Long-Term Relationship between Atrial Fibrillation, Comorbidity and Oral Anticoagulant Use in a Population-Based Cohort Study

Marco Proietti[1,2,3]*, Irene Marzona[1]*, Tommaso Vannini[1], Mauro Tettamanti[1], Maurizio Bersani[4], Angela Bertolotti[4], Luca Merlino[4], Stefania Basili[3], Pier Mannuccio Mannucci[5], Giuseppe Boriani[6], Gregory YH Lip[2,7,8], Maria Carla Roncaglioni[1], Alessandro Nobili[1]

[1]IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; [2]Institute of Cardiovascular Sciences, University of Birminigham, Birmingham, United Kingdom; [3]Department of Internal Medicine and Medical Specialties, Sapienza-University of Rome, Rome, Italy; [4]Regional Ministry of Heath, Milan, Italy; [5]Scientific Direction, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [6]Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [7]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; [8]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

*Both authors equally contributed to this manuscript.

Corresponding Author

Dr. Marco Proietti

IRCCS – Istituto di Ricerche Farmacologiche “Mario Negri”

Via Giuseppe La Masa 19, 20156, Milan, Italy

e-mail: marco.proietti@uniroma1.it

ABSTRACT

Introduction: Atrial fibrillation (AF) is often associated with several comorbidities. The Charlson Comorbidity Index (CCI) is an established tool for evaluating the burden of comorbidity, but limited data are available relating AF and CCI. We analyzed the relationship between AF and CCI in a population-based cohort study over a long-term follow-up period, in relation to oral anticoagulant (OAC) drug prescriptions and major adverse events.

Methods: We used data from the administrative health databases for the whole Lombardy region of Italy (>10 million inhabitants). All patients admitted in 2002 and diagnosed with AF were considered for analysis and subjects were followed up for 12 years. AF diagnosis and CCI were established according to ICD-9 codes retrieved from hospital admissions.

Results: In 2002, 24040 patients were admitted with a diagnosis of AF, and CCI was significantly higher in AF patients compared to non-AF subjects (1.8±2.1 vs. 0.2±0.9, p<0.001). Over 12-years follow-up, AF was associated with an independent increased risk of higher CCI, compared to non-AF subjects (beta coefficient: 1.69, 95% confidence interval [CI]: 1.67-1.70). Adjusted logistic regression analysis found that in AF patients, CCI was inversely associated with OAC prescription at baseline (odds ratio [OR]: 0.91, 95% confidence interval [CI]: 0.89-0.92 per point), as well as at the end of follow-up (OR: 0.98, 95% CI: 0.98-0.99).

Over the 12-years follow-up, AF patients with high CCI (≥4) had a higher cumulative incidence for stroke, major bleeding and all-cause death (all p<0.001), compared to those with low CCI (0-3). Adjusted Cox regression analysis found that CCI, considered as a time-dependent continuous variable, was independently associated with an increased risk for stroke (hazard ratio [HR]: 1.04, 95% CI: 1.02-1.06 per point), major bleeding (HR: 1.03, 95% CI: 1.01-1.06) and all-cause death (HR: 1.10, 95% CI: 1.09-1.11).

Conclusions: In hospitalized patients, AF is associated with an independent increase in CCI, that was inversely associated with OAC prescriptions during follow-up. CCI was independently associated with an increased risk of stroke, major bleeding and all-cause death.

Keywords: atrial fibrillation; comorbidity; oral anticoagulant drugs; outcomes.

INTRODUCTION

Atrial fibrillation (AF) has an increasing incidence, prevalence and impact on healthcare systems globally[1]. The AF worldwide epidemic is mainly owed to the increasing population ageing, affecting more likely older patients[3]. Compared to the past, AF patients are often older and more affected with concomitant cardiovascular (CV) and non-cardiovascular comorbidities, that affect significantly patients' clinical course, leading to an increased risk of CV death and all-cause death[4].

