

## Relationship of adverse events to quality of anticoagulation control in atrial fibrillation patients with diabetes: Real-world data from the FANTASIIA registry.

Amaya García-Fernández (1), María Asunción Esteve-Pastor (2), Inmaculada Roldán Rabadán (3), Javier Muñoz (4), Martín Ruiz Ortiz (5), Ángel Cequier (6), Vicente Bertomeu-Martínez (7), Lina Badimón (8), Déborah Otero (9), Manuel Anguita (5), Gregory Y.H. Lip (10,11), Francisco Marín (2) on behalf of FANTASIIA investigators.

- (1) Department of Cardiology, Alicante General University Hospital, Sanitary and Biomedical Investigation Institute of Alicante (ISABIAL-FISABIO), Spain
- (2) Department of Cardiology. Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, CIBERCV, Murcia, Spain
- (3) University Hospital La Paz, Department of Cardiology, Madrid, Spain
- (4) Instituto Universitario de Ciencias de la Salud de la Universidad de A Coruña; Instituto de Investigación Biomédica de A Coruña (INIBIC), CIBERCV, Spain
- (5) Department of Cardiology, University Hospital Reina Sofia, Cordoba, Spain
- (6) Department of Cardiology, University Hospital of Bellvitge, Barcelona, CIBERCV, Spain
- (7) Department of Cardiology, University Hospital San Juan de Alicante, Alicante, Spain
- (8) Cardiovascular Research Centre(CSIC-ICCC), Barcelona, CIBERCV, Spain
- (9) ODDS, S.L., A Coruña, Spain
- (10) Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom.
- (11) Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark.

### Corresponding author:

María Asunción Esteve-Pastor, MD, PhD

Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca. Ctra. Madrid-Cartagena s/n 30120, Murcia, Spain.

(e-mail: masunep@gmail.com).

## ABSTRACT

**BACKGROUND:** Atrial fibrillation (AF) patients with diabetes (DM) are at increased risk of cardiovascular events and have higher related morbidity and mortality.

**PURPOSE:** To compare clinical characteristics, cardiovascular adverse outcomes and quality of anticoagulation in AF patients with and without DM.

**METHODS:** AF patients from the Spanish national, multicentric, prospective FANTASIIA registry were included. Patients received oral anticoagulation (vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC)) for at least 6 months before inclusion. Baseline clinical characteristics and comorbidities were recorded. After 2-years follow-up, the association between adverse events and the presence of DM was evaluated.

**RESULTS:** 1956 individuals (mean age  $73.8 \pm 9.5$  years, 56% male) were analysed; of these, 574 (29.3%) had DM. Diabetic patients had increased prevalence of other risk factors such as hypertension (90.6% vs 76.1%;  $p < 0.001$ ), renal disease (21.4% vs 15.9%;  $p < 0.001$ ) and heart failure (39.1% vs 24.7%;  $p < 0.001$ ). A rhythm control strategy was applied less often in diabetic patients vs non-diabetics (33.6% vs 40.1%;  $p = 0.007$ ).

After a median follow-up of 1077 days (IQR 766-1113 days), diabetic patients had higher risk of total mortality (16.9%/year vs 11.4%/year;  $p < 0.001$ ), cardiovascular mortality (9.1%/year vs 3.9%/year;  $p < 0.001$ ) and MACE (12.9%/year vs 6.8%/year;  $p < 0.001$ ). Patients with DM had increased total mortality risk [HR 1.58 (95IC% 1.20-2.07);  $p < 0.001$ ], cardiovascular mortality [HR 2.40 (95IC% 1.17-3.53);  $p < 0.001$ ] and MACE [HR 2.03 (IC95% 1.47-2.80);  $p < 0.001$ ]. DM patients had poorer anticoagulation control (time in therapeutic range:  $58.52 \pm 24.37\%$  vs  $62.68 \pm 25.31\%$ ;  $p = 0.002$ ). Among diabetic individuals, those with lower TTR showed higher risk of cardiovascular death [(14.12 vs 4.89%;  $p = 0.001$  for TTR < 65 vs  $\geq 65\%$ ); (13.36 vs 4.55%;  $p = 0.003$  for TTR < 70 vs  $\geq 70\%$ )] and MACE [(16.79 vs 9.78%;  $p = 0.03$  for TTR < 65 vs  $\geq 65\%$ ); (16.44 vs 9.09%;  $p = 0.03$  for TTR < 70 vs  $\geq 70\%$ )]. Multivariate analysis showed an independent association between the presence of DM and cardiovascular mortality [HR 1.73 (IC95% 1.07-2.80);  $p = 0.024$ ].

**CONCLUSION:** Diabetic patients with AF have more associated comorbidities. Quality of anticoagulation control with vitamin K antagonists in these subjects was poorer than in non-diabetic patients. Lower TTR was associated with cardiovascular death and MACE in diabetic patients. The risk of cardiovascular outcomes (total mortality, cardiovascular mortality and MACE events) was higher, with an independent association between DM and increased mortality risk.

**CONFLICTS OF INTEREST:** The FANTASIA registry was funded by an unconditional grant from Pfizer/Bristol-Myers-Squibb and by grants from the Instituto de Salud Carlos III (Madrid)-FEDER (RD12/0042/0068, RD12/0042/0010, RD12/0042/0069 and RD12/0042/0063). The authors are supported by RD12/0042/0049 (RETICS) from ISCIII and PI13/00513/FEDER from ISCIII.

## INTRODUCTION

Atrial fibrillation (AF) is the commonest arrhythmia in clinical practice and represents a major healthcare burden, with an increased risk of stroke and thromboembolism, as well as other cardiovascular events, hospital admissions and mortality. The prevalence of AF is greater in patients with associated comorbidities, such as hypertension, heart failure, chronic kidney disease or diabetes mellitus (DM) (1,2,3).

DM is one of the most common chronic conditions, whereby the incidence in Western countries is increasing and approximately 9% of European adults acquire this disease (4). The association between DM and increased cardiovascular risk is well known (5). AF and DM frequently coexist and about one out of five diabetic patients suffer also from AF (6). The mechanisms of this association are not completely understood, but include atrial electrical, structural, electromechanical and autonomic remodelling, playing an important role in the development of AF in individuals affected by this condition (7). Oxidative stress and inflammation exacerbate atrial electrical and structural remodelling, predisposing to AF initiation and maintenance (8). The effect of glycaemic control on the incidence of new-onset AF is controversial, while some authors have found that poor glycaemic control confers higher risk of arrhythmia occurrence (9), others have shown that intensive glycaemic control does not seem to affect the incidence of new-onset AF (10). On the other hand, some therapies used in diabetic patients, eg. metformin (11), thiazolidinediones (12), angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) (13) could be associated with a decreased risk of developing AF. Moreover, given the possible link between oxidative stress and inflammation and AF occurrence, therapeutic strategies targeting these pathways might be useful for combatting diabetes-related AF (8).

