Experimental Gerontology

Relationship between Multimorbidity and Outcomes in Atrial Fibrillation

--Manuscript Draft--

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Abstract:	Background Multimorbidity is common in atrial fibrillation (AF) patients. Charlson comorbidity index (CCI) is used to evaluate multimorbidity in the general population. Limited long-term data are available on the relationship between CCI and AF. We examined the association between CCI, anticoagulation control and outcomes in AF patients. Methods We studied 1956 from the FANTASIIA registry, an observational Spanish nationwide study on anticoagulated AF patients. Time in therapeutic range (TTR) was used to evaluate anticoagulation control. Stroke/TIA, major bleeding, cardiovascular (CV) death and all-cause death were study outcomes. Results Mean±SD CCI was 1.1±1.2. Based on CCI quartiles, patients were categorised in four groups: 676 (34.6%) in Q1 (CCI 0); 683 (34.9%) in Q2 (CCI 1); 345 (17.6%) in Q3 (CCI 2); and 252 (12.9%) in Q4 (CCI ≥3). In vitamin K antagonist treated patients, the highest CCI quartile was inversely associated with TTR >70% (odds ratio:0.67, 95% confidence interval (CI):0.45-0.99). During observation, a progressively higher rate of major bleeding, CV death and all-cause death was found across the quartiles (all p<0.001). The final Cox multivariable regression analysis showed an association with increasing risk for major bleeding occurrence in Q3 and Q4 (hazard ratio (HR):1.69, 95%CI:1.00-2.87 and HR:1.92, 95%CI:1.08-3.41). An increasing risk for all-cause death and CV death was found across CCI quartiles.

	Conclusions In a nationwide contemporary cohort of AF anticoagulated patients, multimorbidity was inversely associated with good anticoagulation control. A progressively higher risk for major bleeding, CV death and all-cause death was found across CCI quartiles.
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Response to Reviewers:	

UNIVERSITÀ DEGLI STUDI DI MILANO

Istituti Clinici Scientifici Maugeri

Milan, 15th June 2021

To Hélio José Coelho Júnior

To Emanuele Marzetti

Guest Editors

Experimental Gerontology

Dear Prof. Ouslander

RE: **Relationship between Multimorbidity and Outcomes in Atrial Fibrillation**

We are pleased to enclose this paper presenting a secondary analysis derived from the FANTASIIA ('Fibrilación Auricular: influencia del Nivel y Tipo de Anticoagulación Sobre la Incidencia de Ictus y Accidentes hemorrágicos') registry. The FANTASIIA registry is a prospective renown nationwide contemporary registry of Spanish AF patients. Notably, despite being an observational study, in this registry the outcomes were centrally adjudicated.

In this paper we examined the relationship between multimorbidity, defined using the Charlson Comorbidity Index (CCI), and AF. In this large cohort prospective cohort, we found that an increased multimorbidity is quite common in AF. A higher CCI was inversely associated with a lower time in therapeutic range (TTR), with patients with the highest multimorbidity with a significantly lower chance of obtaining an optimal anticoagulation control (TTR ≥70%). Over a long-term observation, an increased burden of multimorbidity is independently associated with an increased risk of major bleeding, cardiovascular death and all-cause death. In particular a progressively higher CCI was associated with a progressively higher risk of all-cause death.

In the light of clinical impact of the results described in this paper, we believe that this could be of great interest to the readers of **JAGS.**

We confirm the following: 1) the paper is not under consideration elsewhere, 2) none of the paper's contents have been previously published, 3) all authors had access to all the study data, take responsibility for the accuracy of the analysis, had authority over manuscript preparation and the decision to submit the manuscript for publication and 4) have read and approved the manuscript; 4) the full disclosure of any potential conflict of interest has been made.

Yours sincerely

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Proietti et al. Relationship between Multimorbidity and Outcomes in Atrial Fibrillation
[EXG-D-21-00511-R1]

REVIEWER COMMENTS

Reviewer #1

The article presented by Proietti et al. explored the association between multimorbidity, expressed as CCI, anticoagulation control and outcomes in AF patients in a observational Spanish nationwide registry.
The Authors found that a higher CCI was associated with a higher thromboembolic and bleeding risk and accordingly with a higher risk of adverse events. Interestingly, they found that CCI was inversely associated with optimal quality of anticoagulation control in patients treated with VKA.

Overall, the article is interesting and well written. The manuscript is well structured and the information provided is clear and concise. Statistical analysis sounds. The main limitation of the study, as correctly reported by the Authors, is related to the observational design.

I have the following minor comments:

-It is known that the use of different VKAs may be variable among countries, with acenocumarol being more commonly used in Spain. Do the Authors think that the use of acenocoumarol instead of warfarin could have partially influenced the results? Please add some comments regarding this issue in the discussion.
>>>REPLY: We thank the reviewer for this comment. We have added about this in the Discussion section (Page 16, Lines 11-19).

-The majority of the patients (75.8%) were treated with a VKA thus limiting the generalization of the results. Please add some comments in the limitation section.
>>>REPLY: We added about this in the limitations section (Page 18, Line 24).

Reviewer #2

The study addressed a clinically relevant topic. The findings are mostly confined to AF patients taking VKAs, thus suggesting that multi morbid AF patients could do better on NOACs
The main study limitations are properly highlighted by the Authors.
The list of references needs to be updated (eg, more recent 2020 ESC AF Guidelines, etc)
>>>REPLY: Many thanks for this comment. We have updated our reference list.

