2018 (*Figure 3B and C*, Supplementary

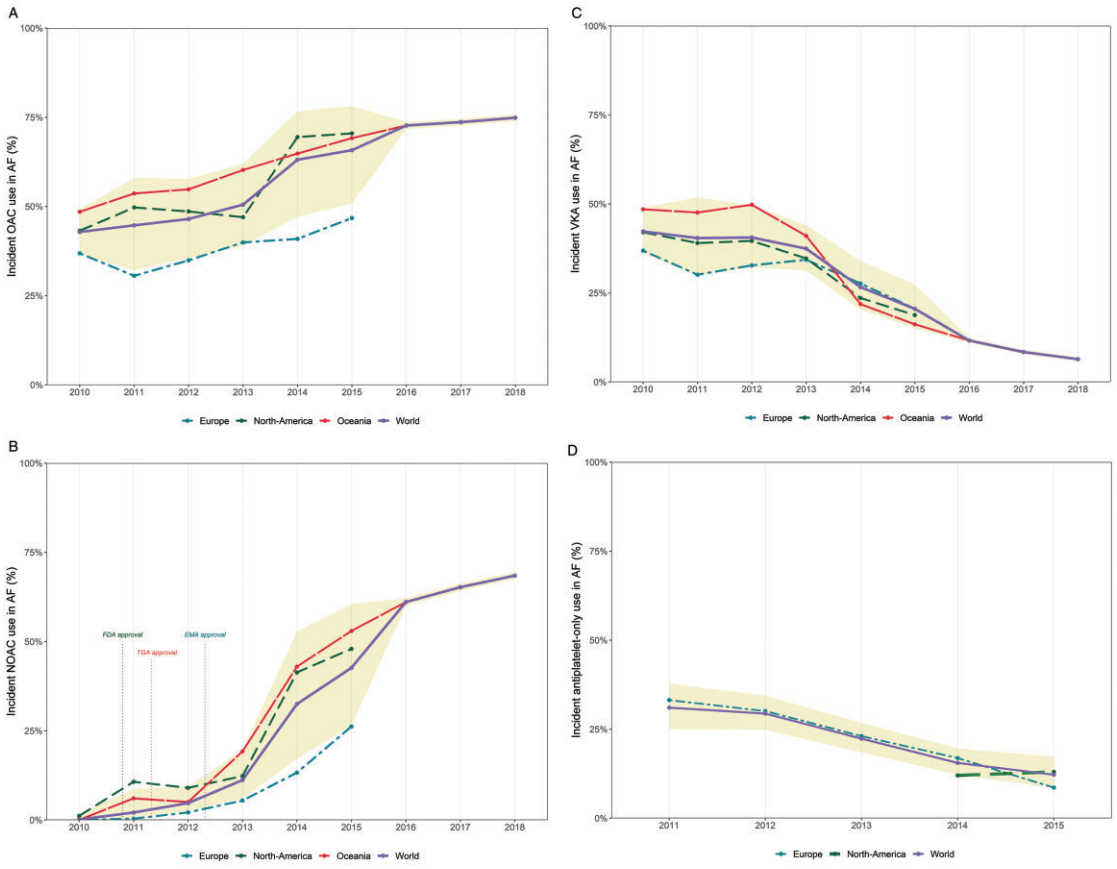

Figure 3 Trends in incident use of (*A*) OACs, (*B*) NOACs, (*C*) VKAs, and (*D*) antiplatelet monotherapy in OAC-eligible, newly diagnosed AF patients from 2010 to 2018, categorized by continent. Yellow band: 95% CI of worldwide meta-analysed proportion per year. (*B*) Approval date of dabigatran by the respective authorities is highlighted. AF, atrial fibrillation; CI, confidence interval; EMA, European Medicine Agency (Europe); FDA, Food and Drug Administration (USA); NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; TGA, Therapeutic Goods Administration (Australia); VKA, vitamin K antagonist.

material online, *Figures S6 and S7*). The worldwide proportion of newly diagnosed eligible AF patients starting on antiplatelet monotherapy decreased from 0.31 (95% CI 0.25–0.38) in 2011 to 0.12 (95% CI 0.08–0.17) in 2015 (no data for 2010 or 2016–20) (*Figure 3D*, Supplementary material online, *Figure S8*).