The concept of comorbidity, or more precisely multimorbidity (defined as the concomitant presence of two or more chronic conditions) has gained much medical attention in the last decades[5]. As with AF, the prevalence of multimorbidity increases with increasing age and is associated with a high risk of mortality, reduced functional status, increased healthcare expenditure and use of resources[6]. As part of the biological, sociological and clinical complexity associated with healthcare[7], multimorbidity demands solid integrated care and a holistic approach to the patient in order to proper manage the associated risks[6]. Moreover, comorbidity/multimorbidity is very common in patients with CV disease[8].

The Charlson Comorbidity Index (CCI) has been validated as a reliable tool to evaluate the burden of comorbidity/multimorbidity in the general population and is significantly associated with an increased risk of all-cause death during long-term follow-up[9]. Furthermore, CCI has been extensively validated in patients with CV disease[10]. Nevertheless, despite AF being associated with several comorbidities[1], scarce data exist about the overall burden of comorbidities and the relationship of CCI with AF.

The aim of this paper is to evaluate the relationship between AF, burden of comorbidity (as defined by CCI), the prescription of oral anticoagulant (OAC) drugs and long-term

outcomes in a large population-based cohort of AF patients from the largest region of Northern Italy.

METHODS

Data Source and Study Population

This study used linkable administrative health databases of the Lombardy Region which include a population registry with the demographic data of all residents and detailed information on drug prescriptions and hospital admissions. To date, with a population of more than 10 million inhabitants, Lombardy is the largest Italian region, comprising highly populated urban areas, as well as industrial and rural ones. The Italian healthcare system is based on a public National Health System, which provides assistance to anyone on national territory, irrespective of any pre-existing condition. A personal identification number is given to each subject and kept in the National Civil Registration System.

All databases are linked anonymously using unique encrypted patient codes, in accordance with Italian privacy regulations. Approval from an ethics committee is not required to analyse encrypted administrative data. Data were available for fifteen consecutive years, from 2000 to 2014. For any hospital admission, all discharge diagnoses have been coded according to International Classification of Disease 9th revision [ICD-9]. Moreover, the hospital discharge database records the date of hospital admission, date of discharge or death and procedures performed during admission. The drug prescription database contains the drug name and its Anatomical Therapeutic Chemical (ATC) classification code, quantity and dispensation date. All data about subjects 40 years and older were included in this analysis.

Data from 2000 to 2001 were used to build the clinical history of patients and to calculate CCI. Year 2002 was used as index year to evaluate AF diagnosis. All discharge diagnoses were searched for codes 427.31 and 427.32, and all subjects with these codes irrespective of diagnosis position, were assigned to the group of patients with prevalent AF. All other subjects entered the control group of non-AF patients.

Definition of Concomitant Comorbidities and CCI Calculation

According to the diagnoses reported at discharge and coded as per ICD-9, all patients were evaluated for concomitant presence of comorbidities (see Supplementary Materials, Table S1). Hypertension was identified on the basis of prescription of at least an antihypertensive drug in the six months after entering the study cohort (see Table S1 for ATC codes). Accordingly, the CHA_2DS_2-VASc score was computed according to the original definitions[11].

In its original definition, CCI comprised 19 diagnosis to which different weights have been assigned and summed to obtain the final calculation of CCI[9] (Table S2). For this study, the CCI was calculated according to a validated method applied to the administrative databases[12]. All AF patients were grouped according to CCI as patients with low comorbidity (CCI 0-3) and high comorbidity (CCI ≥4).

In order to analyze the relationship between AF and CCI, we analyzed differences at baseline between AF and non-AF patients. Then, we analyzed the relationship between AF and CCI throughout the follow-up observation, to establish if a significant association exists between AF and increasing comorbidity burden according to CCI.