Figure 1

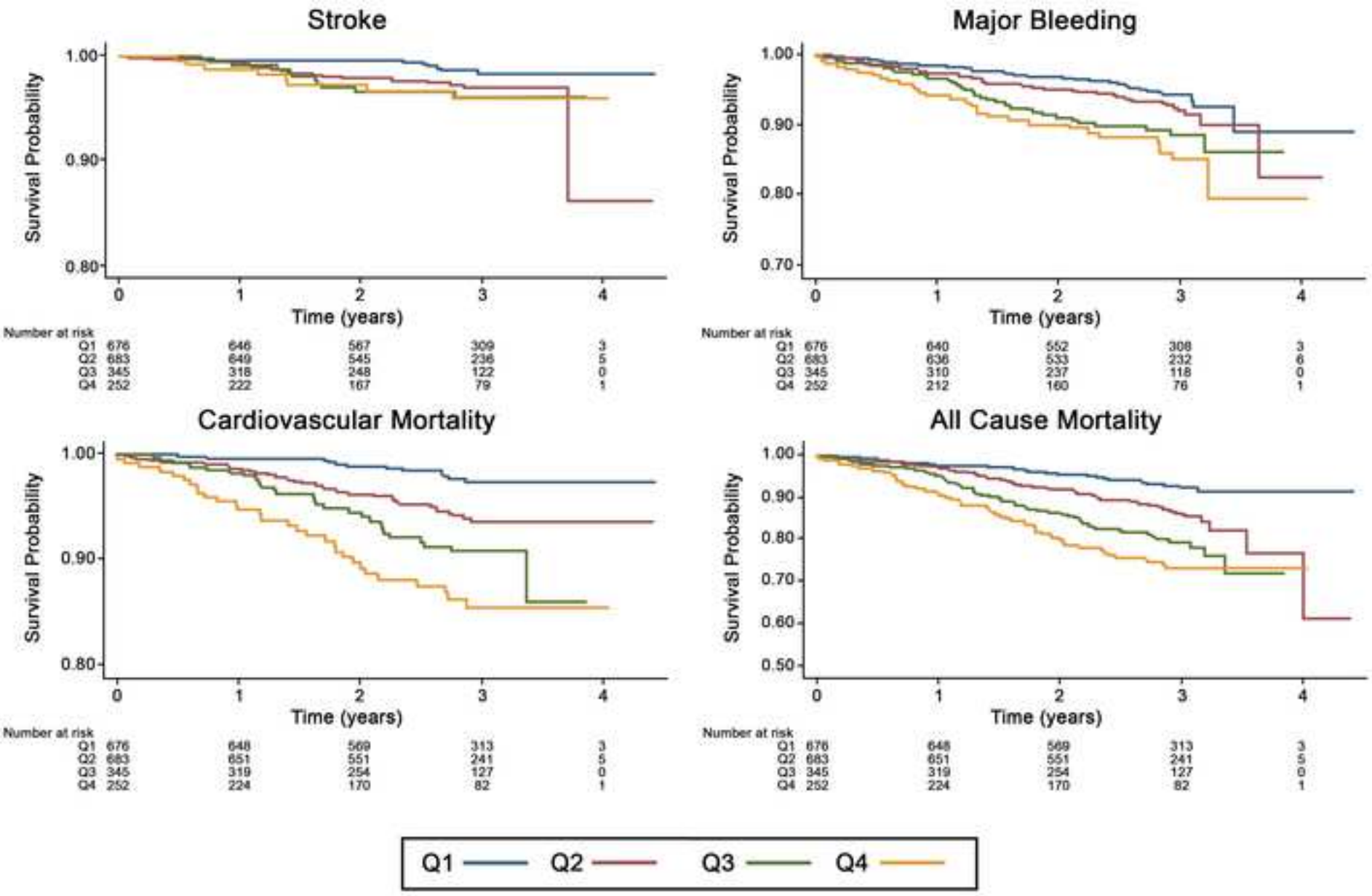
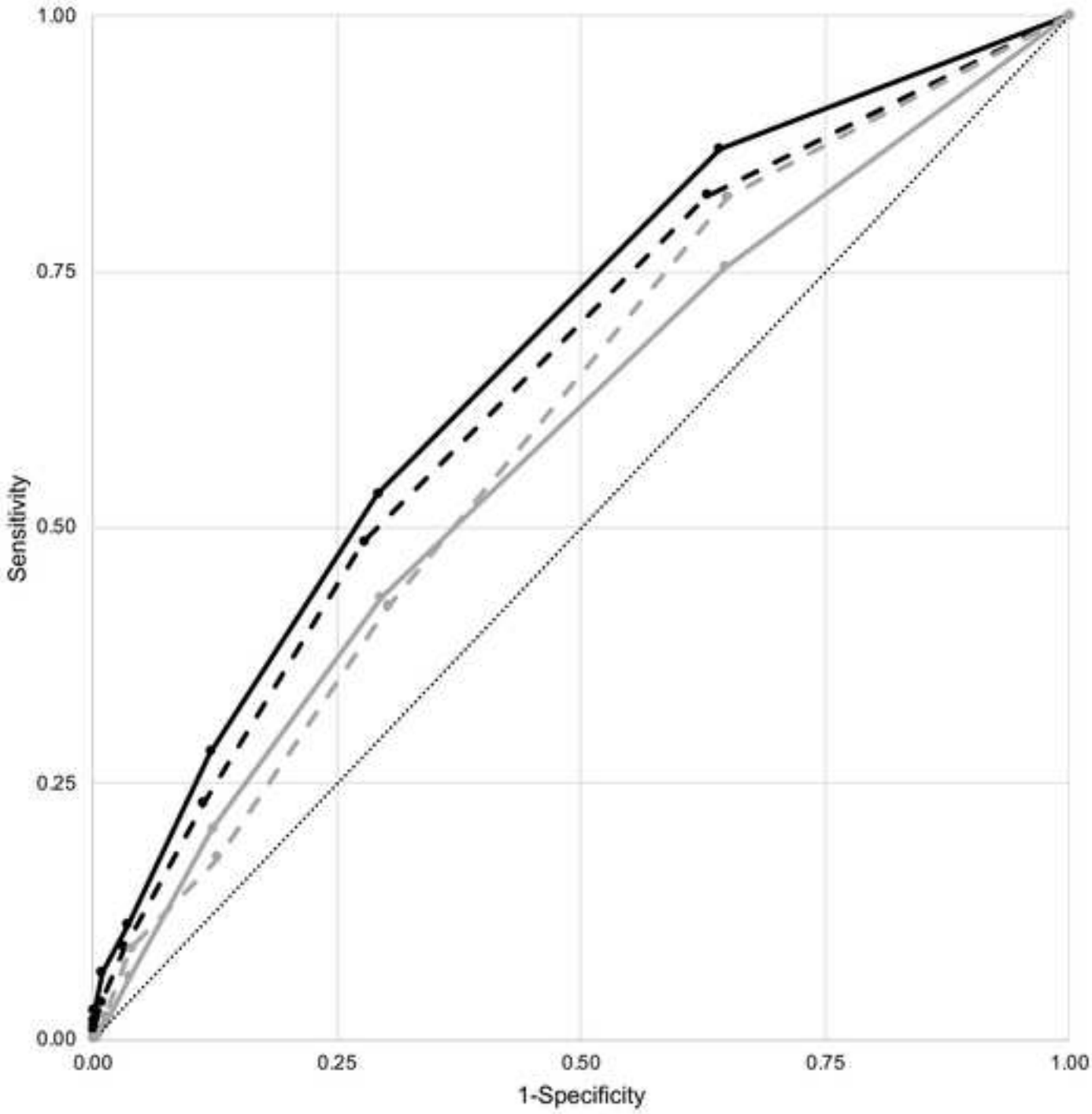


Figure 2



Relationship between Multimorbidity and Outcomes in Atrial Fibrillation

Running Title: Multimorbidity in AF Patients

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†The FANTASIIA investigators are reported in Supplementary Appendix.