Increasing trends were comparable between continents, although the proportion of (N)OAC users among newly diagnosed eligible AF patients was lower in Europe than North America and Oceania (no data from other continents) (Supplementary material online, *Table S4*).

Publication bias and heterogeneity assessment

No publication bias was suspected based on the visual inspection of funnel plots and Peter's regression test (Supplementary material online, *Figure S9*). Considerable heterogeneity (I^2 89–100%) was detected in most outcomes, driven by differential results per year and continent (Supplementary material online, *Figures S1–S8*).

Discussion

Temporal trends

This meta-analysis including nearly 10 million AF patients based on 21 observational studies has demonstrated that the worldwide proportion of OAC users among all OAC-eligible AF patients almost doubled from 42% in 2010 to 78% in 2018, driven by a considerable increase in NOAC users, whereas the proportion of VKA users only slightly decreased (*Figure 4A*). Likewise, the proportion of newly diagnosed eligible AF patients starting OACs increased from 43% to 75% over this time period, due to a substantial increase in the proportion starting NOACs, while the proportion starting VKAs dropped (*Figure 4B*). By 2017, prevalent NOAC users surpassed VKA users worldwide, whereas incident NOAC users already exceeded VKA users in 2014.

Several reasons have been suggested for the increased OAC use among eligible AF patients over the last decade. First, the introduction of NOACs has played a pivotal role in this trend. Intriguingly, rather than switching VKAs to NOACs, their