When AF and DM present together the coexistence of other associated comorbidities is higher and the risk of cardiovascular events seems even greater. In the EORP-AF (EURObservational Research Programme-Atrial Fibrillation) General Registry, the prevalence of DM was around 20%; these patients were older and had a higher prevalence of comorbidities, worse quality of life, and greater all-cause, cardiovascular and non-cardiovascular mortality (14). Furthermore, the presence of DM is a recognised risk factor for thromboembolism in AF patients and stroke

episodes seem to have worse clinical outcomes in the presence of this metabolic disorder (15, 16). Thus, most of these individuals will require long-term oral anticoagulation. Although VKA efficacy does not seem to be reduced in DM-related AF, higher international normalized ratio (INR) variability has been observed in these patients (17). On the other hand, current evidence suggests at least comparable efficacy and safety of DOAC in DM-related AF (18).

The aim of our study was to investigate the prevalence of DM and other comorbidities in a 'real-world' multicentric prospective cohort of anticoagulated AF patients included in the FANTASIA registry. Second, we evaluated the incidence of adverse events during follow-up as well as the differences in clinical management and quality of anticoagulation depending on the presence or absence of DM.

Accepted Manuscript

## METHODS

The FANTASIIA (Spanish acronym for 'Fibrilación Auricular: Influencia del Nivel y Tipo de Anticoagulación Sobre la Incidencia de Ictus y Accidentes hemorrágicos') registry is an observational, prospective, national and multicentre study of clinical and demographic characteristics of Spanish AF patients. The study design of FANTASIIA registry has been described previously (19). In brief, the main objective was to assess the incidence of thromboembolic and bleeding events in an unselected population of patients with AF, specifically the type of oral anticoagulant (VKA or DOAC) used and the quality of anticoagulation control with VKAs.

### Study Population

Between June 2013 and March 2014, all outpatients with confirmed diagnosis of paroxysmal, persistent or permanent AF, were prospectively enrolled. All patients included in the registry had been receiving OAC (VKA or DOAC) for at least 6 months before enrolment. By design, each investigator included 16 patients taking VKA therapy and 4 patients who were taking DOAC treatment. The study was conducted in 50 outpatient clinics by 80 investigators (81% cardiologists, 11% general practitioners and 8% internists). 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 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.

### Data Collection

Clinical and demographic data for all AF patients were collected. Patients were classified as being diabetic if they were under treatment with insulin or other antidiabetic therapies or, for patients without antidiabetic therapy, those who met the 2004 American Diabetes Association criteria (fasting plasma glucose  $\geq 126$  mg/dL in 2 occasions and/or 2-hour plasma glucose value during a 75 g oral glucose tolerance test  $\geq 200$ mg/dL). For assessing glycaemic control in people with diabetes, basal glycated haemoglobin (HbA1c) and subsequent values during follow-up were registered. Poor glycaemic control was defined as one or more measurements of HbA1c over 7.5%. Previous heart disease was defined as the composite of coronary artery disease (CAD), heart failure and other structural cardiomyopathies (such as hypertrophic cardiomyopathy, chronic pericardial disease or congenital diseases). Stroke risk was calculated

using the CHADS<sub>2</sub> (15) (congestive heart failure, hypertension, age  $\geq$  75 years, diabetes mellitus, stroke or transient ischaemic attack) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (16) (congestive heart failure, hypertension, age  $\geq$ 75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65–74 years and sex category [female]). Bleeding risk was calculated using the HAS-BLED score (20) (hypertension [uncontrolled systolic blood pressure  $>$ 160 mm Hg], abnormal renal and/or liver function, previous stroke, bleeding history or predisposition (anaemia), labile INR [only applies to a VKA user; not applicable for a non-VKA user], elderly [age  $\geq$ 65 years], and concomitant drugs [antiplatelet or non-steroidal anti-inflammatory drugs] and/or alcohol excess). Indeed, we assessed the fragility of the population according to Charlson comorbidity index. The latter is the most widely used comorbidity index to predict 1-year mortality in patients based on comorbidity data (21). In order to evaluate AF related symptoms and patients' perception of their health status, the European Heart Rhythm Association (EHRA) functional class score was used (1).

### **Quality of anticoagulation control**

For patients treated with VKA, coagulation status was determined by monthly INR values 6 months before the study inclusion, 6 months after baseline, and at 1 year of follow-up. All available INR of each patient in the 6 months previous were collected at baseline with at least 1 INR per month to calculate the time in the therapeutic range (TTR). The FANTASIA registry is an observational multicentre registry. For that reason, the frequency of the INR determinations to maintain the INR between 2.0 and 3.0 and the frequency of visits to the physicians were performed following the usual clinical practice without any additional intervention. The TTR was estimated according to different methods. The main methodology employed was the classical linear interpolation method of Rosendaal (22); however, the quality of anticoagulation also was studied according to the direct method or percentage of INR in therapeutic range (PINRR). This method calculates the TTR according to the number of visits where the INR is in therapeutic range (between 2.0 and 3.0) and divides it by the total number of visits. Poor quality of anticoagulation or "INR lability" was defined when patients experienced a TTR  $<$ 65% or  $<$  70%.

### **Clinical Outcomes**

Follow-up started the day of the inclusion for 12 months. Thromboembolic events were defined as stroke or transient ischaemic attack (TIA) and peripheral artery embolism. All strokes were evaluated by computed tomographic (CT) scan or magnetic resonance imaging (MRI), according to the neurologist criteria. Major bleeding events were assessed according to the 2005 International Society of Thrombosis criteria (23): 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  $\geq$ 20 g/L, or transfusion of  $\geq$ 2 units of packed red blood cells. We also recorded all-cause mortality and cardiovascular mortality, with the latter defined if it was secondary to a cardiovascular event (acute coronary

syndrome, heart failure, lethal arrhythmia or sudden death, artery aneurysm rupture or stroke). Major adverse cardiovascular event (MACE) was defined as the composite of ischaemic stroke, myocardial infarction and cardiovascular mortality. To guarantee the quality of the FANTASIA registry, an external event assignment committee was formed to evaluate all adverse events.

### **Statistical Analyses**

Normal distribution of continuous variables was tested with the Kolmogorov-Smirnov method. Continuous variables are presented using the mean  $\pm$  standard deviation or median (interquartile range). Categorical variables are expressed as percentages. For comparisons among groups, T-student test was used in the case of continuous variables and the Chi-square test for qualitative variables. Cox regression analyses were used to determine the associations between DM and mortality, bleeding and cardiovascular events. The independent effect of clinical variables on adverse clinical outcomes was calculated using a Cox proportional hazards regression, including in the multivariate model only those values with  $p < 0.15$  on univariate analysis. Differences in event-free survival were examined with log-rank test and Kaplan–Meier curves were drafted accordingly. Statistical significance was defined as  $p < 0.05$ . Statistical analyses were performed using STATA v.12.0 (Stata Corp., College Station, TX, USA) for Windows.