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ABSTRACT

Background: Multimorbidity is common in atrial fibrillation (AF) patients. Charlson comorbidity index (CCI) is used to evaluate multimorbidity in the general population. Limited long-term data are available on the relationship between CCI and AF. We examined the association between CCI, anticoagulation control and outcomes in AF patients.

Methods: We studied 1956 from the FANTASIIA registry, an observational Spanish nationwide study on anticoagulated AF patients. Time in therapeutic range (TTR) was used to evaluate anticoagulation control. Stroke/TIA, major bleeding, cardiovascular (CV) death and all-cause death were study outcomes.

Results: Mean±SD CCI was 1.1±1.2. Based on CCI quartiles, patients were categorised in four groups: 676 (34.6%) in Q1 (CCI 0); 683 (34.9%) in Q2 (CCI 1); 345 (17.6%) in Q3 (CCI 2); and 252 (12.9%) in Q4 (CCI ≥3). In vitamin K antagonist treated patients, the highest CCI quartile was inversely associated with TTR >70% (odds ratio:0.67, 95% confidence interval (CI):0.45-0.99). During observation, a progressively higher rate of major bleeding, CV death and all-cause death was found across the quartiles (all p<0.001). The final Cox multivariable regression analysis showed an association with increasing risk for major bleeding occurrence in Q3 and Q4 (hazard ratio (HR):1.69, 95%CI:1.00-2.87 and HR:1.92, 95%CI:1.08-3.41). An increasing risk for all-cause death and CV death was found across CCI quartiles.

Conclusions: In a nationwide contemporary cohort of AF anticoagulated patients, multimorbidity was inversely associated with good anticoagulation control. A progressively higher risk for major bleeding, CV death and all-cause death was found across CCI quartiles.

Keywords: atrial fibrillation; charlson comorbidity index; multimorbidity; oral anticoagulation control; outcomes.

INTRODUCTION

Multimorbidity represents one of the most complex and relevant current worldwide health issues (National Institute for Health and Care Excellence, 2017). A steady increase in worldwide population age has influenced the increase in multimorbidity burden(National Institute for Health and Care Excellence, 2017), which negatively affects subjects' health status and risk of adverse outcomes, in particular all-cause death, especially in older adults(National Institute for Health and Care Excellence, 2017). Multimorbidity can be evaluated according to various tools, as the mere count of disease or according to weighted scales, as the Charlson Comorbidity Index (CCI) (Charlson et al., 1987). Multimorbidity also significantly affects patients with cardiovascular disease, particularly the elderly, increasing the overall risk of death and demanding specific multidisciplinary approaches(Rashid et al., 2016).

Patients with atrial fibrillation (AF) are known to be affected by several concomitant conditions, affecting morbidity and mortality(Fauchier et al., 2016; Proietti et al., 2018a). Nevertheless, data about the relationship between AF and multimorbidity are limited and heterogeneous(Alexander et al., 2019; Jani et al., 2018; Vanbeselaere et al., 2016). In a recent analysis derived from a large population-based cohort study, a direct relationship was established between AF and increasing multimorbidity, evaluated with a modified ICD-9 codes based version of CCI, also showing a relationship between CCI and adverse outcomes(Proietti et al., 2019).

This study aimed to analyse the impact of an evaluated CCI on the quality of oral anticoagulant (OAC) therapy and secondly, on the risk of adverse outcomes. We performed an ancillary post-hoc analysis of the FANTASIIA (Spanish acronym for

'Fibrilación Auricular: influencia del Nivel y Tipo de Anticoagulación Sobre la Incidencia de Ictus y Accidentes hemorrágicos') registry, a nationwide observational contemporary cohort of AF patients.

METHODS

The FANTASIIA registry is a Spanish observational, prospective, nationwide, multicentre study of clinical and demographic characteristics of Spanish AF patients. The complete study design has been described in detail elsewhere(Bertomeu-González et al., 2015). Briefly, the main objective was to assess the incidence of thromboembolic and bleeding events in an unselected population of patients with AF, specifically analysing the impact of various OAC treatment regimens. Enrolment procedures were undertaken between June 2013 and March 2014, including all outpatients with a confirmed diagnosis of paroxysmal, persistent or permanent AF. All patients included in the registry were treated with an OAC for at least 6 months before enrolment.

The study was conducted in 50 outpatient clinics by 80 investigators. By design, each investigator included 16 patients taking vitamin K antagonist (VKA) therapy and 4 patients who were taking non-VKAs OACs (NOACs) treatment (proportion 4:1). Patients with valvular heart disease (rheumatic valve disease, moderate-severe valve disease and prosthesis or valve repair surgery), younger than 18 years or with recent hospital admission were excluded. All patients provided signed informed consent. The study was conducted according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the Clinical Research Ethics Committee at Hospital Universitario de San Juan

(Spain) with the approval number 12/220 and by the Spanish Agency of Medicine and Health Products as a prospective follow-up post-authorization study with the approval number SEC-ACO-2012–01.

Evaluation of CCI

CCI was collected at baseline in the FANTASIIA case report form, according to its original version as validated by Charlson and colleagues(Charlson et al., 1987). Briefly, CCI uses a system of relative weights to evaluate the impact of a list of chronic conditions on mortality risk, based on the evaluation of 17 chronic conditions, which receive specific relative weights, as follows:

i) myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic obstructive pulmonary disease, connective tissue disease, ulcer disease and mild liver disease is given a relative weight of 1 each;

ii) hemiplegia, moderate/severe renal disease, diabetes mellitus, presence of any kind of neoplastic disease, leukemia and lymphoma has a relative weight of 2 each;

iii) moderate/severe liver disease has a relative weight of 3;

iv) the presence of a metastatic solid neoplasm has a relative weight of 6.

The final CCI of each patient is derived by the arithmetic sum of each weight corresponding to the chronic conditions present for each patient. In order to provide a clinical meaningful message, we evaluated the impact of CCI on the quality of anticoagulation control and adverse outcomes both in its continuous form and categorized according to quartiles.

Quality of Anticoagulation Control

Quality of anticoagulation control at baseline was evaluated according to time in therapeutic range (TTR) as recommended by international guidelines(Hindricks et al., 2021). TTR was calculated using the standardized Rosendaal interpolation method(Rosendaal et al., 1993), by assigning an international normalized range (INR) value to each day between two successive observed INR values, based on monthly INR measured in the 6 months before the enrolment. The percentage of time that the interpolated INR remains between 2 and 3 is used to establish the TTR value, and the cut-off value for defining optimal anticoagulation was a mean individual TTR of ≥70%(Hindricks et al., 2021).

Thromboembolic and Bleeding Risk Evaluation

Baseline thromboembolic and bleeding risk were evaluated according to CHA_2DS_2-VASc(Lip et al., 2010) and HAS-BLED(Pisters et al., 2010) scores.