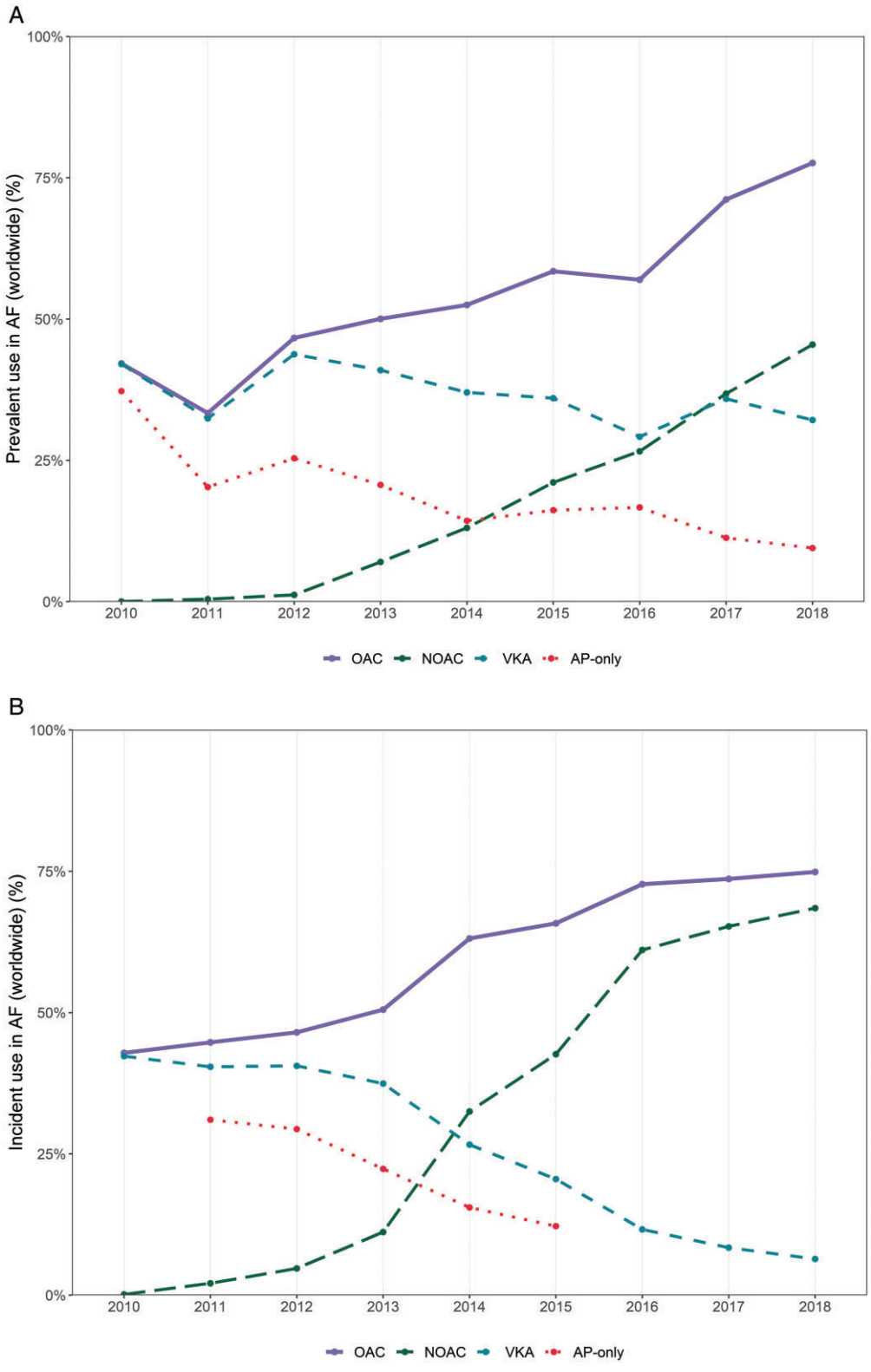

Figure 4 Trends in (*A*) prevalent and (*B*) incident use of OACs, NOACs, VKAs, and antiplatelet monotherapy in AF patients worldwide from 2010 to 2018. AF, atrial fibrillation; AP, antiplatelet; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist.

introduction appeared to have dominated OAC choice among previously non-anticoagulated AF patients. This indicates that NOACs are especially initiated in newly diagnosed eligible AF patients or additionally considered in eligible AF patients who were potentially contra-indicated to or did not tolerate VKAs. Preferential prescribing of NOACs over VKAs among newly diagnosed AF patients is in line with ESC AF guideline recommendations since 2016.[3,7]

Second, other guideline updates may have also contributed. Namely, the recommendation to use the CHA_2DS_2-VASc instead of $CHADS_2$ score to identify patients at moderate to high thromboembolic risk since the 2010 ESC and 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) AF guidelines has increased OAC eligibility.[5,8,23,25,34] Exemplary, Katz *et al.*[8] demonstrated that two-thirds of AF patients previously categorized as low risk by the $CHADS_2$ score did have a Class I indication for OACs based on the CHA_2DS_2-VASc score, mainly due to the inclusion of age ≥65 years as a risk factor. Moreover, the 2012 ESC AF guidelines advised to use antiplatelet monotherapy in AF patients who refused or could not tolerate OACs, whereas since the 2016 ESC AF guidelines, antiplatelets are no longer recommended for stroke prevention in AF.[3,7,35] This is illustrated in our meta-analysis by the considerable decrease in antiplatelet monotherapy use since 2010.

Third, quality improvement initiatives and educational programmes have been undertaken to improve physician knowledge, guideline adherence and OAC use, such as 'Get With The Guidelines—AFIB' by the American Heart Association,[36] the Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) tool in the UK,[23,25,37] and the European Heart Rhythm Association (EHRA) Practical Guide.[3]

Lastly, intensive direct-to-prescriber marketing by pharmaceutical companies and broadened reimbursement criteria may have increased (N)OAC use.[38]

