ANSWERS TO REVIEWER 1

This is a well conducted and useful study on the changing trend of anticoagulation in patients with AF. It should be published, but presently needs some corrections to make it easier to read.

First of all, we wish to thank the reviewer for both appreciation and suggestions.

1. From Figure 2, it appears that 3067 AF patients are included in this study, but this is not mentioned in the abstract.

This is true. We have now added to the abstract the following sentence "For the analysis of antithrombotic treatments, the final sample was made of 3067 patients, after excluding in-hospital deaths, transferred out or self-discharged patients, as well as discharges lacking indications on prescribed treatments". We hope this should better clarify our results.

2. It is not clear from Tables 1 to 4 what makes up the total population of 100%. Showing numbers without the reader understanding what is the base population being looked at is confusing to read.

We fully understand reviewer's doubt. In tables 1-3, reported percentages are relative to the total sample. We added, in order to better clarify our data, the following sentences: "The prevalence in this table is related to the total sample" (table 1); "The prevalence in this table is related to the total sample. Of course, the sum of these percentages exceeds 100%, as a patient could have more comorbidities at the same time." (table 2). "The prevalence in this table is related to the total sample. Of course, the sum of these percentages exceeds 100%, as a patient could have received more diagnostic and therapeutic procedures at the same time." (table 3).

As regards table 4, data were absolute numbers, and we added "(absolute numbers)" to the sentence.

3. Fig 1, 5 and 6 have too many lines. Author should reduce the number of lines, or else thing of a way to highlight differences clearly.

As regards figure 1, we think that the five lines in fig. 1 are very useful in order to describe our sample. We removed instead in figures 5 and 6 the lines relative to SAPT and DAPT, unifying them in antiplatelet therapy (APT) alone. Besides, in order to further improve clearness of these figures, we changed their layout.

4. "The most frequent main diagnosis in patients with AF was acute myocardial infarction (1973 discharges, 48,19%). The most frequent secondary cardiac diagnosis was chronic coronary syndrome (1864 discharges, 45,51%), and the most frequent secondary associated condition was arterial hypertension" - These should be rewritten to make it clear what is being compared. What exactly make up the total population of 100% when various percentages are given?

As previously reported, these percentages are relative to the total sample, and this has been clarified in the main text.

5. "The proportion of patients on OAC therapy, with or without an antiplatelet agent, increased significantly from 35,63% in 2010-2012 to 61,18% in 2019-2021 (+25,55%, p<0.0001). This rise was due to increasing use of DOACs, with or without antiplatelet agents, from 3,04% in 2013-2015 to 50,06% in 2019-2021 (+47,02%, p<0.0001) and was greater for FXa inhibitors, above all apixaban. At the same time, there was a decline in the use of VKA, with or without antiplatelet drugs, from 35,63% in 2010-2012 to 11.12% in 2019-2021 (-24,48%, p<0.0001), as well as of antiplatelet therapy, alone or in double combination, from 49,18% in 2010-2012 to 34,18% in 2019-

2021 (-15,00%, p<0.0001), while the proportion of patients not receiving antithrombotic therapy decreased from 14,58% in 2010-2012 to 1,97% in 2021 (p<0,0001)" - This write up suffers from the same weakness of not explaining what makes up the 100% base population. At present reader cannot understand what is the total population being referred to.

This is true. As reported previously, we added in the abstract a sentence explaining that the final sample was made of 3067 patients, and the reported data are relative to them.

6. "4089 (16.27%, mean age 75,59+/-10,82) were discharged with AF diagnosis. AF was the main diagnosis in 899 patients (21,94%)." - Explanation is needed on why 4089 patients with AF can become only 899 with AF as main diagnosis?

Actually, AF was the main diagnosis only in 899/4089 patients. This low proportion is due to the fact that our sample comes from a general cardiology unit, and most patients were admitted with other cardiac diagnosis (i.e. coronary diseases or heart failure), having also atrial fibrillation. In order to better clarify this, we added in the discussion the following sentence: "This is due to the real-world nature of this observational study, focused on a global sample of patients admitted to a cardiologic Unit.".

What about the 3067 shown in Fig 2 to have known therapy?