## RESULTS

### Baseline characteristics, comorbidities and symptoms.

We enrolled 2,178 patients in FANTASIIA registry (1,648 patients treated with VKAs and 530 patients treated with DOAC). A total of 1,956 patients (89.8% of the total sample) completed 1 year of follow-up and were included in the analysis. Mean age of the patients was  $73.8 \pm 9.5$  years and 56.0% were male. 574 (29.3%) of the patients had DM, most of them, 559 (28.6%), had type 2 DM, whereas only 15 (0.7%) suffered from DM type 1.

Clinical and demographic baseline characteristics classified according to the presence of DM are summarized in Table 1. No differences were found in the age and sex of diabetic versus non-diabetic individuals. Diabetic patients had significantly higher prevalence of associated risk factors and comorbidities, such as hypertension, dyslipidaemia, lung disease, kidney disease, peripheral artery disease and heart disease (heart failure and ischaemic heart disease). Thus, their Charlson comorbidity index was significantly higher ( $2.0 \pm 1.1$  vs  $0.8 \pm 0.9$ ;  $p < 0.001$ ). Haemoglobin (Hb) levels and glomerular filtration rates (GFR) were significantly lower in patients with DM. As expected, thromboembolic and major bleeding risks were significantly higher in these patients (CHA<sub>2</sub>DS<sub>2</sub>-VASc score:  $4.7 \pm 1.5$  vs  $3.3 \pm 1.5$ ;  $p < 0.001$ , HAS-BLED score:  $2.3 \pm 1.1$  vs  $1.9 \pm 1.0$ ;  $p < 0.001$ ). HbA1c levels were available for 536 diabetic patients, of which 143 (26.7%) had bad glycaemic control (HbA1c > 7.5%).

When evaluating AF related symptoms, we found that DM was associated with worse functional class, with most diabetic patients classed as EHRA functional class II or III, while non-diabetics were mostly class I ( $p < 0.001$ ).

Regarding AF subtypes and management, diabetic patients had a higher percentage of long-standing persistent or permanent AF, in contrast with non-diabetics, who had more paroxysmal or persistent AF ( $p = 0.04$ ). A rhythm control strategy was less used in diabetic patients vs non-diabetic (40.1% vs 33.6%;  $p = 0.007$ ). Diabetics more commonly received diuretics, angiotensin-converting enzyme inhibitors (ACEI), aldosterone-receptor inhibitors (ARI), statins and digoxin. Non-diabetic patients were treated more frequently with calcium antagonists.

### Anticoagulation treatment and control.

In FANTASIIA, 1484 patients (75.8%) were taking VKA and 472 (24.2%) DOAC, with no differences between diabetic and non-diabetics ( $p = 0.21$ ). Of those taking VKA, those with DM had poorer anticoagulation control (mean TTR by Rosendaal method:  $58.5 \pm 24.4\%$  vs  $62.7 \pm 25.3\%$ ;  $p = 0.002$ ). When we compared the percentage of patients who were outside therapeutic range, the difference was also significant (58.7% of diabetic patients vs 49.8% non-

diabetics with TTR<65%; p=0.001 and 65.5% vs 56.3% had TTR<70%; p=0.001).

### **Clinical outcomes.**

After a median follow-up of 1077 days (IQR: 766-1113 days), DM patients had a higher risk of major bleeding [HR 1.41 (95%CI 0.99-2.01); p=0.056], myocardial infarction [HR 2.04 (95%CI 1.17-3.53); p=0.01], cardiovascular mortality [HR 2.40 (95%CI 1.62-3.56); p<0.001], total mortality [HR 1.58 (95%CI 1.20-2.07); p<0.001] and MACE [HR 2.03 (95%CI 1.47-2.80); p<0.001] (Table 2). We found no differences in stroke between both groups [HR 0.98 (95%CI 0.51-1.88); p=0.95].

An association between glycated haemoglobin levels and risk of major bleeding was found (HR 1.79; 95%CI 1.01-3.18; p=0.047; however, HbA1c levels did not show a significant relationship with other outcomes: total mortality (HR 1.38; 95%CI 0.88-2.16; p=0.16), cardiovascular mortality (HR 1.53; 95%CI 0.83-2.82; p=0.17) and stroke (HR: 1.41; 95%CI 0.45-4.40; p=0.55). Glycaemic control was not related with quality of anticoagulation control (p=0.35).

Figure 1 shows the incidence of the different outcomes in diabetic patients depending on quality of anticoagulation control. The incidence of cardiovascular death [(14.12 vs 4.89%; p=0.001 for TTR<65 vs ≥65%); (13.36 vs 4.55%; p=0.003 for TTR<70 vs ≥70%)] and MACE [(16.79 vs 9.78%; p=0.03 for TTR<65 vs ≥65%); (16.44 vs 9.09%; p=0.03 for TTR<70 vs ≥70%)] was significantly greater in diabetic patients with lower TTR.

Cox logistic regression analysis showed an independent association between DM and cardiovascular mortality [HR 1.73 (95%CI 1.07-2.80); p=0.024]. Table 34 summarises clinical factors related to the different adverse events on multivariate Cox regression analysis. Differences in event-free survival for mortality, major bleeding and MACE depending on the presence of DM were found (see Kaplan–Meier survival curves, Figure 2).

## DISCUSSION

In the FANTASIIA Registry, which included nearly 2,000 patients with AF, almost 30% of the patients had concomitant DM, which was associated with additional comorbidities and higher thromboembolic and bleeding risks. Second, quality of anticoagulation control with vitamin-K antagonists was poorer in this group. Third, the risk of adverse cardiovascular outcomes and death was higher in diabetic individuals and an independent association with cardiovascular death was evident.

The proportion of patients with DM in this Spanish registry (almost one-third) is similar to that of the ORBIT-AF Registry, which included nearly 10,000 AF individuals from the United States (24), and slightly higher than the number of diabetics from the EORP-AF Registry (14), with 3100 European individuals. These great burden of DM among patients with AF reflects not only the contemporary increasing prevalence of both conditions (4,25), but also an incremented risk for the development of AF in diabetic patients (6). Other studies have shown that DM is an independent risk factor for the occurrence of AF, with higher risk associated with longer duration and worse glycaemic control (9). Although the mechanisms of this relationship are not completely understood, metabolic defects in DM cause endothelial dysfunction, abnormal activation of the renin-angiotensin-aldosterone system and acceleration of atherogenesis. Indeed, DM could cause structural, electrical, electromechanical and autonomic atrial remodelling, leading to an increased susceptibility to AF occurrence (7)(26).