Oral Anticoagulant Drugs

In the purpose of the study we evaluated OAC prescription at baseline and at the end of observation according to CCI. At the beginning of observation, only vitamin K antagonists (VKAs) were available, while at the end of observation the non-vitamin K antagonist oral anticoagulants (NOACs) were available for prescription. OAC drugs prescription were recorded as follows: VKA (warfarin: B01AA03, acenocumarol: B01AA07); NOACs (dabigatran: B01AE07, rivaroxaban: B01AF01, apixaban: B01AF02, edoxaban: B01AF03), antiplatelet drugs (B01AC).

Study Outcomes

Outcomes of interest for the present study were: stroke, major bleeding and all-cause death (see Supplementary Materials, Table S1 for ICD-9 codes). Follow-up observation started when the patient entered the study cohort and proceeded until one of the outcomes occurred or when the follow-up was censored. Reasons to be censored included emigration, admission to a nursing home, occurrence of death or reaching the end of the follow-up observation.

Statistical Analysis

Continuous variables, expressed as mean and standard deviation, were compared across the groups using Student's t-test. Categorical variables, expressed as counts and percentages, were compared using Chi-square test.

To analyse the relationship between AF and CCI over follow-up, we performed a mixed linear effect logistic model adjusted for years of observation, age, sex and an interaction term between AF and follow-up years. A supplementary age-stratified (<65 years, 65-74 years, ≥75 years) analysis was also performed.

To evaluate the impact of CCI in OAC prescription for AF patients, we performed a logistic regression model, adjusted for age and sex, for OAC prescription at baseline and at the end of follow-up. CCI was considered as a continuous variable and as classes (high vs. low comorbidity). At the end of follow-up, we separately prescriptions of VKA and NOACs.

Differences in survival between AF patients with low and high comorbidity were analyzed with Log-Rank test and Kaplan-Meier curves were drafted accordingly. A Cox regression analysis to evaluate the impact of CCI, considered as a continuous time-dependent variable, in determining study outcomes was performed. Two Cox regression models were performed, as follows: i) adjusted for age and sex; ii) adjusted for age, sex and OAC prescription. A two-sided value of $p \leq 0.05$ was considered statistically significant. Analyses were done with Stata 13.0 (Stata Corp LP, College Station, TX, USA), and SAS software, version 9.4 (SAS Institute).

RESULTS

In 2002, a total of 24,040 AF patients were retrieved, as well as 240,400 non-AF patients. At baseline (Table 1), AF patients had a significantly higher mean (±SD) CCI than non-AF subjects (1.8±2.1 vs. 0.2±0.9, $p<0.001$). Patients with AF were significantly older and more likely male, and more likely affected by comorbidities compared to non-AF subjects. Accordingly, AF patients had a significantly higher mean (±SD) CHA_2DS_2-VASc score compared to non-AF subjects (3.3±1.4 vs. 1.4±1.2, $p<0.001$).

Among the overall AF patient cohort, 4295 (17.9%) patients had high comorbidity (CCI ≥4), while 19,745 (82.1%) had low comorbidity (CCI 0-3) (Table 1). Mean (±SD) CCI for the

high comorbidity group was 5.5±1.8, while for the low comorbidity group, 1.1±1.1 (p<0.001). Patients with high comorbidity were older and more likely male than those with low comorbidity (both p<0.001). In patients with high comorbidity all conditions considered were more prevalent, except for hypertension which was more prevalent in the low comorbidity group (p<0.001). Patients with high comorbidity had a higher thromboembolic risk than the low comorbidity group (CHA_2DS_2-VASc score mean [±SD] 4.1±1.5 vs. 3.2±1.3, accordingly; p<0.001). At baseline, patients with high comorbidity group were significantly less prescribed with OAC than those with low comorbidity (30.0% vs. 42.3%, p<0.001).

