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META-ANALYSIS
Arrhythmias

Prevalence, management and impact of chronic obstructive pulmonary disease in atrial fibrillation: a systematic review and meta-analysis of 4,200,000 patients

Giulio Francesco Romiti[1], Bernadette Corica[1], Eugenia Pipitone[2], Marco Vitolo[3,4,5], Valeria Raparelli[6,7], Stefania Basili[1], Giuseppe Boriani[3], Sergio Harari[8,9,10], Gregory Y.H. Lip[4,11†], and Marco Proietti [4,10,12*†]; the AF-COMET International Collaborative Group[‡]

[1]Department of Translational and Precision Medicine, Sapienza—University of Rome, Viale del Policlinico 155, 00161 Rome, Italy; [2]Ospedale Regionale "Beata Vergine", Via Turconi 23, 6850 Mendrisio, Switzerland; [3]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, via Giuseppe Campi 287, 41125, Modena, Italy; [4]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Brownlow Hill, L69 7TX Liverpool, UK; [5]Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, via Giuseppe Campi 287, 41125 Modena, Italy; [6]Department of Translational Medicine, University of Ferrara, Via Luigi Borsari, 46, 44121 Italy; [7]University of Alberta, Faculty of Nursing, 11405-87 Avenue, T6G 1C9 Edmonton, Alberta, Canada; [8]U.O. di Pneumologia e Terapia Semi-Intensiva Respiratoria—Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe—MultiMedica IRCCS, Via San Vittore 12, 20123 Milan, Italy; [9]Department of Medical Sciences, San Giuseppe Hospital MultiMedica IRCCS, Via San Vittore 12, 20123 Milan, Italy; [10]Department of Clinical Sciences and Community Health, University of Milan, Via della Commenda 19, 20122 Milan, Italy; [11]Department of Clinical Medicine, Aalborg University, Søndre Skovvej 15, 9000 Aalborg, Denmark; and [12]Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Via Camaldoli 64, Milano 20138, Italy

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Aim

Prevalence of chronic obstructive pulmonary disease (COPD) in atrial fibrillation (AF) patients is unclear, and its association with adverse outcomes is often overlooked. Our aim was to estimate the prevalence of COPD, its impact on clinical management and outcomes in patients with AF, and the impact of beta-blockers (BBs) on outcomes in patients with COPD.

Methods and results

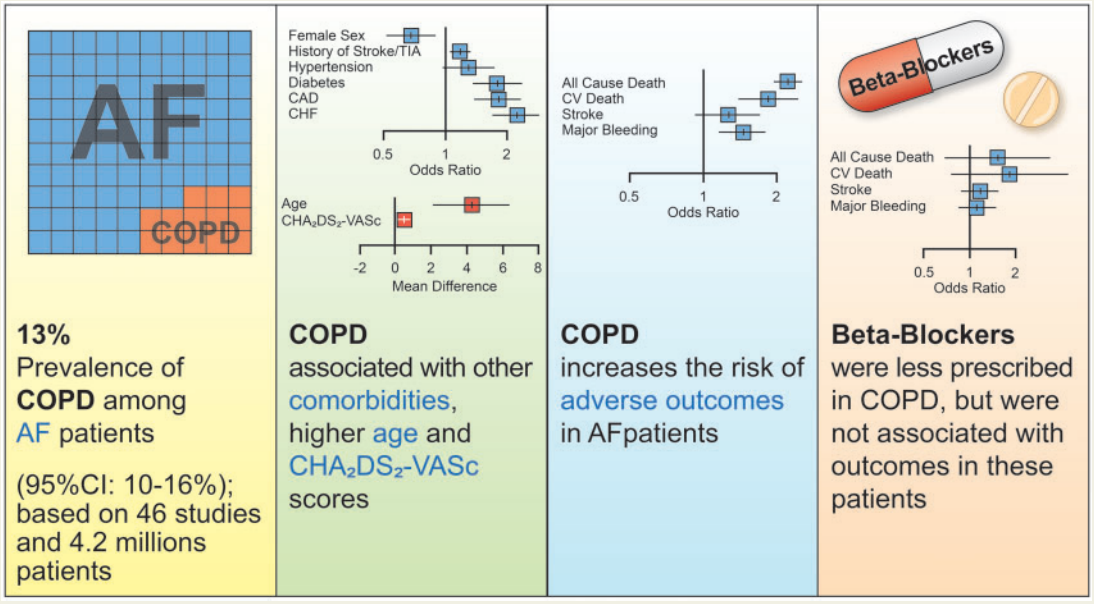
A systematic review and meta-analysis was conducted according to international guidelines. All studies reporting the prevalence of COPD in AF patients were included. Data on comorbidities, BBs and oral anticoagulant prescription, and outcomes (all-cause death, cardiovascular (CV) death, ischaemic stroke, major bleeding) were compared according to COPD and BB status. Among 46 studies, pooled prevalence of COPD was 13% [95% confidence intervals (CI) 10–16%, 95% prediction interval 2–47%]. COPD was associated with higher prevalence of comorbidities, higher CHA_2DS_2-VASc score and lower BB prescription [odds ratio (OR) 0.77, 95% CI 0.61–0.98]. COPD was associated with higher risk of all-cause death (OR 2.22, 95% CI 1.93–2.55), CV death (OR 1.84, 95% CI 1.39–2.43), and major bleeding (OR 1.45, 95% CI 1.17–1.80); no significant differences in outcomes were observed according to BB use in AF patients with COPD.

Conclusion

COPD is common in AF, being found in 13% of patients, and is associated with increased burden of comorbidities, differential management, and worse outcomes, with more than a two-fold higher risk of all-cause death and increased risk of CV death and major bleeding. Therapy with BBs does not increase the risk of adverse outcomes in patients with AF and COPD.

* Corresponding author. Tel: +39-02-50725150, Email: marco.proietti@unimi.it
†These authors are joint senior authors.
‡The members in the AF-COMET International Collaborative Group are listed in the Appendix.

Graphical Abstract



Prevalence, management, and impact of chronic obstructive pulmonary disease in atrial fibrillation. AF, atrial fibrillation; CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack.

Keywords Atrial fibrillation • Chronic obstructive pulmonary disease • Epidemiology • Beta-blockers • Outcomes

Introduction

Increasing attention has been directed to the problem of multimorbidity in patients with atrial fibrillation (AF).[1,2] Indeed, patients with AF often have several concomitant conditions that significantly impact major adverse events, such as ischaemic stroke, cardiovascular (CV) events and all-cause death.[3–5] Among these comorbidities, chronic respiratory conditions are common, though often overlooked in AF studies.

Chronic obstructive pulmonary disease (COPD) is one of the worldwide leading causes of death, accounting for around 3 million deaths each year.[6] Beyond sharing a similar epidemiology,[6,7] connected to the progressive ageing of the population and the increasing prevalence of comorbidities, COPD and AF are intimately related, influencing management and clinical history.[8] For example, while beta-blockers (BBs) are an established approach for rate control in AF,[7] their use in COPD has been subject to controversy.[9]

Despite the postulated association between COPD and AF, few studies have comprehensively analysed the clinical relationships between these two conditions, especially concerning the risks of adverse outcomes and the implications for BB use. Indeed, experts have clearly demanded better evidence on the relationship between COPD and AF.[8]

The primary aim of this systematic review and meta-analysis was to provide a pooled estimate of COPD prevalence among the general AF population. Secondarily, we aimed to evaluate the associations between risk factors and comorbidities with COPD in AF patients, to analyse the management of AF patients with COPD [particularly regarding the use of BBs and oral anticoagulants (OACs)], and to evaluate the impact of COPD on long-term risk of major clinical outcomes. Furthermore, we examined the relationship between BB use and major clinical outcomes in AF patients according to COPD status.

Methods

This systematic review was performed according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[10] and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[11] The protocol was registered into the international prospective register of systematic reviews (PROSPERO, CRD42021227369).

Details regarding the search strategy, inclusion and exclusion criteria, and the processes of study selection and data extraction are reported in the Supplementary material online.