The CHA_2DS_2-VASc score is calculated as follows: i) history of congestive heart failure, hypertension, diabetes mellitus, myocardial infarction/peripheral vascular disease, age 65-74 years and female sex, are scored 1 point; ii) history of stroke/transient ischemic attack and age ≥75 years are scored 2 points. The HAS-BLED score is calculated as follows: uncontrolled hypertension, impaired renal function, impaired liver function, history of stroke, history of bleeding, labile quality of anticoagulation therapy, age >65 years, concomitant use of antiplatelet or non-steroidal anti-inflammatory drugs and concomitant assumption of alcohol (≥8 alcohol units) are all scored 1 point. Final scores are calculated by summing all the points for each patient.

Adverse Outcomes

The FANTASIIA registry used a centralized external event assignment committee to evaluate all adverse outcomes. Thromboembolic events were defined as stroke or transient ischemic attack (TIA) and peripheral artery embolism. All strokes were evaluated by computed tomographic scan or magnetic resonance imaging according to the neurologist criteria. Bleeding events were assessed according to the 2005 International Society of Thrombosis and Haemostasis criteria fatal bleeding or symptomatic bleeding in a critical anatomical site (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial or intramuscular with compartment syndrome) and/or bleeding causing a fall in Hb ≥20 g/L, or transfusion of ≥2 units of packed red blood cells. We also recorded all-cause death and cardiovascular (CV) mortality, with the latter defined if it was secondary to a CV event (acute coronary syndrome, heart failure, lethal arrhythmia or sudden death, artery aneurysm rupture or stroke). In this study aims we evaluated the main study outcomes as follows: i) stroke/TIA; ii) major bleeding; iii) CV death; iv) all-cause death.

Patients Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Statistical Analysis

Normal distribution of continuous variables was tested with the Kolmogorov-Smirnov method. Continuous variables are presented using the mean standard deviation or median (interquartile range [IQR]). Categorical variables are expressed as percentages. For between-group comparisons, we used the Analysis of Variance (ANOVA) test for continuous variables and post hoc test for intergroup differences with Tukey's test. We used the Chi-square test for qualitative variables.

A logistic regression analysis, adjusted for type of AF and CHA_2DS_2-VASc score, was performed to analyse the impact of CCI on prescription of antiplatelet drugs and type of OAC. To evaluate the impact of CCI on the quality of anticoagulation control, we performed a linear regression analysis, with TTR as a continuous dependent variable, and a logistic regression analysis, with TTR ≥70% as a categorical dependent variable. In order to obtain a more solid estimate of the impact of CCI, we compiled two different multivariable models: Model 1) adjusted for type of AF and CHA_2DS_2-VASc score; Model 2) with a larger set of covariates, adjusted for type of AF, CHA_2DS_2-VASc score, body mass index, glomerular filtration rate, smoking habit, excessive alcohol, antiplatelet drugs.

Differences in event-free survival, according to CCI quartiles, were examined with log-rank test and Kaplan–Meier curves were drafted accordingly. A Cox regression analysis was performed to evaluate the association between CCI and CCI quartiles with the occurrence of adverse outcomes. In order to obtain a more solid estimate of the impact of CCI, we compiled two different multivariable models: Model 1) adjusted for type of AF and CHA_2DS_2-VASc score; Model 2) with a larger set of covariates, adjusted for type of AF, CHA_2DS_2-VASc score, body mass index, glomerular filtration

rate, smoking habit, excessive alcohol, antiplatelet drugs. A receiver-operating-characteristic curve was drafted to evaluate the predictive ability of continuous CCI about the occurrence of adverse outcomes. Reporting of the study conforms to broad EQUATOR guidelines(Simera et al., 2010). Statistical significance was defined as $p<0.05$. Statistical analyses were performed with SPSS statistical package version 22.0 for Windows (SPSS Inc, Chicago, Illinois, United States).

RESULTS

We included 1956 patients (mean age 73.8 years; 44.5% female), with a mean (SD) CCI 1.14 (1.16) and a median [IQR] CCI 1 [0-2]. The distribution of CCI in the study population is reported in Figure S1. Based on CCI quartiles, patients were categorised in four groups: 676 (34.6%) patients in Q1 (CCI 0); 683 (34.9%) in Q2 (CCI 1); 345 (17.6%) in Q3 (CCI 2); and 252 (12.9%) in Q4 (CCI ≥3). Baseline characteristics according to CCI quartiles were summarised in Table 1. The proportion of female sex was progressively lower across the quartiles, while the prevalence of permanent AF increased accordingly, being highest in Q3 and Q4. Moreover, body mass index (BMI) was significantly lower in patients included in the Q1 ($p<0.001$). Overall, 75.8% (1483) of patients were treated with a VKA with the remaining 24.2% (473) treated with NOACs.

The proportions of patients treated with a VKA were numerically higher with increasing quartiles, even though not statistically different. Conversely, the proportion of patients concomitantly treated with an antiplatelet drug was progressively higher, up to 1 out of 5 in Q4.

Based on CCI quartiles, the mean CHA_2DS_2-VASc score was progressively higher ($p<0.001$), as well as the proportion with CHA_2DS_2-VASc ≥2 ($p<0.001$), with almost all patients in Q4 reporting a high thromboembolic risk [Table 1]. Similarly, the HAS-BLED score increased across the quartiles ($p<0.001$) with the proportion of high bleeding risk (HAS-BLED ≥3) increasing up to 50% of patients in Q4 ($p<0.001$) [Table 1].

Quality of Anticoagulation Control

In patients treated with VKA, patients in CCI Q4 had the lowest mean TTR compared to other quartiles (Table 2). Furthermore, the prevalence of patients with an optimal quality of anticoagulation control was the lowest in Q4 patients (Table 2).

Linear regression analysis, both for Model 1 and the fully adjusted Model 2, established an inverse relationship of CCL Q4 with continuous TTR. Similarly, the adjusted logistic regression analysis, both for Model 1 and the fully adjusted Model 2, showed an inverse relationship between the highest CCI quartile and optimal control of VKA therapy (Table 2).

Outcomes and CCI

We analysed the occurrence of outcomes according to CCI, over a median (IQR) follow-up of 1070 (750–1110) days. While no difference was found regarding the rates of stroke across the quartiles, progressively higher rates of major bleeding, CV death and all-cause death was evident from Q1 to Q4 (Table 2). Kaplan-Meier curves analysis [Figure 1], reported that while the survival probability across the quartiles for stroke was only marginally different (p=0.055), a proportionally lower survival probability across the quartiles was found for major bleeding, CV death and all-cause death (p<0.001 for all the three outcomes).