Our study showed that diabetic AF patients, when compared to non-diabetics, had significantly more associated risk factors and comorbidities, such as hypertension, dyslipidaemia, pulmonary disease, renal disease, heart failure, ischaemic heart disease and peripheral artery disease. Moreover, the presence of DM was associated to a worse functional class. Although a possible role of neuropathy masking cardiac subjective symptoms in DM has been suggested (27), our findings are consistent with previous European and north-American registries, which also showed that diabetics are more symptomatic and have worse health-related quality of life and greater functional impairment than non-diabetics (14)(24). We used the EHRA score, an instrument to assess AF-related symptoms, not only palpitations, but also fatigue, dizziness, dyspnea, chest pain and anxiety, which may be more related to the severity of heart disease and other underlying conditions. Interestingly, in the ORBIT-AF registry, patients with diabetes less often reported palpitations or syncope, but they reported significantly more dyspnea upon exertion or at rest, exercise intolerance and fatigue (24). In contrast with the EORP-AF, where diabetic individuals were older than non-diabetics, and the ORBIT-AF, where diabetics were younger, the age of the Spanish AF patients with DM was similar from that of those without DM, and therefore age could not explain our findings. As a result of the higher prevalence of coexisting risk factors, and similar to previous reports, both thromboembolic and major bleeding risks (as estimated by the CHA<sub>2</sub>DS<sub>2</sub>-VASc and the HAS-BLED scores) were significantly higher

in individuals with DM (14)(24).

In the FANTASIIA registry, pharmacological treatment and AF management differed between the group of patients with DM and non-diabetics: diuretics, ACEI, ARI and statins were more frequently prescribed if DM was present, given the higher prevalence of hypertension and other comorbidities in this group.

Importantly, we confirm that diabetic patients are significantly less likely to undergo a rhythm control strategy. One possible explanation is the lower prevalence of paroxysmal or persistent AF. Also, the higher prevalence of concomitant risk factors and other diseases (as expressed by higher Charlson index) could make physicians less prone to indicate cardioversion or ablation, given that the presence of one or more risk factors increases the risk of arrhythmia recurrence after ablation by 30% (28). There is also a lower success rate of both cardioversion and subsequent maintenance of sinus rhythm in patients with DM (29), with a possible relationship to glycaemic control (30).

All the patients that entered our registry were taking anticoagulant treatment, most (about 75%) being VKAs. No difference was found between the use of VKAs or DOAC depending on the presence of DM. We found that globally 55% of AF patients had poor anticoagulation control (31). To our knowledge, quality of anticoagulation in diabetic patients with AF has been poorly studied. In the EORP-AF registry, information about anticoagulation control was not available (14). In this substudy of the FANTASIIA we demonstrated that more than two-thirds of diabetic patients had a TTR lower than recommended, and TTR was significantly worse in DM than in non-DM individuals. Nelson and co-workers previously demonstrated that comorbidities were associated with lower TTR, specifically heart failure and DM (32). In the Chinese Atrial Fibrillation registry, DM and other comorbidities, such as coronary heart disease and peripheral artery disease were associated with increased variability in INR (33). Indeed, one of our most outstanding findings is that we specifically demonstrate that among diabetic individuals, poorer TTR confers an increased risk of cardiovascular death and MACE. Therefore, more attention should be paid on trying to achieve better quality of anticoagulation control when VKAs are used in individuals with DM, given that this population is particularly susceptible to cardiovascular outcomes.

One of the main findings of our study is that, compared with non-diabetics, AF patients with DM had worse prognosis at follow-up, with more than two-fold risk for cardiovascular mortality, even after covariate adjustment. The risk for major bleeding, myocardial infarction, total mortality and MACE was also doubled compared to non-diabetics. Nevertheless, we could not demonstrate a difference in the occurrence of stroke between both groups. In the ORBIT-AF Study outcomes also differed between AF patients without and with DM, having the latter an increased risk of death and hospitalizations but similar risk of thromboembolic events and hospitalizations related

to bleeding (24). In the EORP-AF Registry, DM was also an independent predictor of all-cause mortality and coronary events, but the incidence of stroke or TIA and major bleeding was no different between groups(14). Interestingly, the European Prevention of thromboembolic events–European Registry in Atrial Fibrillation (PREFER in AF) demonstrated that the sole presence of DM not requiring insulin did not increase thromboembolic risk, as only insulin-dependent diabetics had significantly higher risk of thromboembolism, compared to non-insulin type 2 DM and non-diabetics (34). However, previous data from earlier trials had identified DM as an independent risk factor for thromboembolism (35). One possible explanation for the lack of influence of DM on thromboembolic risk is the greater use of anticoagulant treatment in all these newer registries (100% in FANTASIIA), leading to a lower incidence of stroke and embolism in both groups.

### **Strengths and limitations**

The FANTASIIA is a multicentre nation-wide registry, with large sample size, a prospective design and a long follow-up. Clinical characteristics and coagulation status of the patients included were thoroughly collected. Moreover, to guarantee the quality of the data, an external event assignment committee evaluated all adverse outcomes. A detailed statistical analysis, with strong adjustment for confounders, allowed us to compare clinical characteristics and long-term outcomes between the groups with and without DM. A substantial number of events took place in each category to estimate the association between this metabolic syndrome and adverse outcomes. Our findings are robust and consistent with previous literature.

There are several limitations that need to be considered. First, as an observational registry, it has the inherent limitations of all observational studies. Second, most of our patients were on anticoagulant treatment with VKA, and the one most used in our country is acenocoumarol, which has a shorter half-life than warfarin, but similar TTR. For these reasons, and even if our sample is representative of the Spanish population, our results might not be fully extrapolated to other countries using other VKA. Furthermore, less than a quarter of the individuals received DOAC, thus, we cannot assure if our outcomes apply to populations with higher use of these anticoagulants. Another limitation of our study is that almost all the diabetic patients included had type 2 DM, with only very few having DM type 1, for that reason our conclusions should only apply to type 2 diabetics. Fifth, the presence of more comorbidities at baseline in diabetic individuals could have influenced our findings, and even if multivariate analysis showed that the impact on cardiovascular outcomes was independent of the coexistence of other risk factors, residual confounding may remain despite multivariate analysis. Regarding DM management, we did not have information about antidiabetic therapies and the possible influence of these medications on our outcomes could not be analysed. Finally, data on glycaemic control were not available for the whole sample, we believe that this may be a reason for the lack of association between HbA1c levels and outcomes during follow-up.

## CONCLUSIONS

In the FANTASIIA Registry, a significant proportion of the patients with AF had DM. Patients with DM had more associated comorbidities, poorer quality of anticoagulant treatment and underwent significantly less rhythm-control strategies for AF. The risk of developing adverse cardiovascular outcomes and death was higher in diabetic patients, particularly in those with worse quality of anticoagulation control. An independent association between DM and cardiovascular mortality was found in AF patients.