Quality assessment

Two co-authors (G.F.R. and B.C.) independently evaluated all studies to assess the risk of bias. We evaluated the risk of bias separately for each outcome of the study: we used a customized tool based on the Newcastle–Ottawa Scale (NOS) for the evaluation of COPD prevalence, composed of five items across three domains (Selection, Comparability, Outcome), with a maximum of five points (Supplementary material

online, *Table S2*). Studies with a score ≤3 were categorized at high risk of bias. For the studies that reported outcomes according to COPD status in AF, we used a customized tool based on the NOS,[12] composed of 8 items across three domains (Selection, Comparability, Outcome) (Supplementary material online, *Table S3*). Each study with a NOS ≤6 was categorized at high risk of bias.

Outcomes definition

The primary aim of our study was to estimate the prevalence of COPD among AF patients. According to the criteria used in the included studies, prevalence of COPD was defined as the proportion of AF patients with a diagnosis of COPD.

In addition, we also investigated: (i) the associations between baseline risk factors and comorbidities related to COPD in AF patients, (ii) the management of AF patients according to COPD status (i.e. rates of BB and OAC prescription); (iii) the impact of COPD on the risk of all-cause death, CV death, ischaemic stroke, and major bleeding; and (iv) the impact of BBs on major outcomes in patients with AF and COPD, also compared to those without COPD. Each outcome was defined as per the original included studies.

Statistical analysis

Prevalence of COPD was pooled with a generalized linear mixed model (specifically, random intercept logistic regression model).[13] Along with the pooled estimate and the relative 95% confidence intervals (CI), we also computed 95% prediction intervals (PI), which represents a predicted range of true prevalence in an individual/new study, and provides helpful information on the variability and heterogeneity of the estimate.[14,15] As a sensitivity analysis, we also computed the prevalence of COPD according to the inverse variance method, with two types of transformation of proportions (logit transformation and Freeman–Tukey double arcsine transformation). Furthermore, we computed COPD prevalence according to the sequential exclusion of studies with sample size below defined cut-offs.

Number of patients with comorbidities, number of patients prescribed BBs and OACs, as well as number of events, and the total number of patients with and without COPD were pooled and compared using random-effects models. For continuous outcomes, mean, standard deviation (SD), and total number in each group were pooled and compared with inverse variance method.

Pooled estimates were reported as odds ratios (OR) and 95% CI, or mean difference and 95% CI for continuous variables. We calculated the inconsistency index (I^2) to measure heterogeneity. According to pre-specified cut-offs,[16] low heterogeneity was defined as an $I^2 < 25\%$, moderate heterogeneity as an I^2 between 25% and 75%, and high heterogeneity as an $I^2 > 75\%$.

For each outcome, a sensitivity analysis was performed with a 'leave-one-out' approach, in which all studies are removed one at a time to analyse their influence on pooled estimate and heterogeneity.

To account for potential sources of heterogeneity in the pooled prevalence of COPD, we performed several subgroup analyses, according to geographical location, study design, type of definition of COPD, age cut-offs (≥75 vs. <75 years), and risk of bias. We did not pre-specify these subgroup analyses in the PROSPERO protocol since we could not anticipate the availability of data.

To further investigate potential sources of heterogeneity for the prevalence of COPD, we performed several meta-regressions. In the first step, we performed univariable meta-regressions according to study-level mean age, sex category, study design, type of COPD definition, risk of bias, and prevalence of relevant comorbidities. A multivariable meta-regression was also performed, with the factors significantly associated with COPD prevalence at univariable meta-regression. We also performed meta-regressions[17] for BB and OAC prescription, and outcomes according to the presence of COPD.

Publication bias was assessed for studies reporting outcomes according to COPD diagnosis, through visual inspection of funnel plots. Egger's test was also performed.

All the statistical analyses were performed using R version 4.0.3 (The R Foundation, 2020), using the 'meta', 'metafor', and 'dmetar'[18] packages.

Results

A total of 5316 results were retrieved from the search (939 from PubMed and 4377 from EMBASE). After duplicates removal, and title and abstract screening, 130 full-texts were assessed for eligibility, and 46 studies were included for quantitative synthesis (*Table 1* and Supplementary material online, *Figure S1*),[19–64] with a total of 4 232 784 AF patients included: 3 studies were secondary analyses of randomized trials,[28,38,62] 19 cohorts were based on administrative databases,[19,20,26,27,31,32,35,36,39,41,49,50,53,55,56,60,61,63,64] 16 were observational multicentre studies,[21,22,24,25,33,34,37,40,42,45–48,52,54,57] and 8 were observational single-centre studies[23,29,30,43,44,51,58,59]. Seven studies were conducted in Asia, 22 in Europe, 11 in North America, and 6 studies in other geographical locations. As for the definitions of COPD and comorbidities, half of the studies relied on International Classification of the Diseases (ICD) codes, comprising ICD-9 and ICD-10 versions, while the other half adopted self-reported definition of COPD and other conditions. Bias assessment for the prevalence of COPD is reported in Supplementary material online, *Table S4*. Among 46 studies, 10 were determined at high risk of bias.[22,29,38,39,41,44,48,51,58,60] Through an international collaboration, we obtained additional data for 12 studies[23,25,30,34,37,43,46–48,52,54,56]; for one study, we included only a subgroup of the original cohort, according to the completeness of data available.[23]

COPD prevalence

Among 46 studies, the pooled prevalence of COPD was found to be as high as 13% (95% CI 10–16%; 95% PI 2–47%) (*Figure 1*), with a high grade of heterogeneity among included studies.

We performed several sensitivity analyses. In the first, according to the 'leave-one-out' method, we did not observe significant influence of single studies on the pooled estimates or heterogeneity (Supplementary material online, *Figure S2*). In the sensitivity analysis performed with the inverse-variance method and different proportion transformations, we found similar COPD prevalence, in both cases falling into the 95% CI of the primary analysis (Supplementary material online, *Table S5*). Finally, in the sensitivity analysis based on the sequential exclusion of studies according to increasing sample size cut-offs (Supplementary material online, *Table S6*), we still observed similar results, with all figures falling into the 95% CI of the primary analysis, being the highest (15.0%, 95% CI 8.8–24.5%) when excluding studies with <20 000 subjects.

To evaluate the potential sources of heterogeneity, we performed several subgroup analyses (*Table 2*). Prevalence of COPD was found higher in North American-based cohorts (20.3%, 95% CI 16.3–25.0%) compared to European and Asian studies; moreover, we found a higher COPD prevalence among studies based on administrative