The Cox regression analysis (Table 3), adjusted for Model 1, showed that the highest CCI quartile (Q4) had an independently higher risk of major bleeding and CV death, while a progressively higher risk was found across the CCI quartiles for all-cause death. CCI as a continuous variable was associated with an independent

increased risk for major bleeding, CV death and all-cause death (Table 3). When performing the final fully adjusted multivariable Model 2, we found an increasing higher risk for major bleeding in CCI Q3 and Q4; moreover, we found a progressively higher risk for both CV death and all-cause death occurrence across the CCI quartiles (Table 3). The relationship between continuous CCI and the risk for major bleeding, CV death and all-cause death remained unaltered in Model 2 analysis (Table 3).

Prediction of Adverse Outcomes

A receiver-operating-characteristic curve analysis was performed to establish the predictive ability of CCI regarding the occurrence of adverse outcomes [Figure 2]. CCI showed a modest predictive ability for stroke and major bleeding. Further, CCI showed a modest-to-good predictive ability for both CV death and all-cause death [see Figure 3 and Figure's Legend].

DISCUSSION

In this study we found that a higher CCI was associated with a higher thromboembolic and bleeding risk. Second, the highest burden of multimorbidity (evident by the highest CCI) was inversely associated with optimal quality of anticoagulation control amongst patients treated with VKAs. Third, high multimorbidity was independently associated with the risk of major bleeding, CV death, and all-cause death, increasing progressively with the increasing CCI quartiles. Also, a 'dose-response' like effect was found between the continuous CCI and the risk of major bleeding, CV death and all-cause death. Finally, CCI was predictive of the occurrence of all the adverse outcomes, particularly for CV death and all-cause death.

Thus far, there is limited evidence regarding the relationship between multimorbidity and AF in the literature. In a Belgian study derived from a primary care registry, a modified version of the CCI was found higher in AF elderly (≥60 years) patients than in non-AF ones, also being associated with AF diagnosis(Vanbeselaere et al., 2016). A recent study derived from the UK Biobank, in a cohort of patients with self-reported AF which examined the presence of multimorbidity, found only 19.6% of patients reported no comorbidities and 11.1% of patients reported 4 or more comorbidities(Jani et al., 2018). In a study derived from a large population-based registry based on ICD-9 codes, AF was associated with a higher burden of multimorbidity (evaluated with a modified version of CCI)(Proietti et al., 2019). In our study, we provided the first evidence that a properly recorded CCI, based in its original form(Charlson et al., 1987), was significantly associated with poorer quality

of anticoagulation control and risk of adverse outcomes in a nationwide representative cohort of AF patients.

These results extend previous evidence regarding the impact of multimorbidity and the use of OAC. To date, available data document how patients with a higher burden of multimorbidity have a lower chance of being prescribed OAC(Proietti et al., 2019; Vanbeselaere et al., 2016). We were also able to determine that even in a cohort of anticoagulated AF patients, managed in highly experienced centres, those patients with the highest degree of multimorbidity were those more likely to have suboptimal anticoagulation control, which is a major determinant of adverse outcomes in VKA treated patients(Hindricks et al., 2021). Despite not being directly related to multimorbidity, we should consider that the presented cohort is entirely treated with acenocumarol, which is the more largely used VKA drugs in Spain(Esteve-Pastor et al., 2018; Le Heuzey et al., 2014). Hence, some reports underlined how obtaining a good control of quality of anticoagulant therapy could be more difficult with acenocumarol or in countries using prevalently acenocumarol(Le Heuzey et al., 2014; Menichelli et al., 2021). This aspect could have generally influenced the level of TTR, which was already described as quite low in our cohort(Roldán Rabadán et al., 2018).

Furthermore, our follow-up analysis shows the negative impact of multimorbidity on the risk of adverse clinical outcomes. The Framingham Heart Study previously showed that AF patients with comorbidities have a consistently increased risk for cardiovascular events and all-cause death compared to those without(Kim et al., 2016). An analysis from the “Outcomes Registry for Better Informed Treatment of

Atrial Fibrillation" study showed that when AF patients were clustered according to the more frequent clinical characteristics, those in the 'low-comorbidity' cluster had the lowest risk of major cardiovascular and neurological adverse events compared to all the other identified clusters, variously affected by risk factors and other comorbidities(Inohara et al., 2018). Lastly, in a recent analysis performed in the "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation" trial, multimorbidity was found associated with an increased risk of adverse outcomes(Alexander et al., 2019). Notwithstanding, in that study, the evaluation of multimorbidity was performed by the simple count of diseases, while several studies demonstrated that evaluation of multimorbidity should be performed by specific tools, that could better represent the clinical complexity(Corrao et al., 2019).

More recently, a time-dependent CCI, even though evaluated according to ICD-9 codes, was associated with the occurrence of stroke, major bleeding and all-cause death(Proietti et al., 2019). The evidence provided by the current study strengthens and extends the data regarding the association of multimorbidity and outcomes in AF patients. Indeed, the baseline collection of CCI and the centralized adjudication of events provides even greater strength to prior analyses that were mostly retrospective and based on the simple count of diseases or retrospective evaluation of CCI(Proietti et al., 2019; Vanbeselaere et al., 2016). Moreover, we also confirmed the prognostic association of CCI in a shorter follow-up, while a previous study analysing the impact of CCI on outcomes was based on a longer follow-up(Proietti et al., 2019). Further, we also assessed the association of CCI and CV death, extending previous data about other cardiovascular diseases(Rashid et al., 2016).

The use of a final larger fully adjusted multivariable model further strengthen our findings, showing a dose-response effect for all the outcomes also across the CCI quartiles, entailing a relevant clinical impact. Of note, we also tested the predictive ability of CCI in respect of clinical outcomes, providing evidence of a modest predictive ability for CV death and all-cause death. It is important to underline that a similar predictive ability was found for most of the scores usually used in the AF context(Borre et al., 2018).

Our results underline how important it is to evaluate the multimorbidity burden in AF patients. Indeed, a clinical management strategy entailing a more holistic and comprehensive approach for AF patients, the Atrial Fibrillation Better Care pathway has been proposed, emphasising the proactive management of comorbidities(Proietti et al., 2018b; Romiti et al., 2021). Indeed, clinical management adherent to the Atrial Fibrillation Better Care pathway showed a significant reduction of risk of most adverse outcomes(Proietti et al., 2018b; Romiti et al., 2021; Yoon et al., 2019). Thus, we may hypothesize that those patients with a higher burden of multimorbidity would benefit more from a multifaceted approach as suggested by holistic or integrated care management(Kotecha et al., 2018).

Limitations

The main limitation of the study is clearly due to the observational design, which was also not designed to evaluate the subgroups examined in this study. This aspect could limit the generalizability, together with the Spanish origin of the patients included in the study and the exclusive use of acenocumarol as VKA drug.