Trends in CCI and Relationship with AF

A mixed linear effect logistic model was compiled to analyze the relationship between AF and CCI. Overall, mean CCI progressively increased over time both in non-AF and AF patients, being increasingly and steadily higher in AF patients compared to non-AF ones (p<0.001) [Figure 1]. After adjustment for years of observation, age, sex and an interaction term between AF and years of observation, AF was significantly associated with an increasingly higher CCI (coefficient: 1.69, 95% confidence interval [CI]: 1.67-1.70), F= 99943.8, p<0.001). Subgroup analysis for age classes, showed that this relationship was consistently significant for patients <65 years, 65-74 years and ≥75 years (all p<0.001) [Figure S1-S3].

CCI and OAC Prescription

After multivariable adjustment (Table 2), CCI as a continuous variable was inversely associated with OAC prescription (odds ratio [OR]: 0.91, 95% CI: 0.89-0.92). The high comorbidity category (CCI ≥4) was significantly inversely associated with OAC prescription (OR: 0.65, 95% CI: 0.60-0.70).

At the end of follow-up, even though CCI as a continuous variable was inversely associated with OAC prescription (OR: 0.98, 95% CI: 0.98-0.99), the high comorbidity category was not significantly associated (OR: 0.98, 95% CI: 0.93-1.04). Examining separately VKA and NOACs prescription (Table 2), while there was no difference in VKA prescription, both continuous and categorical CCI were significantly inversely associated with prescription of NOACs (both $p<0.001$).

Survival and Regression Analysis

At follow-up, all the outcomes considered were more likely in the high comorbidity group (Table 3). Kaplan-Meier analysis shows that risk for stroke, major bleeding and all-cause death was consistently higher in high comorbidity group compared to the low comorbidity group [Figure 2].

Cox regression analysis, using CCI as a continuous time-dependent variable to take account of the temporal increase and adjusted for age, sex and use of OAC, CCI was significantly directly associated with an increased risk for stroke (hazard ratio [HR]: 1.04, 95% CI: 1.02-1.06 per increasing point), major bleeding (HR: 1.03, 95% CI: 1.01-1.06 per increasing point) and all-cause death (HR: 1.10, 95% CI: 1.09-1.11 per increasing point).

DISCUSSION

Our study showed that AF patients are exposed to a higher burden of overall comorbidity than compared to non-AF ones, showing for the *first time* that exist a direct relationship between AF and increasing comorbidity burden over long-term follow-up, irrespective of age. Second, an increased burden of comorbidity is inversely associated with OAC prescription, which could significantly affect AF patients' clinical history. Third, an increased burden of comorbidity in AF patients is directly and independently associated with an increased risk for stroke, major bleeding and all-cause death.

The independent relationship between various single diseases and AF has been largely demonstrated. Indeed, several conditions contribute independently to incident AF occurrence and it has been suggested how tight control of concomitant risk factors and comorbidities could significantly reduce the burden of AF[13,14]. Furthermore, several diseases are independently prevalent in AF patients[15,16]. Our paper firstly establishes a direct link between the presence of AF and the development of a progressively higher burden of comorbidity (or better rather, multimorbidity). The evidence presented allows us to speculate about the role of AF as a proxy of a worst clinical status.

Our data are strengthened by the use of a solid and validated tool to evaluate comorbidity/multimorbidity, the CCI. Thus far, data about CCI in the contest of AF are scarce[17]. In a Belgian study derived from a primary care registry, a modified version of the CCI was found significantly higher in AF elderly (≥60 years) patients than in non-AF ones, also being significantly associated with AF diagnosis[17]. The data presented in this study extend this previous evidence, confirming how the burden of comorbidity is significant in AF patients, irrespective of age and of what may be single medical conditions. In

particular, we show how a significant proportion of patients (~20%) had a high level of comorbidity. A recent study derived from the UK Biobank, in a cohort of patients with self-reported AF which examined the presence of multimorbidity as the additive presence of various conditions, only 19.6% of patients reported no comorbidities and 11.1% of patients reported 4 or more comorbidities[18].