Table 1 Main characteristics of the studies included in the systematic review

Study	Year	Geographic location	Study type	Inclusion/ exclusion criteria	*N*	COPD	Age (years)	CHA_2DS_2-VASc score	*F* (%)	HTN (%)	DM (%)	FU (years)	Primary outcome	Secondary outcomes
Abdel-Qadir[19]	2018	Canada	Administrative	AF 66-105 years	136 156	18 607	79.6	4.1	49.8	69.6	28.8	4.4[a]	Stroke	ACD
Andersson[20]	2013	Sweden	Administrative	AF	272 186	13 337	72.3	N/A	44	25.4	13.4	14	ACD	N/A
Angeli[21]	2019	Italy	Observational multicentre	AF	2159	337	75.6	3.7	44.5	80.9	19.7	N/A	N/A	N/A
Balsam[22]	2018	Poland	Observational multicentre	AF with OAC	3504	325	67.9	3.4	40.2	71.4	N/A	N/A	N/A	N/A
Barrett[23]	2015	USA	Observational single centre	Symptomatic AF from ED	829	126	66.7	3.2	41.1	67.4	23.9	N/A	N/A	N/A
Boriani[24]	2018	Europe	Observational multicentre	AF	11 096	979	69.2	3.1	40.7	62.1	23.0	N/A	N/A	N/A
Campanini[25]	2013	Italy	Observational multicentre	AF HOSP IMU	903	220	N/A	N/A	52.4	54.4	16.1	N/A	N/A	N/A
Chamberlain[26]	2017	USA	Administrative	AF	1430	492	73.6	N/A	51.4	71.1	30.6	6.3	HOSP	ACD
Chao[27]	2017	Taiwan	Administrative	AF with sudden death/ VA	352 656	125 058	71.3	N/A	44.6	68.4	28.5	4.9	Sudden death/ VA	N/A
Durheim[28]	2016	Multinational	RCT	AF with ≥1 stroke RF	18 134	1950	70[a]	N/A	35.3	87.5	25.0	1.8[a]	Stroke/SE	ACD, CVD, MB
Elezi[29]	2010	Kosovo	Observational single centre	AF	525	32	66.4	N/A	46.7	27.4	14.3	N/A	N/A	N/A
Guo[30]	2013	China	Observational single centre	AF + renal function	1039	273	72.0	3[a]	27.0	72.2	36.7	1.9[a]	Stroke/SE	MB
Hagengaard[31]	2021	Denmark	Administrative	AF HOSP	150 544	3296	74[a]	3[a]	45.9	54.0	9.2	1	ACD	CVD, HOSP, stroke
Hohnloser[32]	2018	Germany	Administrative	AF with NOACs	61 205	17 403	73.7	3.8	45.9	86.1	34.1	0.94	Stroke/SE	ACD, stroke, MB
Huang[33]	2014	China	Observational multicentre	AF	2016	227	68.4	N/A	53.7	54.6	15.4	1	ACD, stroke	N/A
Jani[34]	2018	UK	Observational multicentre	AF	3651	99	61.9	1[a]	31.7	44.6	9.1	7	ACD	N/A
Komen[35]	2017	Sweden	Administrative	AF with OAC	6765	724	74.3	3.7	45.3	70.2	19.2	N/A	N/A	N/A
Lee[36]	2020	South Korea	Administrative	AF	347 709	65369	71.0	3.4	42.5	79.6	26.8	0.25	ACD	N/A
Lip[37]	2014	France	Observational multicentre	AF	8120	870	70.0	3.2	38.5	41.9	15.3	2.78	Stroke	SE, ACD, MB

Continued

Table 1 *Continued*

Study	Year	Geographic location	Study type	Inclusion/ exclusion criteria	*N*	COPD	Age (years)	CHA_2DS_2-VASc score	*F* (%)	HTN (%)	DM (%)	FU (years)	Primary outcome	Secondary outcomes
Matsumura-Nakano[38]	2019	Japan	RCT	AF with CAD	690	26	75.1	4.6	14.7	85.9	42.0	2.5[a]	ACD, MI, stroke/SE	MB
Méndez-Bailón[39]	2017	Spain	Administrative	AF HOSP	210 605	35897	N/A	N/A	52.7	N/A	N/A	N/A	N/A	N/A
Mert[40]	2017	Turkey	Observational multicentre	AF	5998	1381	69.6	3.3	56.1	68.7	22.6	N/A	N/A	N/A
Monte[41]	2006	Italy	Administrative	AF	1812	351	78.5	N/A	54.7	78.9	20.2	1	ACD	Stroke/SE
Nabauer[42]	2009	Germany	Observational multicentre	AF	8942	1025	68.3	N/A	38.9	69.1	21.7	N/A	N/A	N/A
Naser[43]	2017	Bosnia and Herzegovina	Observational single centre	AF	2352	612	68.0	3.2	48.0	76.0	22.0	9.7	ACD	CVD, stroke, MB
Nguyen[44]	2020	Australia	Observational single centre	AF with OAC	512	90	67.6	N/A	53.9	56.1	45.5	N/A	N/A	N/A
Nieuwlaat[45]	2009	Europe	Observational multicentre	AF	5298	711	67.0	N/A	42.0	63.1	18.1	1	ACD	CVD, stroke, MB
O'Brien[46]	2019	USA	Observational multicentre	AF	9743	1604	73.6	3.9	42.5	83.1	29.5	2.3[a]	Stroke	ACD, MB
Ogawa[47]	2018	Japan	Observational multicentre	AF	4045	212	73.6	3.4	40.4	62.6	23.2	3[a]	Stroke/SE	ACD, MB
Paixão[48]	2020	Brazil	Observational multicentre	AF	20 782	338	71.1	N/A	45.5	49.5	8.5	3.7	ACD	CVD
Panaccio[49]	2015	USA	Administrative	AF	109 181	20112	74.3	N/A	52.5	54.3	21.8	1.7	CV HOSP	ACD
Piccini[50]	2012	USA	Administrative	AF ≥65 years	108 952	35203	79[a]	N/A	55.1	68.3	18.0	1	ACD	N/A
Polovina[51]	2017	Serbia	Observational single centre	AF without CAD	794	38	62.5	2.6	38.9	81.5	18.0	5	MACEs	N/A
Proietti[52]	2016	Europe	Observational multicentre	AF	3086	339	68.9	3[a]	40.4	70.3	20.4	1	Stroke/SE	ACD, CVD, bleeding
Qin[53]	2016	USA	Administrative	AF	5952	623	69.6	2.9	40.9	64.2	21.2	2.2	ACD	Stroke
Raparelli[54]	2018	Italy	Observational multicentre	AF	2027	185	73.4	3[a]	45.3	82.5	23.0	3[a]	MACEs	Stroke, CVD, ACD
Reardon[55]	2013	USA	Administrative	AF in LTC	5211	1387	N/A	N/A	65.3	69.9	35.8	N/A	N/A	N/A
Rodriguez-Manero[56]	2019	Spain	Administrative	AF	7990	937	76.8	3.5	50.8	70.0	23.5	1.9	ACD	Stroke, bleeding
Roldán Rabadán[57]	2020	Spain	Observational multicentre	AF with VKAs	1956	338	73.8	3.7	43.9	80.5	29.2	3	Stroke	ACD, CVD, MB
Shih[58]	2020	USA		AF	2892	511	67[a]	3.5	N/A	81.4	36.4	N/A	Stroke	N/A

Continued

Table 1 *Continued*

Study	Year	Geographic location	Study type	Inclusion/ exclusion criteria	N	COPD	Age (years)	CHA_2DS_2-VASc score	F (%)	HTN (%)	DM (%)	FU (years)	Primary outcome	Secondary outcomes
			Observational single centre											
Suzuki[59]	2017	Japan	Observational single centre	AF	2102	20	63.2	N/A	24.1	44.4	13.6	3.9	Stroke	ICH, MI
Tripathi[60]	2019	USA	Administrative	AF HOSP	1 723 378	37 2077	N/A	N/A	51.7	69.4	25.3	0.08	Re-HOSP	N/A
Wandell[61]	2019	Sweden	Administrative	AF ≥45 years	12 283	1416	74.4	N/A	45.9	44.4	19.3	N/A	N/A	N/A
Washam[62]	2017	Multinational	RCT	AF	14 264	1497	73[a]	N/A	39.7	90.5	39.9	N/A	Stroke/SE	MB
Yavuz[63]	2017	Turkey	Administrative	AF	423 109	13 5141	66.1	N/A	55.9	84.9	19.7	1	ACD	Stroke/SE
Yuan[64]	2015	USA	Administrative	AF ≥65 years	158 199	42 988	79.9	N/A	47.4	85.0	33.1	2.9	Stroke	N/A

AF, atrial fibrillation; ACD, all-cause death; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular death; DM, diabetes mellitus; ED, emergency department; FU, follow-up; HOSP, hospitalization; HTN, hypertension; ICH, intracranial haemorrhage; IMU, internal medicine unit; LTC, long-term care; MACE, major adverse cardiac event; MB, major bleeding; MI, myocardial infarction; N/A, not available; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; RCT, randomised controlled trial; RF, risk factor; SE, systemic embolism; VA, ventricular arrhythmia; VKA, vitamin K antagonist.
[a]Median values.

databases compared to observational studies or randomized trials (17.2%, 95% CI 12.6–23.0%). Furthermore, studies using ICD codes for COPD definition showed higher pooled prevalence of COPD (17.5%, 95% CI 13.5–22.4%) than those relying on self-reported history. Non-significant trends towards higher prevalence were observed in the subgroup of patients aged ≥75 years (data available only for a subgroup of the included studies), and among studies with low risk of bias.