**TABLE 1. Comparison of baseline clinical characteristics according to the presence of diabetes.**

Variable	Non DM N=1382	DM N=574	p value
Age (years)	73.7±9.7	73.9±9.9	0.96
Sex (female)	608 (44.7)	242 (42.3)	0.35
<b>Comorbidities</b>			
Hypertension (%)	1053 (76.2)	520 (90.6)	<0.001
Dyslipidaemia (%)	666 (48.3)	354 (61.7)	<0.001
COPD/SAS (%)	219 (15.9)	123 (21.4)	0.004
Renal disease (%)	229 (16.6)	148 (25.8)	<0.001
PAD (%)	68 (4.9)	50 (8.7)	0.001
Previous stroke (%)	229 (16.6)	102 (17.8)	0.545
Previous bleeding (%)	44 (3.2)	36 (6.3)	0.002
Heart disease (%)	593 (43.0)	344 (59.9)	<0.001
Heart failure (%)	341 (24.7)	213 (39.0)	<0.001
CAD (%)	200 (14.5)	156 (27.0)	<0.001
Hb (g/dL)	13.8±1.7	13.2±1.7	<0.001
GFR (mL/min)	67.2±22.8	63.7±23.2	<0.001
BMI (kg/m <sup>2</sup> )	28.5±4.5	30.0±5.5	<0.001
Charlson Index (Media)	0.8±0.9	2.0±1.1	<0.001
CHADS <sub>2</sub> score (Media)	1.9±1.0	3.2±1.1	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score (Media)	3.3±1.5	4.7±1.5	<0.001
HAS-BLED score (Media)	1.9±1.0	2.3±1.1	<0.001
<b>Concomitant treatment</b>			
Diuretics	52.5	69.2	<0.001
ACEI	29.2	34.7	0.02
ARI	37.6	48.1	<0.001
Statins	50.1	66.9	<0.001
Beta-blockers	59.4	62.5	0.20
Digoxin	16.9	21.1	0.03
Calcium-antagonists	77.3	72.6	<0.001
Antiarrhythmicdrugs	25.6	22.3	0.12
Rhythm control strategy	40.1	33.6	0.007
<b>Anticoagulant therapy</b>			
VKA	75.0	77.7	0.21

DOAC	24.9	22.3	
TTR <sup>1</sup> (mean±SD)	62.7±25.3	58.5±24.4	0.002
TTR <sup>1</sup> < 65%	49.8	58.8	0.001
TTR <sup>1</sup> < 70%	56.3	65.5	0.001
TTR <sup>2</sup> (mean±SD)	66.1±24.5	61.5±23.1	<0.001

COPD: chronic obstructive pulmonary disease; SAS: sleep apnea syndrome; PAD: peripheral artery disease; CAD: coronary artery disease; Hb: haemoglobin; GFR: glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitors; ARI: aldosterone-receptor inhibitors; VKA: vitamin K antagonists; DOAC: direct oral anticoagulants; SD: standard deviation.<sup>1</sup>TTR calculated by Rosendaal method. <sup>2</sup>TTR calculated by direct method.

**TABLE 2. Cardiovascular outcomes according to the presence of diabetes.**

Outcomes	Total (%), n=1956 (%/year)	Non-diabetes, n=1382 (%/year)	Diabetes, n=574 (%/year)	p-value
Thromboembolic events	48 (2.45)	35 (2.53)	13 (2.26)	0.73
Stroke	45 (2.30)	32 (2.32)	13 (2.26)	0.94
TIA		5 (15.63)	2 (15.38)	
Haemorrhagic		5 (15.63)	1 (7.69)	
Ischaemic		22 (68.75)	10 (76.92)	
Major bleeding	146 (7.46)	93 (6.73)	53 (9.23)	0.05
Myocardial infarction	53 (2.70)	29 (2.10)	24 (4.18)	0.001
Total mortality	255 (13.03)	158 (11.43)	97 (16.9)	0.001
Cardiovascular mortality	107 (5.47)	55 (3.98)	52 (9.06)	<0.001
MACE	168 (8.58)	94 (6.8)	74 (12.89)	<0.001

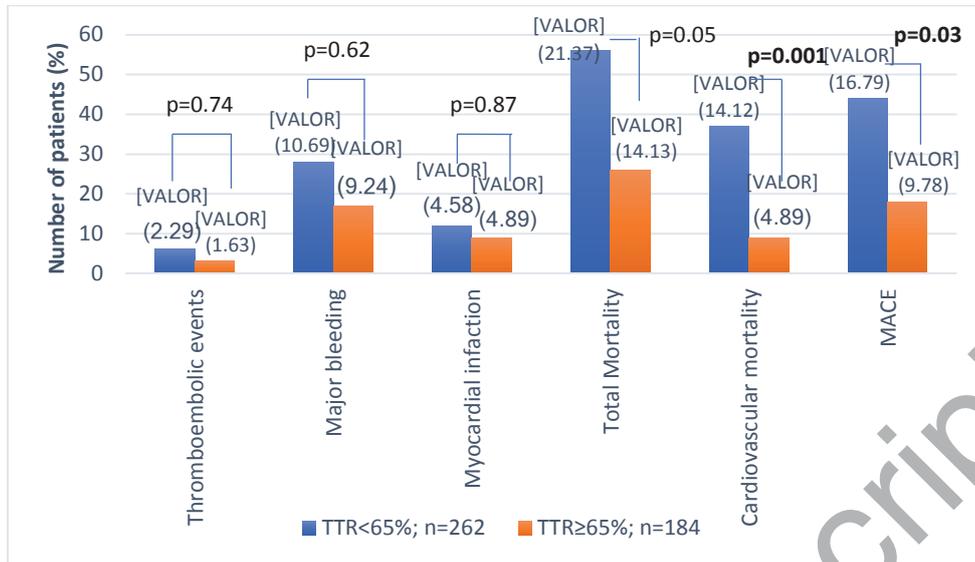
TIA: transient ischemic attack; MACE: Major adverse cardiovascular event (composite of ischaemic stroke, myocardial infarction and cardiovascular mortality).