In conclusion, in this nationwide contemporary cohort of anticoagulated patients with non-valvular AF, multimorbidity was inversely associated with good anticoagulation control. A progressively higher risk for major bleeding, CV death and all-cause death occurrence was found associated to increasing CCI quartiles.

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CONFLICTS OF INTEREST

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REFERENCES

Alexander, K.P., Brouwer, M.A., Mulder, H., Vinereanu, D., Lopes, R.D., Proietti, M., Al-Khatib, S.M., Hijazi, Z., Halvorsen, S., Hylek, E.M., Verheugt, F.W.A., Alexander, J.H., Wallentin, L., Granger, C.B., 2019. Outcomes of apixaban versus warfarin in patients with atrial fibrillation and multi-morbidity: Insights from the ARISTOTLE trial. Am. Heart J. 208, 123–131. https://doi.org/10.1016/j.ahj.2018.09.017

Bertomeu-González, V., Anguita, M., Moreno-Arribas, J., Cequier, Á., Muñiz, J., Castillo-Castillo, J., Sanchis, J., Roldán, I., Marin, F., Bertomeu-Martínez, V., FANTASIIA Study Investigators, 2015. Quality of Anticoagulation With Vitamin K Antagonists. Clin. Cardiol. 38, 357–64. https://doi.org/10.1002/clc.22397

Borre, E.D., Goode, A., Raitz, G., Shah, B., Lowenstern, A., Chatterjee, R., Sharan, L., Allen LaPointe, N.M., Yapa, R., Davis, J.K., Lallinger, K., Schmidt, R., Kosinski, A., Al-Khatib, S.M., Sanders, G.D., 2018. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. Thromb. Haemost. 118, 2171–2187. https://doi.org/10.1055/s-0038-1675400

Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. 40, 373–83.

Corrao, S., Natoli, G., Nobili, A., Mannucci, P.M., Pietrangelo, A., Perticone, F., Argano, C., 2019. Comorbidity does not mean clinical complexity: evidence from the RePoSI register. Intern. Emerg. Med. https://doi.org/10.1007/s11739-019-02211-3

Esteve-Pastor, M.A., Rivera-Caravaca, J.M., Roldán-Rabadán, I., Roldán, V., Muñiz,

J., Raña-Míguez, P., Ruiz-Ortiz, M., Cequier, Á., Bertomeu-Martínez, V., Badimón, L., Anguita, M., Lip, G.Y.H., Marín, F., 2018. Quality of oral anticoagulation with Vitamin K antagonists in “real-world” patients with atrial fibrillation: A report from the prospective multicentre FANTASIIA registry. Europace 20, 1435–1441. https://doi.org/10.1093/europace/eux314

Fauchier, L., Villejoubert, O., Clementy, N., Bernard, A., Pierre, B., Angoulvant, D., Ivanes, F., Babuty, D., Lip, G.Y.H., 2016. Causes of Death and Influencing Factors in Patients with Atrial Fibrillation. Am. J. Med. 129, 1278–1287. https://doi.org/10.1016/j.amjmed.2016.06.045

Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J.J., Blomström-Lundqvist, C., Boriani, G., Castella, M., Dan, G.-A., Dilaveris, P.E., Fauchier, L., Filippatos, G., Kalman, J.M., La Meir, M., Lane, D.A., Lebeau, J.-P., Lettino, M., Lip, G.Y.H., Pinto, F.J., Thomas, G.N., Valgimigli, M., Van Gelder, I.C., Van Putte, B.P., Watkins, C.L., ESC Scientific Document Group, 2021. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur. Heart J. 42, 373–498. https://doi.org/10.1093/eurheartj/ehaa612

Inohara, T., Shrader, P., Pieper, K., Blanco, R.G., Thomas, L., Singer, D.E., Freeman, J. V, Allen, L.A., Fonarow, G.C., Gersh, B., Ezekowitz, M.D., Kowey, P.R., Reiffel, J.A., Naccarelli, G. V, Chan, P.S., Steinberg, B.A., Peterson, E.D., Piccini, J.P., 2018. Association of of Atrial Fibrillation Clinical Phenotypes With Treatment Patterns and Outcomes: A Multicenter Registry Study. JAMA Cardiol. 3, 54–63. https://doi.org/10.1001/jamacardio.2017.4665

Jani, B.D., Nicholl, B.I., McQueenie, R., Connelly, D.T., Hanlon, P., Gallacher, K.I., Lee, D., Mair, F.S., 2018. Multimorbidity and co-morbidity in atrial fibrillation and

effects on survival: findings from UK Biobank cohort. Europace 20, f329–f336. https://doi.org/10.1093/europace/eux322

Kim, E.-J., Yin, X., Fontes, J.D., Magnani, J.W., Lubitz, S.A., McManus, D.D., Seshadri, S., Vasan, R.S., Ellinor, P.T., Larson, M.G., Benjamin, E.J., Rienstra, M., 2016. Atrial fibrillation without comorbidities: Prevalence, incidence and prognosis (from the Framingham Heart Study). Am. Heart J. 177, 138–44. https://doi.org/10.1016/j.ahj.2016.03.023

Kotecha, D., Breithardt, G., Camm, A.J., Lip, G.Y.H., Schotten, U., Ahlsson, A., Arnar, D., Atar, D., Auricchio, A., Bax, J., Benussi, S., Blomstrom-Lundqvist, C., Borggrefe, M., Boriani, G., Brandes, A., Calkins, H., Casadei, B., Castellá, M., Chua, W., Crijns, H., Dobrev, D., Fabritz, L., Feuring, M., Freedman, B., Gerth, A., Goette, A., Guasch, E., Haase, D., Hatem, S., Haeusler, K.G., Heidbuchel, H., Hendriks, J., Hunter, C., Kääb, S., Kespohl, S., Landmesser, U., Lane, D.A., Lewalter, T., Mont, L., Nabauer, M., Nielsen, J.C., Oeff, M., Oldgren, J., Oto, A., Pison, L., Potpara, T., Ravens, U., Richard-Lordereau, I., Rienstra, M., Savelieva, I., Schnabel, R., Sinner, M.F., Sommer, P., Themistoclakis, S., Van Gelder, I.C., Vardas, P.E., Verma, A., Wakili, R., Weber, E., Werring, D., Willems, S., Ziegler, A., Hindricks, G., Kirchhof, P., 2018. Integrating new approaches to atrial fibrillation management: The 6th AFNET/EHRA Consensus Conference. Europace 20, 395–407. https://doi.org/10.1093/europace/eux318