Oral anticoagulant underuse

Despite the increasing trend, one-quarter of OAC-eligible AF patients were still not anticoagulated in 2018. Several predictors for OAC underuse have been identified in the studies included in our meta-analysis, such as a high bleeding risk (including peptic ulcer disease and prior major bleeding), underestimated stroke risk (especially among younger patients), geriatric profile (older age, high risk of falls, frailty, dementia, multimorbidity, and polypharmacy), female sex, alcohol abuse, paroxysmal AF and restoration of the sinus rhythm following cardioversion or ablation.[8,14,16,18,20,23,25,30,32,39,40] Likewise, physician specialty, knowledge, and preference (e.g. unawareness of guideline updates, lack of experience, therapeutic inertia, or reluctance to prescribe OACs due to overestimated bleeding and underestimated thromboembolic risks), patient refusal (e.g. due to prior (bad) treatment experience), and health insurance factors (level of reimbursement) may affect OAC prescribing and adherence.[15,32,39–41]

Furthermore, 9% of OAC-eligible AF patients were treated with antiplatelet monotherapy in 2018, although the proportion of users substantially decreased over the last decade. Factors associated with antiplatelet instead of OAC use in AF patients includes vascular disease (e.g. myocardial infarction and peripheral artery disease), older age, and high bleeding risk.[18,30,40–42] An underestimation of vascular disease being a thromboembolic risk factor and misconception that antiplatelets have a better safety profile than OACs, have been suggested as reasons for persistent antiplatelet monotherapy use in AF.[30,42] Since antiplatelets are associated with significantly higher thromboembolic and similar major bleeding risks as OACs in AF patients, further efforts to reduce the use of antiplatelet monotherapy in AF are warranted.[2]

Regional differences

First, even though trends were mostly comparable, some differences between continents were observed, such as the earlier uptake of NOACs in North America than Europe. Although NOACs are recommended in preference of VKAs for stroke prevention in AF only since the 2019 AHA/ACC/HRS AF guidelines[10] compared with 2016 by the ESC AF guidelines,[7] the earlier approval date of NOACs in the USA (October 2010 for dabigatran by the Food and Drug Administration, FDA)[43] than in Europe (May 2012 by the European Medicine Agency, EMA)[44] may have played a more important role in the faster uptake of NOACs in North America than the updated guideline recommendations (illustrated in *Figures 2B and 3B*). Moreover, direct-to-consumer marketing in the USA, which is not allowed in Europe, could also have contributed to this earlier uptake.[38]

Second, prevalent OAC use was generally lower in Asia than North America or Europe. This is in line with the lower OAC use in Asian than Caucasian patients with AF observed in the GARFIELD-AF registry.[45] However, it should be noted that our results were mainly driven by the Korean study of Yu *et al.*, while OAC use was considerably higher in the Japanese study of Yamashita *et al.*[15,31] In Korea, NOACs were partially and fully reimbursed since January 2013 and July 2015, respectively, by the National Health Insurance System (NHIS), whereas the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) already reimbursed dabigatran since January 2011.[15,30,46] This illustrates that NOAC approval dates and reimbursement criteria may influence (N)OAC prescription rates.

Lastly, we observed a delayed (N)OAC uptake in the treatment of newly diagnosed AF patients in Europe compared with North America and Oceania. This finding was primarily driven by the large study of Bakhai *et al.*[26] which was conducted in a primary care setting in the UK from 2011 to 2015, including AF patients irrespective of their CHA_2DS_2-VASc score.[26] This trend may not be generalizable to continental Europe since the National Institute for Health and Care Excellence (NICE) AF guidelines in the UK recommended the use of NOACs as an equal alternative to VKAs 2 years later than the ESC (June 2014 compared with May 2012).[35,47] Indeed, the proportion of incident OAC users among eligible AF patients was considerably higher in the Swedish study of Mochalina *et al.*[21] from 2011 to 2013 which may indicate earlier NOAC uptake in continental European countries than in the UK.[25]

Strengths and limitations of available literature

This meta-analysis has several strengths, such as the inclusion of almost 10 million non-selected OAC-eligible AF patients, representative of real-world prescribing on a full population scale, based on

pooled data from 21 large observational cohort studies conducted in 10 different countries across 5 continents.