As regards the 3067 patients shown in the study flow-chart in figure 2, they were the final sample (after excluding in-hospital deaths, transferred out or self-discharged patients, as well as discharges lacking indications on prescribed treatments) that we considered to describe the pattern of antithrombotic therapy, regardless whether atrial fibrillation was the main or a secondary diagnosis.

ANSWERS TO REVIEWER 2

The authors describe a retrospective single center study analyzing the trends in OAC prescription for patients with atrial fibrillation in Italy. The article is written in considerable detail considering multiple clinical aspects of OAC prescription in a fib patients as well. Many findings are in line with developments across the world, increase in DOAC use and decline in VKA use.

First of all, we wish to thank the reviewer for both appreciation and suggestions.

In the second paragraph on page 28, authors suggest that 95% of patients with a fib have moderate-severe MS or mechanical heart valve, this does not seem to the case in our clinical experience.

We thank very much the reviewer for having noticed a mistake in the sentence. Actually, AF patients with moderate-severe MS or mechanical heart valve accounts for about 5% in the study of Go, and even less in our study, so we corrected 95% to 5%.

There appears to be a significant increase in frequency of OAC therapy according to the current study which appears encouraging and suggests better adherence with guidelines as suggested by study.

It appears contrary that while the incidence of atrial fibrillation is expected to increase with aging population, the number of discharges with atrial fibrillation was noted to decrease in the study period.

It is absolutely correct that the incidence and prevalence of atrial fibrillation are expected to increase due to progressive increase in the number of of elderly people in a general population; however, our sample reflects only patients hospitalized in a cardiology unit and, as shown in figure 1, the number of global admissions is progressively decreasing in time. This phenomenon is not limited to atrial fibrillation, and it is due to the progressive shift of medical resources from hospital to the territory in Italy; in particular, reduction in the hospital admission of patients with a paroxysmal AF now is considered inappropriate. We added this sentence in the discussion: "Although the incidence and prevalence of atrial fibrillation are expected to increase due to progressive increase in the number of elderly people in a general population, our sample reflects only patients hospitalized in a cardiology unit. Thus, the decrease in discharges with AF diagnosis may be explained in general by the decrease of total hospital admissions and, in particular, by the reduction in admission of patients with a paroxysmal AF, that now is considered inappropriate"

Several limitations exist in the study and have been acknowledged by the authors.

Recommend making the article more concise focusing on the study's findings with less repetition of information.

According to this suggestion, we deleted the following periods/sentences:

Introduction:

Although several global and European registries have demonstrated an overall increase in anticoagulant use and adherence to guidelines for patients with NVAF since the introduction of DOACs[60], albeit other studies suggest that improvements are still needed[46,61],

Considering the huge clinical impact and healthcare economic burden (in terms of both direct medical costs and indirect productivity losses, e.g. absenteeism, presenteeism, disability associated with AF), there are a number of reasons why it is important to complement experimental data with real-life or observational data, understanding the rates of anticoagulant treatment, as well as the burden posed by nonadherence to treatment guidelines.

Discussion:

In the 2010 ESC Guidelines[18], antithrombotic therapy to prevent thrombo-embolism was recommended for all patients with AF, except in those at low risk (lone AF, aged <65 years, or with contraindications) (class IA). For the patients with a CHADS2 score of >2, chronic OAC therapy with a VKA is recommended in a dose adjusted regimen to achieve an INR range of 2.0–3.0 (target 2.5), unless contraindicated (class IA). In patients with 1 'major' or > 2 'clinically relevant non-major' risk factors OAC therapy was recommended, unless contraindicated (class IA). Finally, patients with one 'clinically relevant non-major' risk factor are at intermediate risk and antithrombotic therapy is recommended, either as OAC therapy (e.g. VKA) (class IA) or aspirin 75–325 mg daily (class IB). The 2012 ESC Guidelines[19] introduced the CHA2DS2-VASc score. In patients with a CHA2DS2-VASc score ≥2, OAC therapy with adjusted-dose VKA or a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor was recommended, unless contraindicated (class IA). In patients with a CHA2DS2-VASc score of 1, OAC therapy with adjusted-dose VKA or a direct thrombin inhibitor or an oral factor Xa inhibitor should be considered, based upon an assessment of the risk of bleeding complications and patient preferences (class IIaA). When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the DOACs was recommended (class IB). Finally, where OAC is recommended, one of the DOACs should be considered rather than adjusted-dose VKA for most patients with NVAF, based on their