Le Heuzey, J.Y., Ammentorp, B., Darius, H., De Caterina, R., Schilling, R.J., Schmitt, J., Zamorano, J.L., Kirchhof, P., 2014. Differences among western European countries in anticoagulation management of atrial fibrillation: Data from the PREFER IN AF Registry. Thromb. Haemost. 111, 833–841. https://doi.org/10.1160/TH13-12-1007

Lip, G.Y.H., Nieuwlaat, R., Pisters, R., Lane, D.A., Crijns, H.J.G.M., 2010. 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 137, 263–72. https://doi.org/10.1378/chest.09-1584

Menichelli, D., Poli, D., Antonucci, E., Cammisotto, V., Testa, S., Pignatelli, P., Palareti, G., Pastori, D., Paoletti, O., Lodigiani, C., Ferrazzi, P., Quaglia, I., Coffetti, N., Marotta, R., Brusegan, V., Bergamelli, O., Serricchio, G., Sarpau, S., Brevi, F., Falco, P., Silverio, G., Mangione, C., Bellomo, G., Masottini, S., Cosenza, A., Ruocco, L., Chiarugi, P., Casini, M., Cafolla, A., Ferretti, A., Micucci, G., Rupoli, S., Canafoglia, L., Pedico, P., Galasso, R., Rotunno, R., Insana, A., Valesella, P., Santoro, A., Marongiu, F., Barcellona, D., Pengo, V., Denas, G., Paparo, C., Bucherini, E., Tani, F., Carioli, E., Violi, F., Saliola, M., Masciocco, L., Saracino, P., Benvenuto, A., Turrini, A., Ciaffone, S., Toma, A., Barbera, P., Gresele, P., Fierro, T., Pasquino, S., La Rosa, L., Morales, R., Ronchi, F., Isu, G., Lerede, T., Barcella, L., Ria, L., Crisantemo, R., Suriano, L., Lorusso, L., De Sarlo, M., Carrato, P., Oricchio, C., Grandone, E., Colaizzo, D., Molinatti, M., 2021. Comparison of anticoagulation quality between acenocoumarol and warfarin in patients with mechanical prosthetic heart valves: Insights from the nationwide PLECTRUM study. Molecules 26, 1425. https://doi.org/10.3390/molecules26051425

National Institute for Health and Care Excellence, 2017. Multimorbidity Overview. London.

Pisters, R., Lane, D.A., Nieuwlaat, R., de Vos, C.B., Crijns, H.J.G.M., Lip, G.Y.H., 2010. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 138,

1093–100. https://doi.org/10.1378/chest.10-0134

Proietti, M., Laroche, C., Nieuwlaat, R., Crijns, H.J.G.M., Maggioni, A.P., Lane, D.A., Boriani, G., Lip, G.Y.H., 2018a. 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. 55, 28–34. https://doi.org/10.1016/j.ejim.2018.05.016

Proietti, M., Marzona, I., Vannini, T., Tettamanti, M., Fortino, I., Merlino, L., Basili, S., Mannucci, P.M., Boriani, G., Lip, G.Y.H., Roncaglioni, M.C., Nobili, A., 2019. Long-Term Relationship Between Atrial Fibrillation, Multimorbidity and Oral Anticoagulant Drug Use. Mayo Clin. Proc. 94, 2427–2436. https://doi.org/10.1016/j.mayocp.2019.06.012

Proietti, M., Romiti, G.F., Olshansky, B., Lane, D.A., Lip, G.Y.H., 2018b. Improved Outcomes by Integrated Care of Anticoagulated Patients with Atrial Fibrillation Using the Simple ABC (Atrial Fibrillation Better Care) Pathway. Am. J. Med. 131, 1359-1366.e6. https://doi.org/10.1016/j.amjmed.2018.06.012

Rashid, M., Kwok, C.S., Gale, C.P., Doherty, P., Olier, I., Sperrin, M., Kontopantelis, E., Peat, G., Mamas, M.A., 2016. 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 3, 20–36. https://doi.org/10.1093/ehjqcco/qcw025

Roldán Rabadán, I., Esteve-Pastor, M.A., Anguita-Sánchez, M., Muñiz, J., Camacho Siles, J., Quesada, M.A., Ruiz Ortiz, M., Marín, F., Martínez Sellés, M., Bertomeu, V., Lip, G.Y.H., Cequier Fillat, A., Badimón, L., 2018. Relation of quality of anticoagulation control with different management systems among patients with atrial fibrillation: Data from FANTASIIA Registry. Eur. J. Clin.

Invest. 48, e12910. https://doi.org/10.1111/eci.12910

Romiti, G.F., Pastori, D., Rivera-Caravaca, J.M., Ding, W.Y., Gue, Y.X., Menichelli, D., Gumprecht, J., Kozieł, M., Yang, P.-S., Guo, Y., Lip, G.Y.H., Proietti, M., 2021. Adherence to the 'Atrial Fibrillation Better Care' Pathway in Patients with Atrial Fibrillation: Impact on Clinical Outcomes—A Systematic Review and Meta-Analysis of 285,000 Patients. Thromb. Haemost. https://doi.org/10.1055/a-1515-9630

Rosendaal, F.R., Cannegieter, S.C., van der Meer, F.J., Briët, E., 1993. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb. Haemost. 69, 236–9.

Simera, I., Moher, D., Hoey, J., Schulz, K.F., Altman, D.G., 2010. A catalogue of reporting guidelines for health research. Eur. J. Clin. Invest. 40, 35–53. https://doi.org/10.1111/j.1365-2362.2009.02234.x

Vanbeselaere, V., Truyers, C., Elli, S., Buntinx, F., De Witte, H., Degryse, J., Henrard, S., Vaes, B., 2016. Association between atrial fibrillation, anticoagulation, risk of cerebrovascular events and multimorbidity in general practice: a registry-based study. BMC Cardiovasc. Disord. 16, 61. https://doi.org/10.1186/s12872-016-0235-1

Yoon, M., Yang, P.-S., Jang, E., Yu, H.T., Kim, T.-H., Uhm, J.-S., Kim, J.-Y., Sung, J.-H., Pak, H.-N., Lee, M.-H., Joung, B., Lip, G.Y.H., 2019. Improved Population-Based Clinical Outcomes of Patients with Atrial Fibrillation by Compliance with the Simple ABC (Atrial Fibrillation Better Care) Pathway for Integrated Care Management: A Nationwide Cohort Study. Thromb. Haemost. https://doi.org/10.1055/s-0039-1693516

Table 1: Baseline Characteristics according to Charlson Comorbidity Index Quartiles