Our results presented show that increased comorbidity in AF patients is significantly inversely associated with OAC prescription. This is a concerning trend, considering the associated increased thromboembolic risk. In the study by Vanbeselaere and colleagues, there was a possible inverse relationship between increasing CCI and reduced OAC prescription[17]. Our study extends the previous knowledge, showing how this inverse relationship is consistent in general population and over a long-term observation period. Moreover, we showed that if physicians appear to be more confident in prescribing VKA, the prescription of NOACs is significantly reduced in patients with increased comorbidity. Our results substantiate previous observations that seem to suggest that AF patients prescribed with NOACs are relatively healthier and have less prevalent comorbidities[15,19].

In the recent years, the increased risk of CV-related and all-cause death in AF cohorts has shifted the main focus of prevention of adverse events from stroke to mortality[20–25]. Our data show that the increased and increasing comorbidity burden is strongly associated with an increased risk of all the adverse events, stroke, major bleeding and all-cause death. The Framingham Heart Study previously showed how AF patients with comorbidities have a consistently increased risk for cardiovascular events and all-cause death compared to those without[26]. An analysis from the “Outcomes Registry for Better Informed Treatment of Atrial Fibrillation” (ORBIT-AF) study showed that when clustering AF patients according to the more frequent clinical characteristics, those patients in the

‘low-comorbidity’ cluster had the lowest risk major cardiovascular and neurological adverse events than all the other identified clusters, variously affected by risk factors and other comorbidities[16].

Our paper also extends previous knowledge about the usefulness of CCI in AF patients. Thus far CCI have been already validated in patients with acute coronary syndrome[27] and stroke[28] and other cardiovascular conditions[10]. Our study represents the first large evaluation of CCI in a population-based AF patients’ cohort.

In the recent years there has been an increasing need of new approaches to manage AF patients, considering them in a more comprehensive, integrated and holistic way. A systematic review and meta-analysis by Gallagher and colleagues showed how an integrated care approach can significantly reduce hospitalization and mortality in AF patients[29]. Various expert opinions and international consensus statements have proposed new integrated models to proper manage AF patients, with the ultimate objective to reduce the risk of adverse events[30,31]. The ABC pathway has recently been proposed as a possible model to integrate the various main aspects related to AF patients’ management, in order to streamline and facilitate integrated care and holistic evaluation of these patients[32]. Our data support this new approach and advocate the need for structured integrated and holistic management of AF patients.

Limitations

The main limitation of this study is related to the use of ICD-9 codes, that even if largely validated in clinical research, cannot completely exclude some risk of bias related to inaccuracies and coding mistakes; furthermore, this tool does not allow us to consider and evaluate some relevant factors for adverse outcomes in AF patients. Second, since all

data are retrieved from hospital admissions, our study results need to be cautiously generalized to the overall AF population. Lastly, we used an adapted model of CCI conceived for the use in health administrative databases, which was also evaluated retrospectively and not at the baseline observation. Notwithstanding these limitations, we provided the first evidence of a direct relationship between AF and increasing burden of comorbidity and the largest validation of CCI as a reliable tool for evaluation of comorbidity in AF patients and its association with major adverse events.

CONCLUSION

In hospitalized patients, AF is associated with an independent increase in CCI, that was inversely associated with OAC prescriptions during follow-up. CCI was independently associated with an increased risk of stroke, major bleeding and all-cause death. New models of care able to consider the burden of comorbidities in AF patients and offer holistic approaches to AF management are needed.