**TABLE 3. Clinical factors related to adverse outcomes by multivariate Cox regression analysis.**

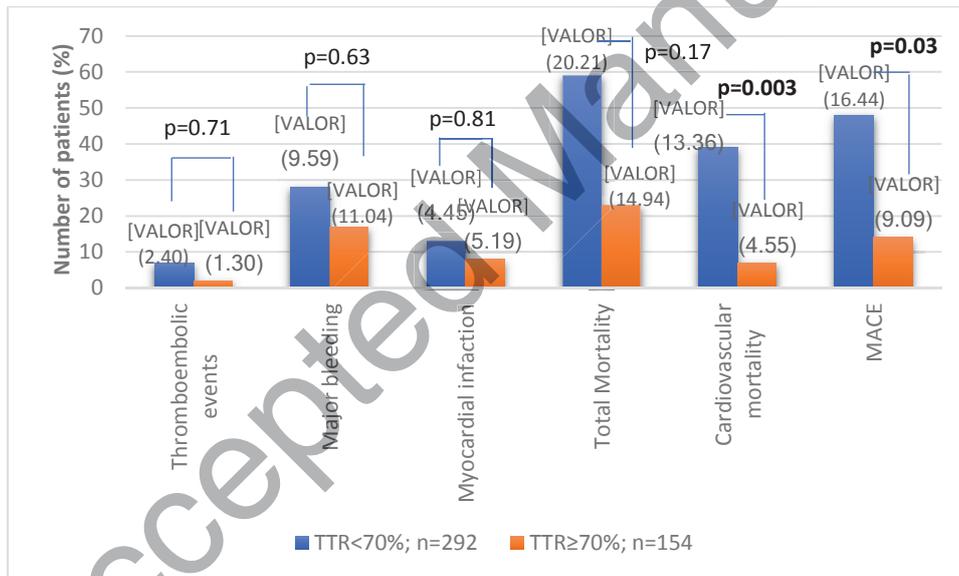
	HR	95% CI	p-value
	Major bleeding		
Renal disease	1.56	1.06-2.28	0.023
HAS-BLED score	1.29	1.08-1.55	0.005
	Total mortality		
Age	1.09	1.07-1.11	<0.001
Heart failure	1.71	1.25-2.34	0.001
Charlson index	1.33	1.15-1.54	<0.001
HAS-BLED score	1.34	1.16-1.55	<0.001
	Cardiovascular mortality		
DM	1.73	1.07-2.80	0.024
Age	1.08	1.05-1.12	<0.001
Heart failure	2.42	1.49-3.91	<0.001
Charlsson index	1.27	1.02-1.58	0.03
HAS-BLED score	1.27	1.02-1.57	0.03
	MACE		
Age	1.05	1.03-1.08	<0.001
Ischaemic heart disease	1.91	1.34-2.73	<0.001
Heart failure	1.90	1.23-2.93	0.004
HAS-BLED score	1.23	1.03-1.45	0.02

**FIGURE 1. Cardiovascular outcomes in diabetic patients according to Time in Therapeutic Range.**

A) TTR<65% versus TTR≥65%.



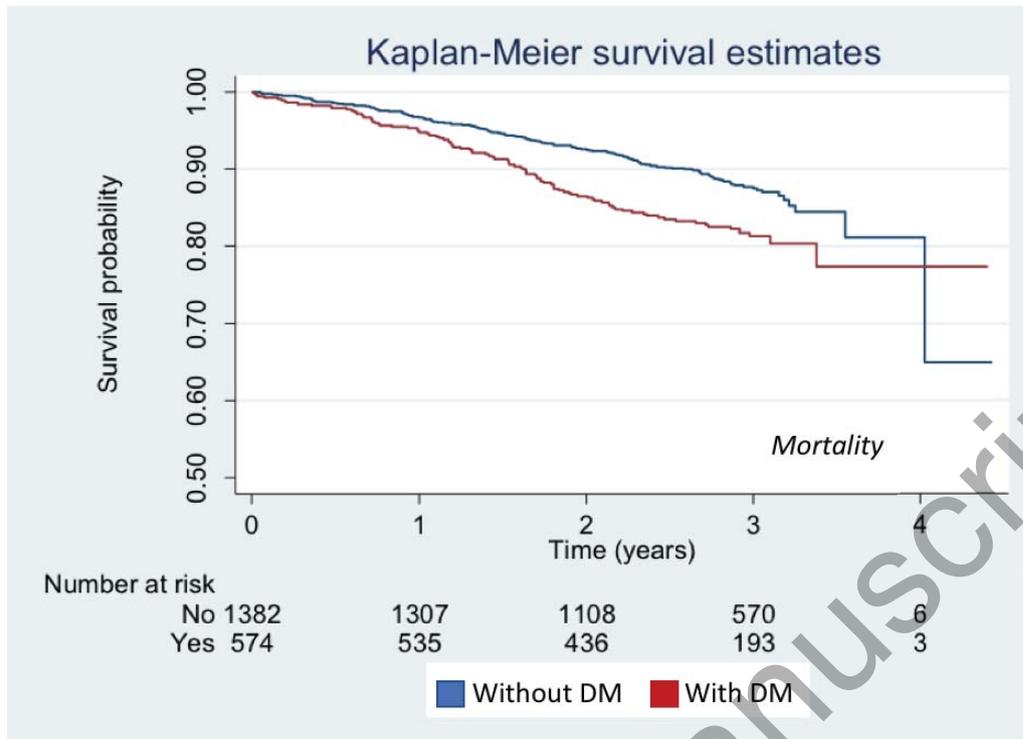
B) TTR<70% versus TTR≥70%.



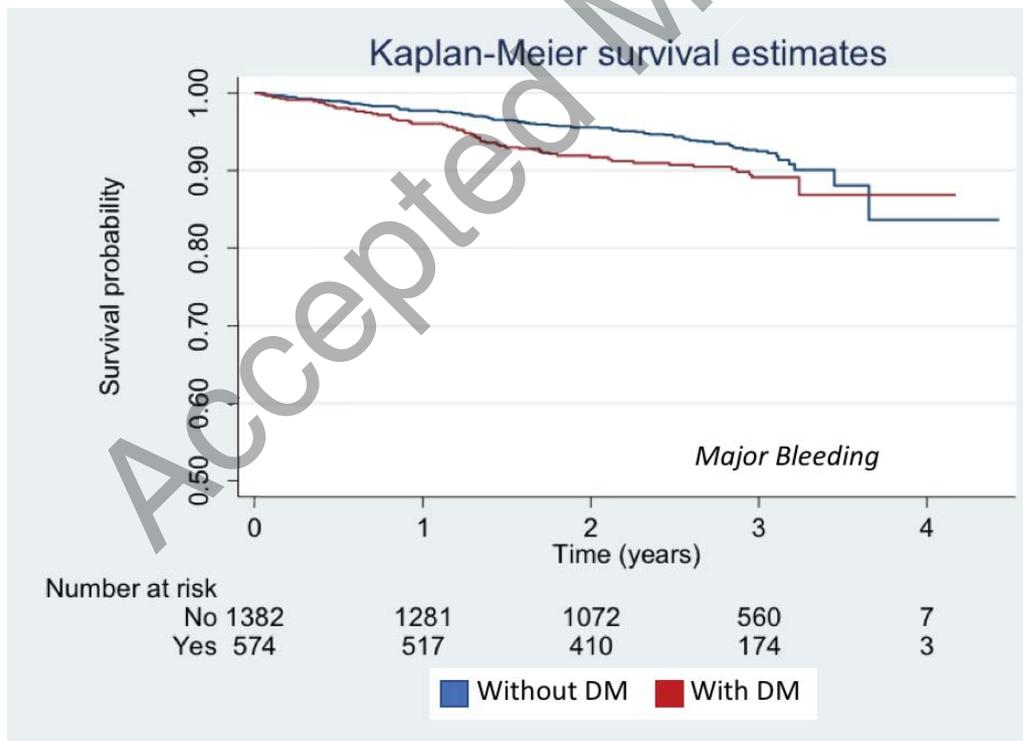
TTR: time in therapeutic range; MACE: Major adverse cardiovascular event (composite of ischaemic stroke, myocardial infarction and cardiovascular mortality).