Univariable meta-regression analyses showed that mean age, proportion of females and prevalence of hypertension, diabetes mellitus, and CHF in the included studies were associated with a higher prevalence of COPD, while self-reported definition of COPD was inversely associated (*Table 3*). Graphical representations of the univariable meta-regressions for mean age, female sex, hypertension, diabetes, and CHF are reported in Supplementary material online, *Figure S3*. The final multivariable meta-regression model, with the inclusion of these factors, was able to explain a significant proportion of the heterogeneity reported ($R^2 = 69.8\%$, $P < 0.001$) (*Table 3*).

Risk factors and management of AF patients with COPD

We examined the association of the main thromboembolic risk factors with COPD in AF patients (*Table 4*), in all studies for which we retrieved data broken down by COPD status. Overall, 17 studies were included for female sex,[21,23,25,28,30,33,34,39,43,46–48,52,54,56,57,61] 14 studies for CHF,[21,23,25,28,30,33,34,43,45–47,52,54,56] hypertension, diabetes mellitus, and CAD,[21,23,25,28,30,33,34,43,46–48,52,54,56] 13 studies for history of stroke/transient ischaemic attack (TIA),[21,23,25,28,30,33,34,43,46,47,52,54,56] while 12 studies were combined for mean age.[21,23,30,33,34,39,43,46,47,52,54,56] Furthermore, 7 studies reported mean (SD) data on CHA_2DS_2-VASc score in COPD and non-COPD patients.[21,23,43,46,47,52,54] Patients with AF and COPD had a clinical history with more prevalent diabetes mellitus, CAD, CHF, and stroke (*Table 4*) than those without COPD. Furthermore, AF COPD patients were less likely to be female but were significantly older compared to non-COPD patients. AF patients with concomitant COPD had a significantly higher mean CHA_2DS_2-VASc score (+0.49, 95% CI 0.16–0.81) than those without COPD (*Table 4*).

Overall, 14 studies reported or provided data on BB use according to COPD status,[23,25,28,30,33,34,37,43,46–48,52,54,56] while 11 on OAC prescription.[23,25,30,33,34,43,46,47,52,54,56] Compared to AF patients without COPD, those with concomitant COPD were less likely prescribed with a BB (OR 0.77, 95% CI 0.61–0.98) (*Figure 2A*), with a high degree of heterogeneity; conversely, no significant differences were observed for OAC prescription (*Figure 2B*). To account for potential sources of heterogeneity in the pooled estimates for BB use, we performed univariable meta-regressions according to several study-level baseline characteristics (Supplementary material online, *Table S7*), without observing any significant association. However, a multivariable meta-regression model that combines study type and prevalence of clinical comorbidities that may be associated with BB prescription (i.e. hypertension, CAD and CHF) was able to explain most of the heterogeneity ($R^2 = 81.8\%$, $P = 0.017$, Supplementary material online, *Table S7*). As for OAC prescription, we found a significant and inverse relationship between the proportion of patients with a previous history of stroke/TIA and the OR for OAC prescription of patients with vs. without

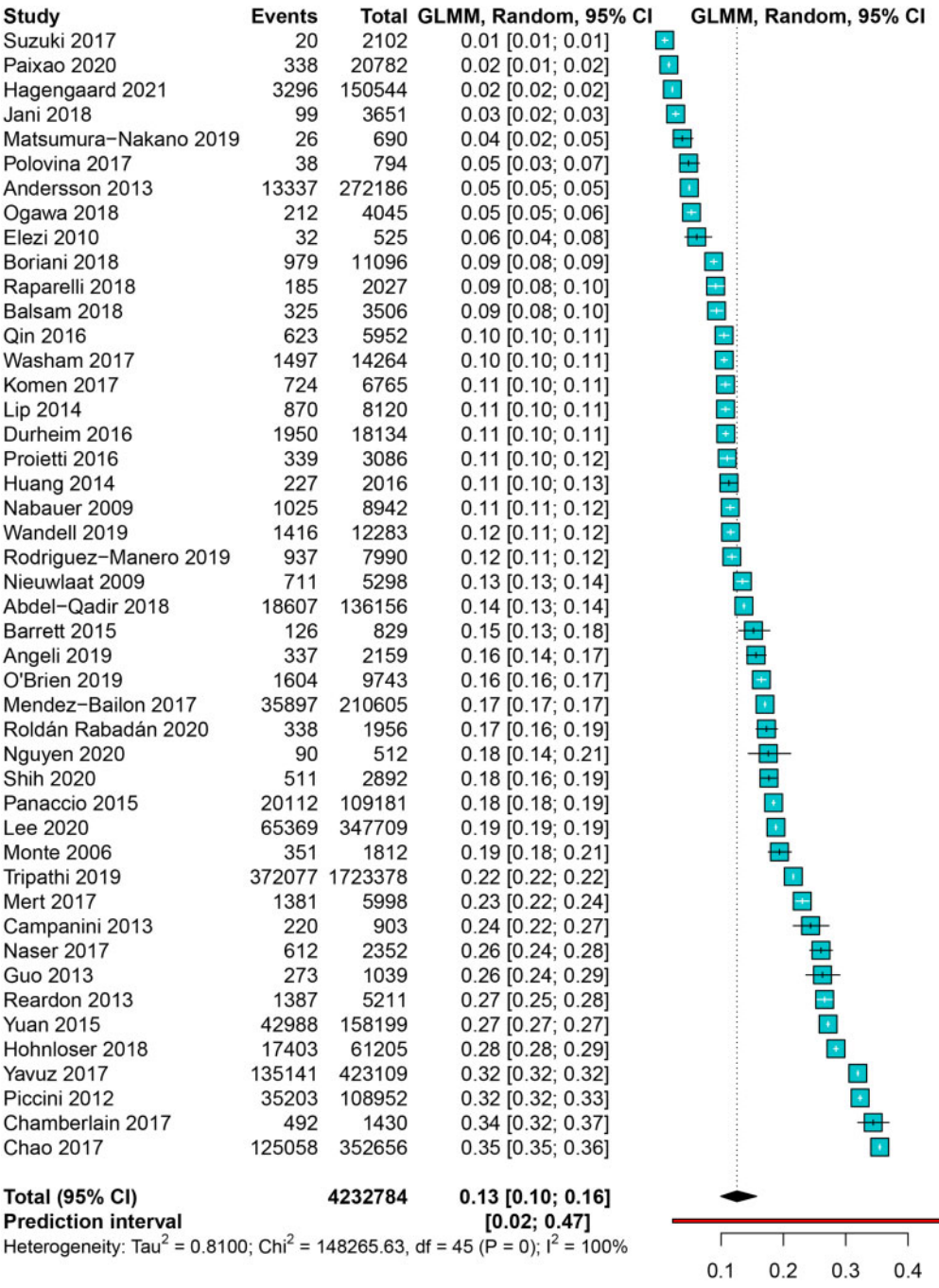


Figure 1 Pooled prevalence of chronic obstructive pulmonary disease in atrial fibrillation patients. CI, confidence interval; COPD, chronic obstructive pulmonary disease; GLMM, general linear mixed model.

COPD (Supplementary material online, *Figure S4*). We did not observe any other significant relationship with other study-level characteristics (Supplementary material online, *Table S8*).