However, several limitations should be mentioned. First, sufficient data matching our study selection criteria were lacking from specific continents (e.g. Africa), countries (e.g. China), or years (e.g. 2019–20), which may have influenced our results. For example, only one study[25] provided data on prevalent OAC use in 2018, whereas only one study[14] on incident use in 2016–18 (which is also illustrated by the narrow 95% CI of the worldwide proportion of OAC users in the respective years). Moreover, results categorized by continent were often limited to one or two country-specific studies per year, reducing the generalizability of these subgroup results to the whole continent. Therefore, observed geographical differences over time should be considered as explorative and should not be overemphasized. Furthermore, considerably less data were available on incident than prevalent OAC users ($n = 197\,483$ vs. $9\,758\,637$) and on incident antiplatelet monotherapy use ($n = 80\,178$), so these results should be interpreted with some caution. Second, 12 studies matching our selection criteria were identified with missing data, of which only 3 authors[13–15] replied to our request to provide these results. Consequently, 9 of these 12 studies (e.g. from Denmark or Canada) had to be excluded. Third, included observational studies were mostly retrospective in design and based on administrative healthcare databases, which are prone to coding errors, misclassification bias, and unmeasured confounding (e.g. unidentified contra-indications for OAC use). Fourth, as only eight studies[15,20,23,25,27,28,30,33] specifically investigated AF patients with a CHA_2DS_2-VASc score of ≥ 1 or ≥ 2, inclusion of AF patients at low thromboembolic risk (score 0 in men, 1 in women) in other studies may have underestimated the proportion of OAC use. In line, due to a lack of sufficient data on the proportion of OAC use per specific CHA_2DS_2-VASc score category, we could not further stratify our results by the baseline thromboembolic risk of included AF patients. Fifth, as studies that included subjects during hospitalizations, with specific comorbidities or following an adverse event (e.g. stroke), were not considered, our results do not reflect user patterns among these specific AF subgroups. Sixth, the proportion of prevalent and incident users was based on the dispensing of OACs, which does not necessarily correspond with the actual intake of OACs by patients (e.g. non-initiation of dispensed medication, suboptimal implementation or early discontinuation). Lastly, given that over-the-counter aspirin use is not identified in some databases, the proportion of antiplatelet monotherapy use may have been underestimated. Likewise, AF patients using free drug samples are not identified in prescription claims-based databases.

Implications for clinical practice

The fact that the proportion of eligible AF patients using OACs almost doubled over the last decade suggests that the introduction of NOACs, updated guideline recommendations and quality improvement initiatives did have a profound impact on real world, guideline-adherent OAC prescribing in AF. However, as one-quarter of OAC-eligible AF patients were not anticoagulated in 2018 and 9% were still treated with antiplatelet monotherapy, there is still some room for improvement. Therefore, continued efforts targeted at both physicians and patients are still needed to increase the knowledge and awareness of the thromboembolic risk of AF and the expected risk-benefit profile of OACs. However, achieving theoretical 100% OAC coverage among all AF patients eligible for anticoagulation mainly based on their CHA_2DS_2-VASc score, is unrealistic and unfeasible in clinical practice, e.g. due to a subset of patients with (relative) contra-indications to OACs.

Research gaps

First, in order to adequately assess the worldwide OAC use and identify differences between continents, more data are needed from other continents, such as Africa, South-America (only results from 1 study in 1 year[32]), or Oceania (no data on prevalent use). Second, it would be of interest to have the most recent data on OAC use in AF to investigate subsequent trends after 2018.

Conclusion

In conclusion, from 2010 to 2018, the worldwide proportion of OAC-eligible AF patients using OACs has almost doubled to 78%. The proportion of NOAC users surpassed VKA users worldwide by 2017, whereas incident NOAC users already exceeded incident VKA users by 2014. However, as one-quarter of OAC-eligible AF subjects were not anticoagulated and 9% were still treated with antiplatelet monotherapy in 2018, opportunities to further reduce morbidity and mortality risks among AF patients are still present.

Supplementary material

Supplementary material is available at *Europace* online

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