FIGURE 2. Kaplan Meier survival curves for the different outcomes according to the presence of diabetes.

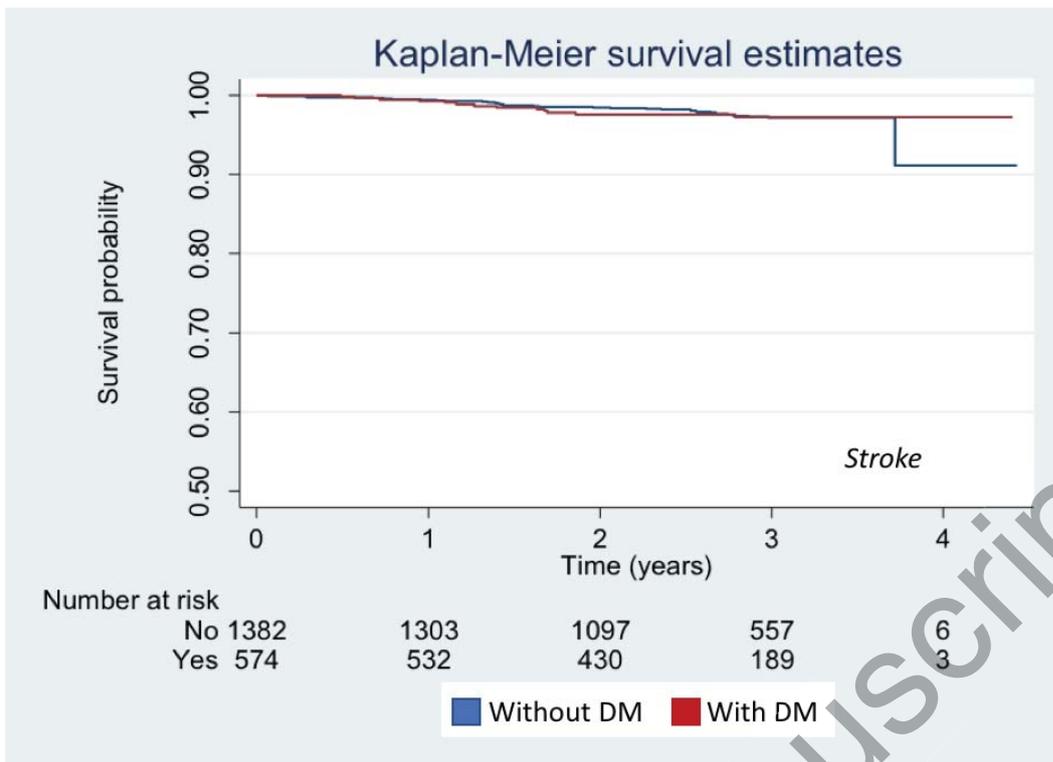
A) Total mortality ( $p < 0.001$ )



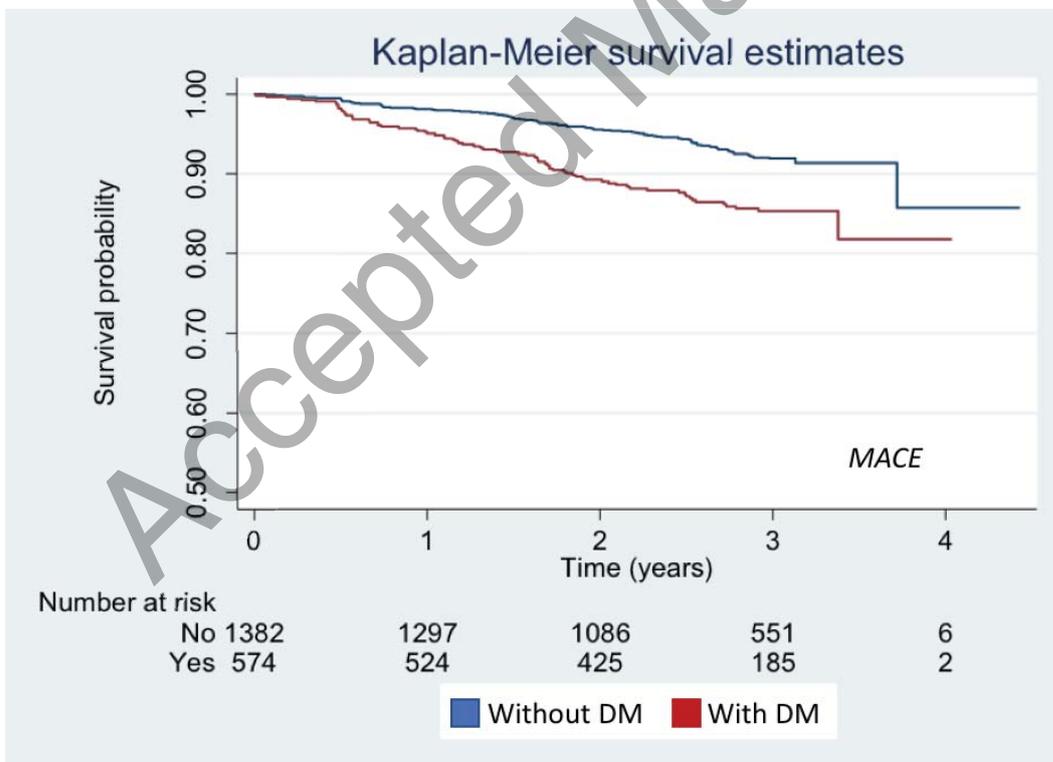
B) Major bleeding ( $p = 0.025$ )



**C) Stroke** ( $p=0.941$ )



**D) MACE** ( $p<0.001$ )



**Table 4. What is known and what the study adds to current knowledge on diabetes related atrial fibrillation.**

**WHAT IS KNOWN**

Atrial fibrillation and diabetes frequently coexist.

The risk of cardiovascular events seems greater in diabetes-related atrial fibrillation.

**WHAT THE STUDY ADDS**

A significant proportion (30%) of atrial fibrillation patients have diabetes.

Atrial fibrillation patients with diabetes are more likely to have other comorbidities.

Among those under vitamin K antagonists, coagulation status was more unstable than in non-diabetic individuals.

Diabetic subjects were less prone to undergo a rhythm control strategy.