Outcomes according to COPD diagnosis

Overall, 14 studies reported or provided data on outcomes according to the diagnosis of COPD.[19,28,30,33,34,37,41,43,46–48,52,54,56] Among these, all reported data on all-cause death, 10 studies on CV death,[28,33,34,37,43,46–48,52,54] 11 on stroke,[19,30,33,34,37,43,46,47,52,54,56] and 6 on major bleeding.[28,30,37,46,47,52] Bias assessment for study reporting outcomes is reported in Supplementary material online, *Table S9*. Scores were consistent across outcomes; overall, only three studies were reported at high risk of bias.[41,43,48]

Patients with COPD showed an increased risk for both all-cause death (OR 2.22, 95% CI 1.93–2.55, *Figure 3A*) and CV death (OR 1.84, 95% CI 1.39–2.43, *Figure 3A*). We also observed a non-significant trend for higher risk of stroke in COPD patients (*Figure 3C*). Finally, patients with COPD were at higher risk for major

Table 2 Subgroup analysis for chronic obstructive pulmonary disease prevalence

Subgroups	Number of studies	Pooled prevalence	95% CI	I^2
Geographical location (*P* for subgroup differences = 0.002)				
North America	11	20.3	16.3–25.0	99.9
Europe	22	10.7	8.1–14.0	100.0
Asia	7	9.4	3.8–21.4	100.0
Others	6	12.1	5.5–24.5	99.9
Study type (*P* for subgroup differences = 0.030)				
Administrative databases	19	17.2	12.6–23.0	100.0
Observational single centre	8	10.4	5.0–20.5	98.5
Observational multicentre	16	10.2	7.2–14.1	99.5
Randomized controlled trial	3	7.8	4.6–13.0	93.6
COPD definition (*P* for subgroup differences = 0.001)				
ICD codes	23	17.5	13.5–22.4	100.0
Self-reported	23	8.8	6.4–12.1	99.4
Age class (*P* for subgroup differences = 0.322)				
≥75 years	9	14.1	8.0–23.8	99.4
<75 years	9	9.4	5.2–16.5	99.4
Risk of bias (*P* for subgroup differences = 0.195)				
Low risk	36	13.6	10.6–17.3	100.0
High risk	10	9.4	5.5–15.4	99.8

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases.

bleeding than those without (*Figure 3D*). Sensitivity analysis with the 'leave-one-out' approach showed an overall low influence of single studies on pooled estimates or heterogeneity for all-cause death and CV death (Supplementary material online, *Figure S5A* and *B*). Regarding the stroke outcome, removal of the Abdel-Qadir *et al.* study[19] resulted in a significantly increased risk for stroke in patients with COPD (OR 1.36, 95% CI 1.00–1.85) (Supplementary material online, *Figure S5C*). Finally, removing the study by O'Brien *et al.*[46] from the pooled estimate for major bleeding led to a critical reduction of heterogeneity, with the risk still being significantly higher in patients with vs. without COPD (Supplementary material online, *Figure S5D*).

To further explore potential causes of heterogeneity, we performed meta-regressions for all the outcomes investigated. Among the study-level baseline characteristics, we found that only CHF prevalence was inversely associated with COPD-associated risk of all-cause death (Supplementary material online, *Table S10* and Supplementary material online, *Figure S6*), although the risk was significantly higher in COPD patients in all included studies. Similarly, the stroke risk of COPD patients was inversely associated with the mean age of the included cohorts (Supplementary material online, *Table S12* and *Figure S7*), becoming non-significant for patients aged >70 years. We did not observe a significant association between any study-level characteristics and COPD-related risk of CV death (Supplementary material online, *Table S11*) or major bleeding (Supplementary material online, *Table S13*).

To further investigate the effect of study-level mean age on the association between COPD and stroke, we performed an exploratory subgroup analysis. In studies with a mean age ≥70 and ≥75 years, we found that COPD did not provide additional risk, while in younger cohorts COPD was significantly associated with an increased risk of stroke (Supplementary material online, *Figure S8*).

Finally, the analysis regarding the impact of BBs on the occurrence of clinical outcomes demonstrated no significant differences in the risk of all-cause death, CV death, stroke and major bleeding among AF and COPD patients treated with or without BBs (*Figure 4*). In this analysis, no difference in outcomes was found regarding the use of BBs even in non-COPD patients, with the notable exception of major bleeding, for which non-COPD patients treated with BBs showed a higher risk, although in a limited number of studies (*Figure 4*).

Publication bias

Visual inspection of the funnel plots revealed potential asymmetry for all-cause death, with a significant Egger's test (*P* = 0.031; Supplementary material online, *Figure S9A*). The plot inspection showed potentially missing studies, both in the right side (where one would expect to find studies with a stronger association between COPD and all-cause death) and the bottom left-hand side of the plot. Thus, the addition of potential further studies was judged unlikely to influence the pooled estimate critically. We did not observe significant publication bias for the other outcomes (Supplementary material online, *Figures S9B–D*).

Discussion

In this systematic review and meta-analysis of 4 232 784 AF patients, we found that a significant proportion of patients with AF have concomitant COPD, with a prevalence of 13%. Geographical location, type of study, and particular study definition(s) influenced the prevalence of COPD, this being higher in studies based on North

Table 3 Meta-regression analysis for chronic obstructive pulmonary disease prevalence

Variable	Coefficient	Standard error	Lower 95% CI	Upper 95% CI	*P*-value	R^2
Univariable analysis						
Age	0.075	0.027	0.021	0.129	0.008	0.150
Female sex	5.727	1.288	3.129	8.324	<0.001	0.305
Study type					0.099	0.127
Administrative databases (ref.)	–	–	–	–		
Observational multicentre	-0.610	0.286	-1.189	-0.034	0.039	
Observational single centre	-0.569	0.357	-1.290	0.152	0.119	
Randomized controlled trial	-0.922	0.527	-1.984	0.141	0.087	
COPD definition					0.002	0.188
ICD codes (ref.)	–	–	–	–		
Self-reported	-0.782	0.240	-1.266	-0.298		
Hypertension	2.695	0.785	1.112	4.279	0.001	0.212
Diabetes mellitus	5.535	1.350	2.810	8.259	<0.001	0.283
CAD	1.046	0.763	-0.496	2.588	0.178	0.045
CHF	2.192	0.928	0.320	4.065	0.023	0.113
History of stroke/TIA	2.192	1.356	-0.552	4.937	0.114	0.061
Risk of bias					0.194	0.037
High risk (ref.)	–	–	–	–		
Low risk	0.419	0.318	-0.221	1.060		
Multivariable analysis					<0.001	0.698
Age	-0.045	0.023	-0.092	0.003	0.062	
Female sex	5.249	0.999	3.217	7.281	<0.001	
COPD definition						
ICD codes (ref.)	–	–	–	–	–	
Self-reported	-0.561	0.195	-0.958	-0.164	0.007	
Hypertension	1.805	0.605	0.573	3.037	0.005	
Diabetes mellitus	3.851	1.303	1.200	6.501	0.006	
CHF	0.662	0.674	-0.710	2.034	0.334	

CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases; TIA, transient ischaemic attack.

Table 4 Association between risk factors/comorbidities and chronic obstructive pulmonary disease in atrial fibrillation patients

Conditions	Number of studies	OR	95% CI	τ^2	$\chi 2$	I^2 (%)
Hypertension	14	1.30	0.97–1.73	0.2795	184.77	93
Female sex	17	0.68	0.52–0.90	0.3234	406.82	96
Diabetes mellitus	14	1.80	1.38–2.35	0.2342	172.51	93
CAD	14	1.84	1.44–2.35	0.1905	133.67	90
CHF	14	2.24	1.73–2.90	0.2174	189.60	93
History of stroke/TIA	13	1.18	1.05–1.32	0.0180	23.87	50
	Number of studies	MD	95% CI	τ^2	$\chi 2$	I^2
Age (years)	12	4.26	2.12–6.41	14.0610	490.06	98
CHA_2DS_2-VASc score	7	0.49	0.16–0.81	0.1786	322.77	98

CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval; OR, odds ratio; TIA, transient ischaemic attack.