net clinical benefit (Class IIaA). In the 2016 ESC Guidelines[20], OAC therapy was recommended for all male AF patients with a CHA2DS2-VASc score of 2 or more and in all female AF patients with a CHA2DS2-VASc score of 3 or more (class IA). OAC therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score of (class IIaB). When OAC is initiated in a patient with AF who is eligible for a DOAC, it is recommended in preference to a VKA (class IA). Finally, in the 2020 ESC Guidelines[21], OAC is recommended in AF patients with CHA2DS2-VASc score >=2 in men or >=3 in women (class IA) and should be considered for stroke prevention in AF patients with a CHA2DS2-VASc score of 1 in men or 2 in women (class IIA). In AF patients who are eligible for OAC, DOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis) (class IA).

(REALISE-AF - Real-life global survey evaluating patients with atrial fibrillation[69], GLORIA-AF - Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation[45,46], and GARFIELD-AF - Global Anticoagulant Registry in the FIELD-Atrial Fibrillation[70-72]) ... (PREFER-AF - Prevention of thromboembolic events–European Registry in Atrial Fibrillation[9,44], Euro-Heart Survey[10,73], and EORP-AF - EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Registry[74-76].

other many countries, such as the U.S.A. (PINNACLE - Practice INNovation And Clinical Excellence[77], ORBIT-AF - Outcomes Registry for Better Treatment of Atrial Fibrillation[71,78], ATRIA - AnTicoagulation and risk factors in atrial fibrillation[6], and AVAIL - Adherence eValuation After Ischemic Stroke Longitudinal Registry[51]), the U.K. (local GARFIELD data[59]), the Netherlands (local GARFIELD data[79,80]), Spain (FANTAS.tic study[55]), France (OCTOFA - Atrial Fibrillation in Octogenarians[81]), Germany (AFNET - German Competence Network on Atrial Fibrillation[82]), Italy (REPAIR[58], ATA-AF[83], local PREFER-AF data[62], REGINA - REGIstry of patients on Non-vitamin K oral Anticoagulants[52]), Turkey (PROPER - PRescriptiOn PattERns of Oral Anticoagulants in Nonvalvular Atrial Fibrillation[84] and RAMSES - ReAl-life Multicenter Survey Evaluating Stroke Study[85]), Japan (J-RHYTHM - Japanese Rhythm Management Trial for Atrial Fibrillation[53], ANAFIE - All Nippon AF In Elderly[86-88], and FUSHIMI-AF[89]), Korea (CODE-AF - COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation[90] and K-NHID - Korean National Health Insurance Data Sample Cohort[91]), and China (CAMI - China Acute Myocardial Infarction[92] and China Atrial Fibrillation Registry Study[93].

but antiplatelet treatments have no clinical benefit in the treatment of AF[67].

In fact, elderly patients with AF exposed to moderate polypharmacy (five to nine drugs) and extensive polypharmacy (ten+ drugs) were 39% and 63% less likely to receive a DOAC compared to warfarin in Ireland, showing that multiple concomitant medications were negatively associated with DOAC initiation[96].

Besides, in some studies the number of patients treated with VKAs still far exceeds the number of patients treated with DOACs[78].

The proportion of high-risk patients being untreated or treated with antiplatelet drugs is yet higher than expected, as reported in the 1-year follow-up from the EORP-AF General Registry Pilot Phase[74,75].

K-NHID-Sample Cohort reported that from 2004 through 2013 the proportion of patients who received therapy with warfarin was 18.2–16.7%, showing no significant change for the decade[91]. The GARFIELD-AF, which enrolled patients from 35 countries revealed an increase in

the use of ACs from 57.4% to 71.2% of patients between 2010 and 2016[72]. In the UK GARFIELD registry, between 2011 and 2016 the proportion of patients prescribed OAC therapy, with or without an antiplatelet drug, increased consistently from 54.7% to 73.9% (p for trend <0.0001) [59]. In Japan, in the Fushimi AF Registry, the total prevalence of OAC increased over time from 53% in 2011 to 64% in 2015[89]. In China, the use of DOACs increased rapidly, whereas the use of warfarin declined so that the total proportion of patients on oral anticoagulation remained stable[15].

Therefore, OAC use does appear to vary according to age and geographical location.