REFERENCES

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–962.
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, *et al.* Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**:837–47.
3. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 2014;**11**:639–54.
4. Proietti M, Laroche C, Nieuwlaat R, Crijns HJGM, Maggioni AP, Lane DA, *et al.* Increased burden of comorbidities and risk of cardiovascular death in atrial fibrillation patients in Europe over ten years: A comparison between EORP-AF pilot and EHS-AF registries. *Eur J Intern Med* 2018;
5. Akker M van den, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol* 1998;**51**:367–75.
6. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;**380**:37–43.
7. Plsek PE, Greenhalgh T. Complexity science: The challenge of complexity in health care. *BMJ* 2001;**323**:625–8.
8. Forman DE, Maurer MS, Boyd C, Brindis R, Salive ME, Horne FM, *et al.* Multimorbidity in Older Adults With Cardiovascular Disease. *J Am Coll Cardiol* 2018;**71**:2149–61.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic*

Dis 1987;**40**:373–83.

10. Rashid M, Kwok CS, Gale CP, Doherty P, Olier I, Sperrin M, *et al.* Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis. *Eur Hear J - Qual Care Clin Outcomes* 2016;**3**:20–36.
11. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;**137**:263–72.
12. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. *J Clin Epidemiol* 1996;**49**:1429–33.
13. Boriani G, Proietti M. Atrial fibrillation prevention: an appraisal of current evidence. *Heart* 2018;**104**:882–7.
14. Gorenek B, Pelliccia A, Benjamin EJ, Boriani G, Crijns HJ, Fogel RI, *et al.* European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (AP. *Europace* 2017;**19**:190–225.
15. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, *et al.* Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace* 2018;**20**:747–57.
16. Inohara T, Shrader P, Pieper K, Blanco RG, Thomas L, Singer DE, *et al.* Association of of Atrial Fibrillation Clinical Phenotypes With Treatment Patterns and Outcomes: A Multicenter Registry Study. *JAMA Cardiol* 2018;**3**:54–63.

17. Vanbeselaere V, Truyers C, Elli S, Buntinx F, Witte H De, Degryse J, *et al.* Association between atrial fibrillation, anticoagulation, risk of cerebrovascular events and multimorbidity in general practice: a registry-based study. *BMC Cardiovasc Disord* BMC Cardiovascular Disorders; 2016;**16**:61.

18. Jani BD, Nicholl BI, McQueenie R, Connelly DT, Hanlon P, Gallacher KI, *et al.* Multimorbidity and co-morbidity in atrial fibrillation and effects on survival: findings from UK Biobank cohort. *Europace* 2017;

19. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, *et al.* Factors associated with non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with new-onset atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II). *Am Heart J* 2017;**189**:40–7.

20. Marijon E, Heuzey J-Y Le, Connolly S, Yang S, Pogue J, Brueckmann M, *et al.* Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation* 2013;**128**:2192–201.

21. Fauchier L, Villejoubert O, Clementy N, Bernard A, Pierre B, Angoulvant D, *et al.* Causes of Death and Influencing Factors in Patients with Atrial Fibrillation. *Am J Med* 2016;**129**:1278–87.

22. Pokorney SD, Piccini JP, Stevens SR, Patel MR, Pieper KS, Halperin JL, *et al.* Cause of Death and Predictors of All-Cause Mortality in Anticoagulated Patients With Nonvalvular Atrial Fibrillation: Data From ROCKET AF. *J Am Heart Assoc* 2016;**5**.

23. Proietti M, Laroche C, Opolski G, Maggioni APAP, Boriani G, Lip GYHGYH, *et al.* 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General

Registry Pilot Phase. *Europace* 2017;**19**:722–33.