The risk of developing adverse cardiovascular outcomes and death was greater in diabetic patients, particularly with lower TTR, and an independent association with cardiovascular mortality was found.

Accepted Manuscript

## 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(38):2893-962.
2. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R, Schilling R, et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemost*. 2017;117(5):837-850.
3. Deng H, Guo P, Zheng M, Huang J, Xue Y, Zhan X, et al. Epidemiological Characteristics of Atrial Fibrillation in Southern China: Results from the Guangzhou Heart Study. *Sci Rep*. 2018;8(1):17829.
4. Tamayo T, Rosenbauer J, Wild SH, Spijkerman AM, Baan C, Forouhi NG, et al. Diabetes in Europe: an update. *Diabetes Res Clin Pract*. 2014;103(2):206-17.
5. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, Del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes*. 2014;5(4):444-70.
6. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol*. 2005;105(3):315-8.
7. Tadic M, Cuspidi C. Type 2 diabetes mellitus and atrial fibrillation: From mechanisms to clinical practice. *Arch Cardiovasc Dis*. 2015;108(4):269-76.
8. KaramBS, Chavez-Moreno A, Koh W, Akar JG, Akar FG. Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes. *Cardiovasc Diabetol*. 2017;16(1):120.
9. Dublin S, Glazer NL, Smith NL, Psaty BM, Lumley T, Wiggins KL, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. *J Gen Intern Med*. 2010;25(8):853-8.
10. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, et al. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol*. 2014;114(8):1217-22.
11. Chang SH, Wu LS, Chiou MJ, Liu JR, Yu KH, Kuo CF, et al. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. *Cardiovasc Diabetol*. 2014;13:123.
12. Chao TF, Leu HB, Huang CC, Chen JW, Chan WL, Lin SJ, et al. Thiazolidinediones can prevent new onset atrial fibrillation in patients with non-insulin dependent diabetes. *Int J Cardiol*. 2012;156(2):199-202.
13. Zhang Y, Zhang P, Mu Y, Gao M, Wang JR, Wang Y, et al. The role of renin-angiotensin system blockade therapy in the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. *Clin Pharmacol Ther*. 2010;88(4):521-31.
14. Fumagalli S, Said SA, Laroche C, Gabbai D, Boni S, Marchionni N, et al. Management and prognosis of atrial fibrillation in diabetic patients: an EORP-AF General Pilot Registry report. *Eur Heart J Cardiovasc Pharmacother*. 2018;4(3):172-9.

15. Gage BF, Waterman AD, Shannon W, Boehler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864-70.
16. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. 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(2):263-72.
17. Liang HF, Du X, Zhou YC, Yang XY, Xia SJ, Dong JZ, et al. Control of Anticoagulation Therapy in Patients with Atrial Fibrillation Treated with Warfarin: A Study from the Chinese Atrial Fibrillation Registry. *Med Sci Monit*. 2019;25:4691-4698.
18. Prídavková D, Samoš M, Bolek T, Škorňová I, Zžolková J, Kubisz P, et al. Type 2 Diabetes, Atrial Fibrillation, and Direct Oral Anticoagulation. *J Diabetes Res*. 2019; 2019:5158308.
19. Bertomeu-González V, Anguita M, Moreno-Arribas J, Cequier Á, Muñoz J, Castillo-Castillo J, et al. Quality of Anticoagulation With Vitamin K Antagonists. *Clin Cardiol*. 2015;38(6):357-64.
20. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. 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*. 2010;138(5):1093-100.
21. 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(5):373-83.
22. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69(3):236-9.
23. Schulman S, Kearon C, Haemostasis SoCoAotSaSCotIsoTa. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-4.
24. Echouffo-Tcheugui JB, Shrader P, Thomas L, Gersh BJ, Kowey PR, Mahaffey KW, et al. Care Patterns and Outcomes in Atrial Fibrillation Patients With and Without Diabetes: ORBIT-AF Registry. *J Am Coll Cardiol*. 2017;70(11):1325-35.
25. Lane DA, Skjøth F, Lip GYH, Larsen TB, Kotecha D. Temporal Trends in Incidence, Prevalence, and Mortality of Atrial Fibrillation in Primary Care. *J Am Heart Assoc*. 2017;6(5). doi: 10.1161/JAHA.116.005155.
26. Wang A, Green JB, Halperin JL, Piccini JP. Atrial Fibrillation and Diabetes Mellitus: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;74(8):1107-15.
27. Sugishita K, Shiono E, Sugiyama T, Ashida T. Diabetes Influences the Cardiac Symptoms Related to Atrial Fibrillation. *Circ J* 2003; 67: 835 – 838.
28. Trines SA, Stabile G, Arbelo E, Dagues N, Brugada J, Kautzner J, et al. Influence of risk factors in the ESC-EHRA EORP atrial fibrillation ablation long-term registry. *Pacing Clin Electrophysiol*. 2019.; 42(10):1365-1373.
29. Soran H, Banerjee M, Mohamad JB, Adam S, Ho JH, Ismaeel SM, et al. Risk Factors for Failure of Direct Current Cardioversion in Patients with Type 2 Diabetes Mellitus and Atrial Fibrillation. *Biomed Res Int*. 2018;2018:5936180.
30. Donnellan E, Aagaard P, Kanj M, Jaber W, Elshazly M, Hoosien M, et al. Association Between Pre-Ablation Glycemic Control and Outcomes Among Patients

With Diabetes Undergoing Atrial Fibrillation Ablation. *JACC Clin Electrophysiol.* 2019;5(8):897-903.

31. Esteve-Pastor MA, Rivera-Caravaca JM, Roldán-Rabadán I, Roldán V, Muñiz J, Raña-Míguez P, et al. Quality of oral anticoagulation with vitamin K antagonists in 'real-world' patients with atrial fibrillation: a report from the prospective multicentre FANTASIA registry. *Europace.* 2018;20(9):1435-41.

32. Nelson WW, Choi JC, Vanderpoel J, Damaraju CV, Wildgoose P, Fields LE, et al. Impact of co-morbidities and patient characteristics on international normalized ratio control over time in patients with nonvalvular atrial fibrillation. *Am J Cardiol.* 2013;112(4):509-12.

33. Liang HF, Du X, Zhou YC, Yang XY, Xia SJ, Dong JZ, et al. Control of Anticoagulation Therapy in Patients with Atrial Fibrillation Treated with Warfarin: A Study from the Chinese Atrial Fibrillation Registry. *Med Sci Monit.* 2019;25:4691-8.

34. Patti G, Lucerna M, Cavallari I, Ricottini E, Renda G, Pecan L, et al. Insulin-Requiring Versus Noninsulin-Requiring Diabetes and Thromboembolic Risk in Patients With Atrial Fibrillation: PREFER in AF. *J Am Coll Cardiol.* 2017;69(4):409-19.

35. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154(13):1449-57.

Accepted Manuscript