	Q1 N= 676	**Q2** N= 683	**Q3** N= 345	**Q4** N= 252	**p *for trend***
Age, *years* (mean±SD)	73.6±9.3	73.2±10.0	74.4±9.6	74.9±8.2	0.118
Female, n (%)	356 (52.7)	293 (42.9)	131 (38.0)	80 (31.7)	<0.001
Type of AF, n (%)					<0.001
Paroxysmal	245 (36.2)	181 (26.5)	82 (23.8)	62 (24.6)	
Persistent	125 (18.5)	125 (18.3)	44 (12.7)	34 (13.5)	
Long-Term Persistent	29 (4.3)	32 (4.7)	16 (4.6)	14 (5.6)	
Permanent	277 (41.0)	345 (50.5)	203 (58.8)	142 (56.3)	
BMI, kg/m^2 (mean±SD)	28.3±4.3	29.1±4.7	29.8±5.6	29.0±5.4	<0.001
GFR, *mL/min* (mean±SD)	71.8±27.1	75.1±34.7	72.5±40.7	61.92±28.1	<0.001
Smoking Habit, n (%)	34 (5.0)	35 (5.1)	17 (4.9)	13 (5.2)	0.999
Excessive Alcohol, n (%)	11 (1.6)	34 (5.0)	15 (4.3)	12 (4.8)	0.006
OAC Drugs, n (%)					0.152
VKA	505 (74.7)	506 (74.1)	270 (78.3)	202 (80.2)	
NOACs	171 (25.3)	177 (25.9)	75 (21.7)	50 (19.8)	
Antiplatelet Drugs, n (%)	43 (6.4)	62 (9.1)	47 (13.6)	55 (21.8)	<0.001

CHA_2DS_2-VASc, mean (SD)	2.78 (1.14)	3.70 (1.39)	4.54 (1.53)	5.08 (1.57)	<0.001
CHA_2DS_2-VASc Classes, n (%)					<0.001
0	19 (2.8)	4 (0.6)	1 (0.3)	0 (0)	
1	82 (12.1)	41 (6.0)	5 (1.5)	1 (0.4)	
≥*2*	575 (85.1)	638 (93.4)	339 (98.3)	251 (99.6)	
HAS-BLED, mean (SD)	1.71 (0.89)	1.92 (1.02)	2.28 (1.01)	2.66 (1.18)	<0.001
HAS-BLED Classes, n (%)					<0.001
0-2	269 (39.8)	230 (33.7)	80 (23.2)	39 (15.5)	
≥*3*	407 (60.2)	453 (66.3)	265 (76.8)	213 (84.5)	

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; GFR= Glomerular Filtration Rate; NOACs= Non-vitamin K Oral Anticoagulants; OAC= Oral Anticoagulant; SD= Standard Deviation; VKA= Vitamin K Antagonist.

Table 2: Quality of Anticoagulation Control according to Charlson Comorbidity Index Quartiles

	Q1 N= 505	**Q2** N= 506	**Q3** N= 270	**Q4** N= 202	**p *for trend***
TTR (%)					
Mean±SD	63.1±24.5	62.0±25.3	62.2±25.7	54.7±24.2	<0.001
ß Coeff. (95% CI) Model 1*	Ref.	-0.59 (-3.81 / 2.63)	-0.07 (-4.08 / 3.94)	**-6.97 (-11.59 / -2.36)**	
ß Coeff. (95% CI) Model 2†	Ref.	-0.13 (-3.40 / 3.14)	0.56 (-3.55 / 4.67)	**-6.13 (-10.81 / -1.45)**	
TTR >70%					
N (%)	219 (43.4)	214 (42.3)	113 (41.8)	61 (30.2)	0.010
OR (95% CI) Model 1*	Ref.	1.01 (0.78-1.31)	1.02 (0.74-1.41)	**0.64 (0.43-0.94)**	
OR (95% CI) Model 2†	Ref.	1.03 (0.79-1.35)	1.06 (0.76-1.48)	**0.67 (0.45-0.99)**	

Legend: *Adjusted for type of AF and CHA_2DS_2-VASc score; †Adjusted for type of AF, CHA_2DS_2-VASc score, body mass index, glomerular filtration rate, smoking habit, excessive alcohol, antiplatelet drugs; Bold character depicts a statistically significant result; CI= Confidence Interval; OR= Odds Ratio; SD= Standard Deviation; TTR= Time in Therapeutic Range.

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

	Q1	Q2	Q3	Q4	Continuous CCI	p *for trend*
Stroke/TIA, n (%)	8 (1.2)	18 (2.6)	11 (3.2)	8 (3.2)	-	0.104
*HR (95% CI) Model 1**	Ref.	1.78 (0.75-4.22)	1.87 (0.68-5.08)	1.80 (0.59-5.53)	1.16 (0.88-1.52)	
HR (95% CI) Model 2†	Ref.	1.85 (0.77-4.43)	1.98 (0.71-5.52)	1.82 (0.59-5.67)	1.16 (0.88-1.53)	
Major Bleeding, n (%)	36 (5.3)	47 (6.9)	33 (9.6)	30 (11.9)	-	0.003
*HR (95% CI) Model 1**	Ref.	1.18 (0.75-1.86)	1.52 (0.90-2.56)	**1.93 (1.10-3.40)**	**1.19 (1.02-1.38)**	
HR (95% CI) Model 2†	Ref.	1.28 (0.81-2.02)	**1.69 (1.00-2.87)**	**1.92 (1.08-3.41)**	**1.18 (1.02-1.38)**	
CV Death, n (%)	14 (2.1)	36 (5.3)	27 (7.8)	30 (11.9)	-	<0.001
*HR (95% CI) Model 1**	Ref.	1.78 (0.95-3.37)	1.98 (0.98-4.01)	**2.72 (1.30-5.69)**	**1.32 (1.13-1.56)**	
HR (95% CI) Model 2†	Ref.	**1.97 (1.04-3.73)**	**2.35 (1.16-4.75)**	**2.99 (1.43-6.24)**	**1.34 (1.14-1.57)**	
All-Cause Death, n (%)	45 (6.7)	86 (12.6)	65 (18.8)	59 (23.4)	-	<0.001
*HR (95% CI) Model 1**	Ref.	**1.52 (1.05-2.20)**	**1.91 (1.25-2.89)**	**2.30 (1.47-3.61)**	**1.26 (1.13-1.41)**	
HR (95% CI) Model 2†	Ref.	**1.67 (1.15-2.44)**	**2.20 (1.45-3.34)**	**2.40 (1.53-3.78)**	**1.26 (1.13-1.40)**	

Legend: *Adjusted for type of AF and CHA_2DS_2-VASc score; †Adjusted for type of AF, CHA_2DS_2-VASc score, body mass index, glomerular filtration rate, smoking habit, excessive alcohol, antiplatelet drugs; Bold character depicts a statistically significant result; CCI= Charlson Comorbidity Index; CI= Confidence Interval; CV= Cardiovascular; HR= Hazard Ratio; TIA= Transient Ischemic Attack.