24. Boriani G, Proietti M, Laroche C, Diemberger I, Popescu MI, Riahi S, *et al.* Changes to oral anticoagulant therapy and risk of death over a 3-year follow-up of a contemporary cohort of European patients with atrial fibrillation final report of the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) pilot general r. *Int J Cardiol* 2018;
25. Perera KS, Pearce LA, Sharma M, Benavente O, Connolly SJ, Hart RG, *et al.* Predictors of Mortality in Patients With Atrial Fibrillation (from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events [ACTIVE A]). *Am J Cardiol* 2018;**121**:584–9.
26. Kim E-J, Yin X, Fontes JD, Magnani JW, Lubitz SA, McManus DD, *et al.* Atrial fibrillation without comorbidities: Prevalence, incidence and prognosis (from the Framingham Heart Study). *Am Heart J* 2016;**177**:138–44.
27. Radovanovic D, Seifert B, Urban P, Eberli FR, Rickli H, Bertel O, *et al.* Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012. *Heart* 2014;**100**:288–94.
28. Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. *Stroke* 2004;**35**:1941–5.
29. Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, *et al.* Integrated care in atrial fibrillation: A systematic review and meta-analysis. *Heart* 2017;**103**:1947–53.
30. Kirchhof P. The future of atrial fibrillation management: integrated care and stratified therapy. *Lancet (London, England)* 2017;**390**:1873–87.
31. Kotecha D, Breithardt G, Camm AJ, Lip GYH, Schotten U, Ahlsson A, *et al.* Integrating new approaches to atrial fibrillation management: The 6th AFNET/EHRA Consensus Conference. *Europace* 2018;**20**:395–407.

32. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol* 2017;**14**:627–8.

FIGURES LEGENDS

Figure 1: Charlson Comorbidity Index Trends according to Atrial Fibrillation Diagnosis

Legend: Whiskers stand for standard deviation of mean; AF= Atrial Fibrillation; CCI= Charlson Comorbidity Index.

Figure 2: Kaplan-Meier Curves for Major Adverse Events according to Charlson Comorbidity Index Classes

Legend: CCI= Charlson Comorbidity Index.

Table 1: Baseline Characteristics according to Atrial Fibrillation and Charlson Comorbidity Index

	Non-AF	**AF**	**p**	**AF**		
	N= 240400	N= 24040		**CCI 0-3**	**CCI ≥4**	**p**
				N= 19745	N= 4295	
Age, *years* mean±SD	59.7±13.2	76.1±9.8	<0.001	75.7±9.9	77.8±8.8	<0.001
Age classes, n (%)			<0.001			<0.001
<65 years	155310 (64.6)	2964 (12.3)		2651 (13.4)	313 (7.3)	
65-74 years	47525 (19.8)	6702 (27.9)		5611 (28.4)	1091 (25.4)	
≥75 years	37565 (15.6)	14374 (59.8)		11483 (58.2)	2891 (67.3)	
Male, n (%)	11096 (46.2)	12079 (50.2)	<0.001	9841 (49.8)	2238 (52.1)	<0.001
Charlson Comorbidity Index, (mean±SD)	0.2±0.9	1.8±2.1	<0.001	1.1±1.1	5.5±1.8	<0.001
Hypertension, n (%)	79801 (33.2)	18605 (77.4)	<0.001	15452 (78.3)	3153 (73.4)	<0.001
Diabetes Mellitus, n (%)	4316 (1.8)	3555 (14.8)	<0.001	1763 (8.9)	1792 (41.7)	<0.001
Myocardial Infarction, n (%)	1723 (0.7)	1400 (5.8)	<0.001	869 (4.4)	531 (12.4)	<0.001
Congestive Heart Failure, n (%)	2919 (1.2)	7249 (30.1)	<0.001	4882 (24.7)	2367 (55.1)	<0.001
Cerebrovascular Disease, n (%)	3216 (1.3)	3605 (15.0)	<0.001	1625 (8.2)	1980 (46.1)	<0.001
Hemiplegia, n (%)	2282 (0.9)	2830 (11.8)	<0.001	1027 (5.2)	1803 (42.0)	<0.001
Dementia, n (%)	489 (0.2)	400 (1.7)	<0.001	197 (1.0)	203 (4.7)	<0.001
COPD, n (%)	3125 (1.3)	4017 (16.7)	<0.001	2523 (12.8)	1494 (34.8)	<0.001
Connective Tissue Disease, n (%)	560 (0.2)	303 (1.3)	<0.001	228 (1.1)	75 (1.7)	0.002
Ulcer, n (%)	620 (0.3)	440 (1.8)	<0.001	287 (1.4)	153 (3.6)	<0.001
Mild Liver Disease, n (%)	1918 (0.8)	1212 (5.0)	<0.001	669 (3.4)	543 (12.6)	<0.001
Moderate/Severe Liver disease, n (%)	769 (0.3)	334 (1.4)	<0.001	44 (0.2)	290 (6.7)	<0.001