American cohorts or administrative databases, and in those that assessed COPD through ICD codes. Furthermore, we found that the proportion of females, and prevalence of other risk factors and comorbidities were associated with a higher prevalence of COPD among AF patients. The 95% PI provided in our analysis indicates that the actual prevalence of COPD in AF patients could be higher,

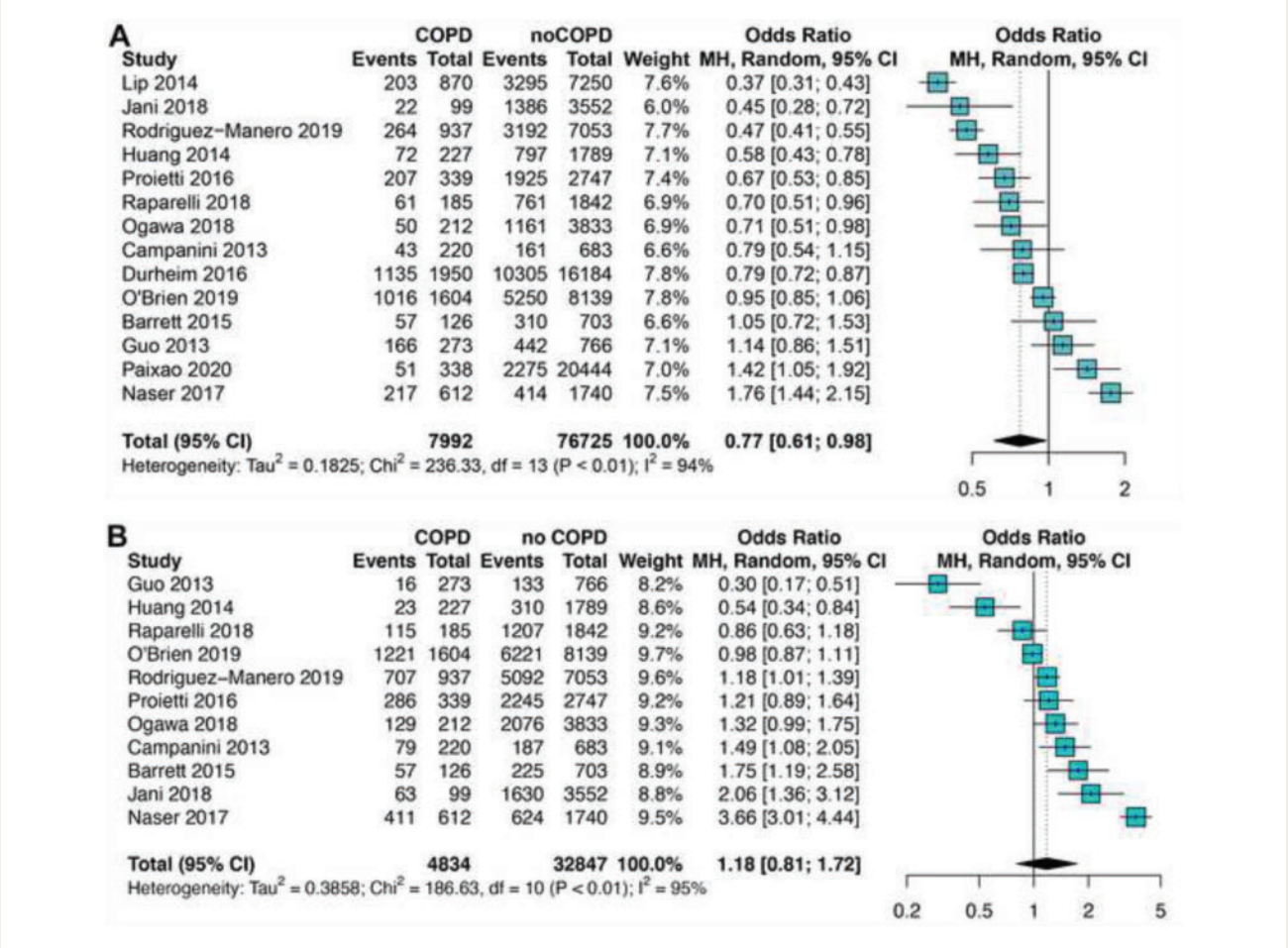


Figure 2 Pooled prescription of beta-blockers and oral anticoagulant drugs. (*A*) Beta-blockers and (*B*) Oral anticoagulants. BBs, beta-blockers; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MH, Mantel–Haenszel; OACs, oral anticoagulants.

reflecting the potential impact of other evidence coming from possible future studies. Patients with AF and COPD had an increased prevalence of the main thromboembolic risk factors, with an overall higher thromboembolic risk (*Graphical abstract*).

Furthermore, despite the higher burden of CV comorbidities, AF patients with COPD were less treated with BBs, with no differences in OAC prescription. Finally, COPD patients showed an increased long-term risk of all-cause death, CV death, and major bleeding, with a non-significant trend in higher risk for stroke occurrence. No influence of BBs on the risk of major adverse outcomes was evident among COPD patients, and no significant subgroup difference was observed between COPD and non-COPD patients.

According to the most recent estimates, COPD affects 11.3% of the general population.[6] Our meta-analysis is the first to estimate the pooled prevalence of COPD in AF patients, showing that COPD might be even more prevalent in this population, as suggested by the 95% PI. Furthermore, our subgroup analyses demonstrated that in certain regions (i.e. North America), COPD prevalence rises up to 20% of the AF patients. Also, it revealed that when COPD diagnosis was established through ICD codes—hence reflecting a potential more extensive reporting than the patients' self-reporting—the prevalence increased up to 17.5%, suggesting a possible underestimation of the overall pooled prevalence. Differences in geographical location may be driven by several factors, including prevalence of smoking habits and differences in body mass index; however, we were not able to explore the role of these and other variables, due to the limited data available. Moreover, study design and definition of COPD may have also played a role in our analysis, since most North American studies were based on administrative databases. Finally, older AF patients appeared to have a higher prevalence than younger ones, though we did not find a significant difference in the smaller number of studies with available age-stratified data.

The high between-study variability in the prevalence of COPD is not surprising and is consistent with the results of previous meta-analyses that estimated COPD prevalence in the general population.[65,66] High variability of COPD prevalence also emerged in large cohort studies,[67] and even across different sites in the same region.[68] The variability in COPD prevalence may result from differential exposure to risk factors, the heterogeneous definition of the disease, and other epidemiological characteristics. Consistently, COPD prevalence observed among AF patients may have been influenced by the overall prevalence registered in the population to which these