Renal Disease, n (%)	1244 (0.5)	2087 (8.7)	<0.001	788 (4.0)	1299 (30.24)	<0.001
Metastatic Tumor, n (%)	1162 (0.5)	503 (2.1)	<0.001	0 (0.0)	503 (11.7)	<0.001
Leukemia, n (%)	117 (0.1)	86 (0.4)	<0.001	49 (0.2)	37 (0.9)	<0.001
Lymphoma, n (%)	305 (0.1)	190 (0.8)	<0.001	90 (0.5)	100 (2.3)	<0.001
Any Tumor, n (%)	4423 (1.8)	2189 (9.1)	<0.001	1124 (5.7)	1065 (24.8)	<0.001
CHA_2DS_2-VASc, (mean±SD)	1.4±1.2	3.3±1.4	<0.001	3.2±1.3	4.1±1.5	<0.001
Oral Anticoagulant Drugs, n (%)	4141 (1.7)	9646 (40.1)	<0.001	8358 (42.3)	4295 (30.0)	<0.001

Legend: AF= Atrial Fibrillation; CCI= Charlson Comorbidity Index; COPD= Chronic Obstructive Pulmonary Disease; SD= Standard Deviation.

Table 2: Logistic Regression Analysis for Oral Anticoagulant Drugs Prescription according to Charlson Comorbidity Index

	OAC Prescription at Baseline			OAC Prescription at End of Follow-Up		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
CCI (*as continuous variable*)	0.91	0.89-0.92	<0.001	0.98	0.98-0.99	<0.031
CCI ≥4 (*vs. CCI 0-3*)	0.65	0.60-0.70	<0.001	0.98	0.93-1.04	0.494
	VKA Prescription at End of Follow-Up			**NOACs Prescription at End of Follow-Up**		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
CCI (*as continuous variable*)	0.99	0.98-1.00	0.220	0.86	0.81-0.90	<0.001
CCI ≥4 (*vs. CCI 0-3*)	1.00	0.95-1.06	0.944	0.48	0.37-0.63	<0.001

Legend: CCI= Charlson Comorbidity Index; NOACs= Non-Vitamin K Antagonists Oral Anticoagulants; OAC= Oral Anticoagulants; VKA= Vitamin K Antagonist.

Table 3: Major Adverse Events according to Charlson Comorbidity Index Classes

	CCI 0-3 N= 19745		**CCI ≥4** N= 4295		p
	N	Cumulative Incidence*	N	Cumulative Incidence*	
Stroke	1826	17.4	412	26.0	<0.001
Major Bleeding	1120	12.0	197	15.7	<0.001
All-Cause Death	13831	76.0	3650	95.0	<0.001

Legend: *per 100 patients; CCI= Charlson Comorbidity Index.

Table 4: Cox Regression Analysis for Major Adverse Events

	Charlson Comorbidity Index (as continuous time-dependent variable)					
	Model 1*			Model 2†		
	HR	95% CI	p	HR	95% CI	p
Stroke	1.04	1.03-1.06	<0.001	1.04	1.02-1.06	<0.001
Major Bleeding	1.02	0.99-1.04	0.146	1.03	1.01-1.06	<0.001
All-Cause Death	1.10	1.09-1.11	<0.001	1.10	1.09-1.11	<0.001

Legend: *adjusted for sex and age; †adjusted for sex, age and use of OAC; CI= Confidence Interval; HR= Hazard Ratio; OAC= Oral Anticoagulant.