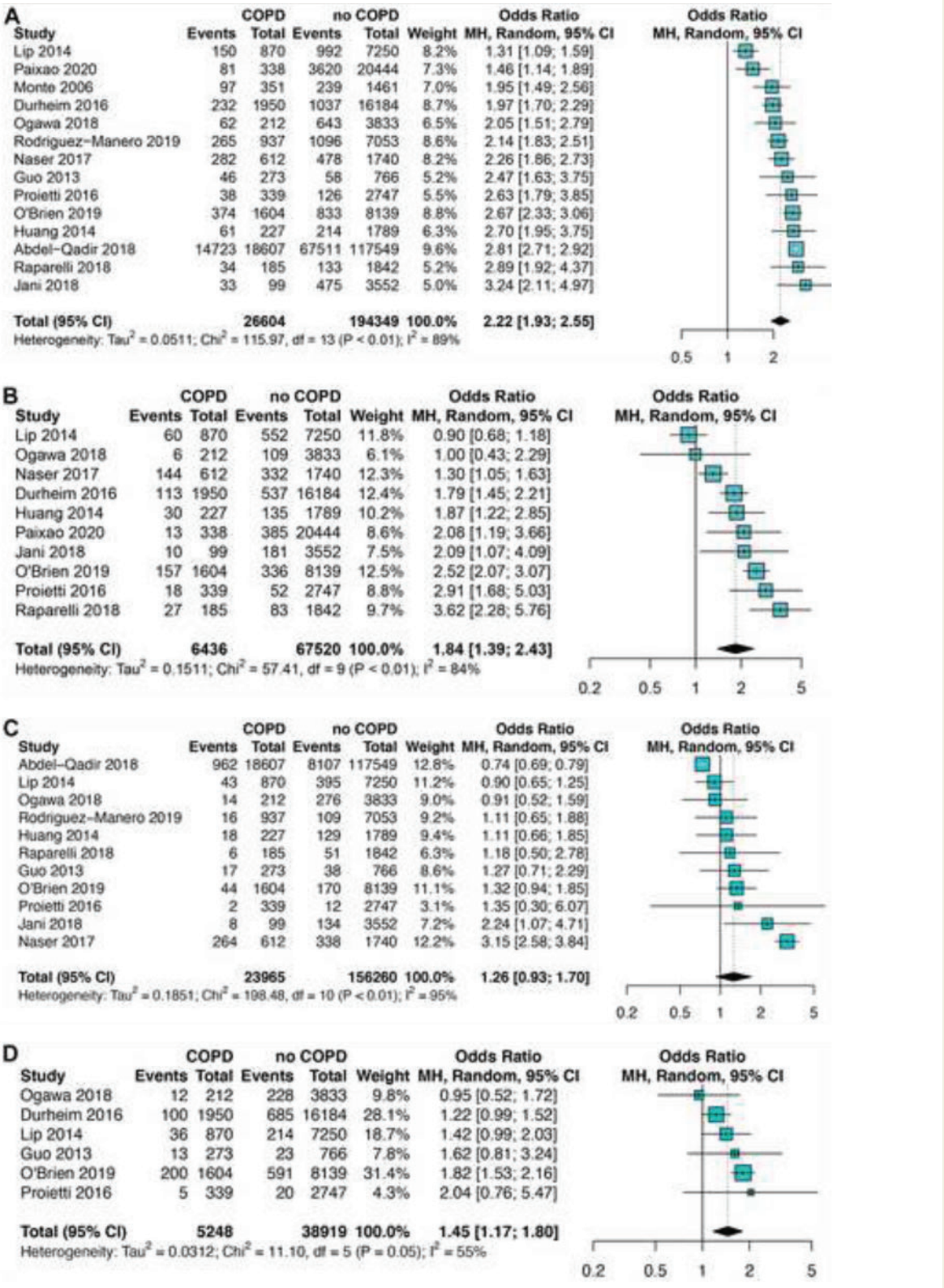


Figure 3 Risk of outcomes in chronic obstructive pulmonary disease vs. non-chronic obstructive pulmonary disease patients. (*A*) All-cause death; (*B*) cardiovascular death; (*C*) ischemic stroke; and (*D*) major bleeding. CI, confidence interval; COPD, chronic obstructive pulmonary disease; MH, Mantel–Haenszel.

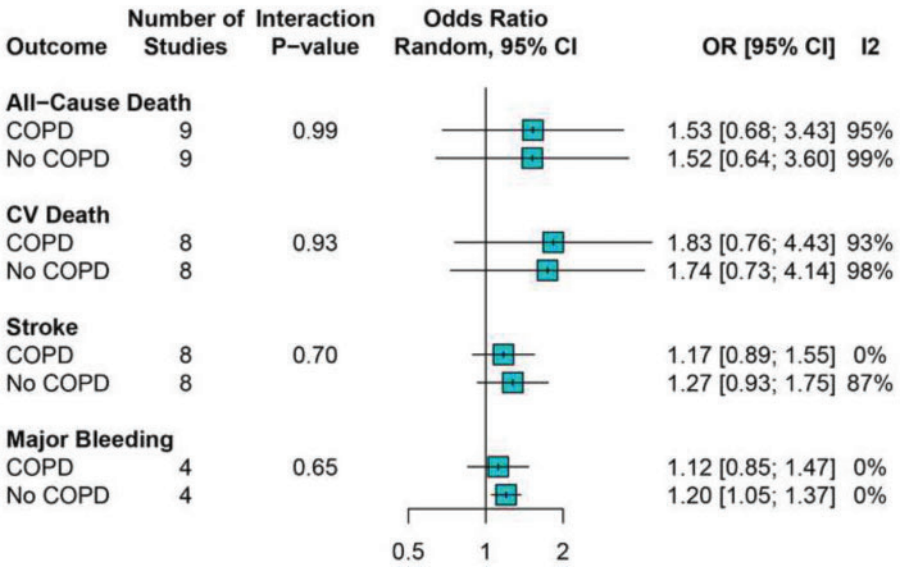


Figure 4 Risk of outcomes in chronic obstructive pulmonary disease and non-chronic obstructive pulmonary disease patients according to beta-blocker use. CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio

patients belong: for example, a low prevalence of COPD among AF patients was found in the UK Biobank (2.7%),[34] consistent with the 1.7% COPD prevalence in the overall cohort.[69] Similarly, Paixão *et al.*[48] found a COPD prevalence of 1.6% in AF patients, compared to 0.8% of the overall cohort. Among the studies with the highest prevalence, Chao *et al.*[27] found that 35.5% of AF patients had COPD, compared to the 23.2% in the propensity-score matched non-AF controls—a higher prevalence than those reported by several cohorts included in our analysis. These data suggest that variability in the original cohorts may also influence the heterogeneity of COPD prevalence in the AF subgroup.

Our study allows us to emphasize the evidence for the close relationship between AF and COPD.[8] These diseases share similar epidemiology, being more common in male subjects, the elderly, and developing countries.[6,7] Moreover, there is evidence that COPD promotes the occurrence of CV diseases, with a 50% increased risk of developing AF, as a result of the complex interplay between cardiac morpho-functional changes (i.e. right and left atrial dilatation, pulmonary hypertension, left ventricular diastolic dysfunction), cellular/systemic modifications (i.e. chronic hypoxia, hypercapnia, acid/base imbalance), inflammation, and pro-oxidative status.[70,71] As described in detail in a recent narrative review, all these mechanisms can contribute to establishing a pro-arrhythmogenic cardiomyopathy,[8] through several mechanisms (i.e. expression of hypoxia-inducible factor 1, pro-fibrotic remodelling, sympathetic activity). This is in part similar to what is observed in other conditions, like chronic infections, in which inflammation promotes the onset of AF.[72] Moreover, AF has been reported both to be triggered by and to trigger COPD exacerbations,[6] and the use of non-selective beta-2 agonist inhalers in COPD has been linked to increased risk of arrhythmias.[73] Indeed, COPD is part of the C_2HEST score, used to predict the incidence of AF in patients with risk factors/comorbidities.[74] Finally, COPD has been found to promote AF progression, and may increase the recurrence rate after a cardioversion procedure.[71] This is also reflected by the inclusion of COPD into the HATCH score, used to predict AF relapse/progression.[75] All these data support the association between a close mechanistic relationship between AF and COPD, and may explain the link between these two conditions and their mutual influence. In this light, our data reinforce the idea that COPD may be more prevalent among AF patients, being also associated with an increased burden of comorbidities and a higher thromboembolic risk. Finally, although our analysis was not specifically designed to evaluate how disease severity may modulate the effect of COPD in AF patients, it is conceivable that the contribution of COPD may be different according to the stage of the disease. Therefore, patients with greater functional impairment, a higher number of exacerbations, more severe hypoxia and more prone to pulmonary hypertension, may experience a worse prognosis than patients with mild COPD. Further studies are required to confirm this hypothesis.

Beyond speculation, our analysis showed that COPD is associated with a higher burden of several comorbidities and risk factors in patients with AF, including diabetes mellitus, CAD, CHF, history of stroke/TIA, and older age. This is reflected in the higher mean CHA_2DS_2-VASc score among COPD patients. These findings allow us to reflect on the role of multimorbidity in both AF and COPD patients. Indeed, if the presence of multiple conditions strongly influences both diseases,[2,76] our data suggest that the concomitant presence of AF and COPD increases further the burden of comorbidities, leading to a significantly higher risk for major adverse outcomes. Apart from its direct effect on prognosis, COPD may indicate additional clinical complexity in AF patients. Our results supported this hypothesis, as COPD was associated with a 2.2-fold and 1.8-fold increased risk of all-cause mortality and CV death, respectively. Also, the incidence of major bleeding was increased, up to 45% in patients with COPD, underlining how COPD may indicate a clinical situation

in which AF patients are more susceptible to all events. Meta-regressions demonstrated that CHF prevalence was the only moderator for COPD effect in all-cause death risk, while increasing mean age was the only moderator for COPD effect in stroke risk.

Although speculative and limited by the study-level nature of these associations, these findings may indicate that the influence of COPD on some outcomes might be mitigated in cohorts with increased clinical complexity, as suggested by increased age and higher prevalence of comorbidity such as CHF. This hypothesis is consistent with the findings of the additional analysis that we performed on the risk of stroke: the exclusion of the Abdel-Qadir study (among those with a higher average age) led to an increase in the stroke risk in patients with vs. without COPD; moreover, in the exploratory subgroup analysis, we found an increased risk of stroke in COPD patients among the younger cohorts. On the other side, the absence of any other moderator for these two outcomes, and the absence of any specific moderator for CV death and major bleeding support our hypothesis of an independent role of COPD in determining higher risk for the main AF-related clinical outcomes.

All these findings should be interpreted in the light of the current holistic approach to manage patients with AF. The 2020 ESC guidelines[7] on AF endorses the application of the ABC (Atrial Fibrillation Better Care) pathway to manage AF patients,[77,78] comprising a specific focus on symptom control and management of concomitant diseases, including non-CV comorbidities. In this scenario, recognizing COPD as a frequent comorbidity and a potentially important factor in influencing the prognosis would be essential to achieve a more holistic and integrated management of AF patients. Moreover, COPD may also influence symptoms in patients with AF, through direct effects, and because COPD symptoms may be incorrectly attributed to AF.[8]

Our study also confirms that COPD may influence the management of AF patients significantly. The results of our analysis showed that patients with COPD were 23% less likely to receive BBs, while no significant differences were observed for OACs. Analysing the heterogeneity found in our analyses, we could highlight how BB use is still influenced by the presence of various comorbidities which may need BB treatment, such as hypertension, CAD and CHF. On the other side, increasing prevalence of previous stroke/TIA was the only study-level characteristic associated with a reduced probability of OAC prescription in COPD patients. This finding could appear to be counterintuitive, as a higher prevalence of stroke entails an increased thromboembolic risk. Notwithstanding, history of stroke is also associated with higher bleeding risk, being also included in the HAS-BLED score. In this context, and also based on our results showing that COPD patients have a higher burden of all main AF-associated risk factors and comorbidities, we can speculate that the presence of COPD indicates increased clinical complexity and a perceived higher risk of bleeding, resulting in a lower OAC prescription. This is consistent with data from other large observational studies.[79,80]

The use of BBs in COPD patients with CV conditions has been largely debated, with controversial evidence on their effect on outcomes.[81–84] Although some studies described an association between BB use and increased risk of COPD exacerbations and CV hospitalization,[81,82] others have shown no association with worse respiratory functional outcomes.[83,84] These conflicting data may have contributed to significant underuse of BBs in CV patients.[85,86] Notwithstanding this, a recent large meta-analysis showed how COPD patients with CV conditions treated with BBs had a significant reduction for all the outcomes considered (COPD exacerbation, hospital mortality, all-cause mortality), even irrespective of the type of BBs (selective vs. non-selective),[87] while non-selective BBs were previously considered unsafe.[88] Despite the large number of studies included in this meta-analysis, no specific data are available about COPD patients with AF.[87] Our findings directly reflect the concerns about the safety of BBs in patients with COPD; however, they also suggest that undertreatment of COPD patients with AF may exist, especially in obtaining a better symptom control, which is one of the main aspects of the therapeutic approach to AF patients.[7] Although not primarily focused on the impact of BBs on outcomes, the results of our meta-analysis showed no differences in the risk of major outcomes in COPD patients with AF treated with BBs, providing valuable information to treating clinicians.

In view of these findings, our study underlines the importance of a systematic assessment of respiratory function in AF patients, as well as the application of an integrated care approach to manage these patients.

Limitations

The main limitation of our analysis is the high heterogeneity in the estimates of COPD pooled prevalence. However, high heterogeneity is a common concern in epidemiological meta-analyses exploring the prevalence of several diseases, in which we expect the results to vary from study to study.[89,90] Indeed, we performed an exploratory analysis from the same studies included in our meta-analysis about the prevalence of other thromboembolic risk factors (Supplementary material online, *Table S14*), which showed similar high heterogeneity, suggesting that the influence of study-to-study variability is relevant. Moreover, similar heterogeneity was found in another systematic review that estimated the prevalence of COPD in the general population[65] and in a large cohort study,[67] suggesting that specific issues in the definition, awareness and diagnosis of the disease may explain, at least partially, the high between-study variance observed. Consistently, in several studies included in our meta-analysis, we observed a relationship between the prevalence of COPD in AF patients and the one found in the overall cohort. Furthermore, we performed multiple additional analyses to account for heterogeneity, including a multivariable meta-regression which allowed us to account for roughly 70% of the observed heterogeneity.

Despite our best efforts to include any relevant cohort in our analysis, it is possible that some studies were not included (e.g. because not captured by our search strategy or excluded for irrelevance according to the abstract). However, we included 46 studies in our analysis, collecting more than 4 000 000 AF subjects. Since our screening process was performed according to our primary objective, it is possible that case-control studies (potentially eligible for inclusion for evaluation of the outcomes) were not captured in our screening phase, being not eligible for estimation of COPD prevalence. However, we have gathered additional data on outcomes through international collaboration, so that it is unlikely that these issues significantly affected our pooled estimates for outcomes. Notwithstanding, potential residual confounders, which we cannot take into account, may still persist, and require further studies to strengthen our findings.

Another limitation is related to the absence of data about respiratory functional assessment, COPD severity, or disease-specific treatment. Limited data were also available on symptom control, and specifically on symptoms disaggregated by COPD diagnosis. This prevented us from analysing the effect of COPD on symptom control. Also, due to the limited data, we could not evaluate the role and impact of smoking in determining the prevalence of COPD and its impact on clinical events, though it is plausibly involved in both determining a higher prevalence of COPD among AF patients and a presumably higher risk of clinical events. Moreover, in the analysis regarding prescription and impact of BB, we were unable to assess the type (selective vs. non-selective) or dosage of BBs and indications and administration of other antiarrhythmics, or parameters of clinical response to these drugs, such as ventricular rate. Finally, although we provided extensive meta-regression analyses, with the aim of identifying potential moderators of the impact of COPD on outcomes, the results may not fully elucidate the complex interrelationships that exist between comorbidities in AF patients, considering that other factors not available in the studies selected by the systematic search could have a significant impact. For all these reasons, these findings should be interpreted with caution.

Conclusions

In this systematic review and meta-analysis, we found that COPD is common in AF, affecting 13% of patients, and is associated with an increased burden of comorbidities, differential management, and worse outcomes, with a more than two-fold higher risk of all-cause death and increased risk of CV death and major bleeding. Therapy with BBs was not associated with increased risk of adverse outcomes among COPD patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request, and after approval of all other co-investigators.

Appendix

The Atrial Fibrillation and Comorbidities Systematic Reviews and Meta-Analyses (AF-COMET) Collaborative Group

Masaharu Akao, Department of Cardiology, National Hospital Organisation Kyoto Medical Center, Kyoto, Japan; Tyler Warren Barrett, Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN, United States; Mauro Campanini, Department of Internal Medicine, Hospital 'Maggiore della Carità', Novara, Italy; Laurent Fauchier, Service de Cardiologie, Hôpital Trousseau and Université François-Rabelais, Chambray-les-Tours, France; Yutao Guo, PLA General Hospital, Geriatric cardiology, Beijing, China; Gualberto Gussoni, Research Department, FADOI Foundation, Milan; Bhautesh D. Jani, General Practice and Primary Care, Institute of Health and Wellbeing, MVLS, University of Glasgow, Glasgow, UK; Cathy A. Jenkins, Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN, United States; Mehmed Kulić, Cardioteam Clinic, Sarajevo, Bosnia and Herzegovina; Frances Mair, General Practice and Primary Care, Institute of Health and Wellbeing, MVLS, University of Glasgow, Glasgow, UK; Milena Soriano Marcolino, Telehealth Center, Hospital das Clínicas, and Department of Internal Medicine, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; Nabil Naser, Polyclinic 'Dr Nabil', Sarajevo, Sarajevo, Bosnia and Herzegovina; Emily C. O'Brien, Duke Clinical Research Institute, Durham, NC, United States; Hishashi Ogawa, Department of Cardiology, National Hospital Organisation Kyoto Medical Center, Kyoto, Japan; Gabriela MM Paixão, Telehealth Center, Hospital das Clínicas, and Department of Internal Medicine, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; Jonathan P. Piccini, Duke Clinical Research Institute, Durham, NC, United States; Antonio Luiz Ribeiro, Telehealth Center, Hospital das Clínicas, and Department of Internal Medicine, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; Moisés Rodriguez-Mañero, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain; Cardiology Department, Complejo Hospital Universitario de Santiago, Santiago de Compostela, Spain.

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