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Insulin-requiring versus non-insulin requiring diabetes and thromboembolic risk in patients with atrial fibrillation: a PREFER in AF Registry substudy

Short title: Types of diabetes and thromboembolism in AF

Giuseppe Patti[a], MD, FACC, Markus Lucerna[b], PhD, Ilaria Cavallari[a], MD,

Elisabetta Ricottini[a], MD, Giulia Renda[c], MD, PhD, Ladislav Pecen[d], PhD, Fabio Romeo[e], MD,

Jean-Yves Le Heuzey[f], MD, Josè Luis Zamorano[g], MD, PhD, Paulus Kirchhof[h,i], MD,

and Raffaele De Caterina[c,l], MD, PhD

[a] Department of Cardiovascular Sciences, Campus Bio-Medico University of Rome, Italy; [b] Daiichi Sankyo Europe, Munich, Germany; [c] G. d'Annunzio University of Chieti, Italy; [d] Institute of Informatics, Academy of Sciences of Czech Republic, Prague, Czech Republic; [e] Daiichi Sankyo Italy, Rome, Italy; [f] Cardiology and Arrhythmology, Georges Pompidou Hospital, René Descartes University, Paris, France; [g] Department of Cardiology, University Hospital Ramòn y Cajal, Madrid, Spain; [h] Institute of Cardiovascular Sciences, University of Birmingham and SWBH and UHB NHS Trust, Birmingham, UK; [i] Hospital of the University of Münster, Germany; [l] Fondazione G. Monasterio, Pisa, Italy

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Address for correspondence:

Giuseppe Patti, MD,
Department of Cardiovascular Sciences,
Campus Bio-Medico University of Rome,
Via Alvaro del Portillo, 200
00128 Rome, Italy
Tel. +39-06-225411612
Fax. +39-06-225411935
Email g.patti@unicampus.it

ABSTRACT

Objectives. We evaluated the differential role of diabetes with insulin versus without insulin therapy on the thromboembolic risk in patients with atrial fibrillation (AF).

Background. Diabetes is a known risk predictor for thromboembolic events in patients with AF, but no study has explored the prognostic weight of insulin-requiring versus non-insulin requiring diabetes in this setting.

Methods. We accessed individual patients' data from the prospective, real-world, multicenter, European Prevention of thromboembolic events-European Registry in Atrial Fibrillation (PREFER in AF). We compared the rates of stroke/systemic embolism at one year according to the diabetic status (no diabetes, diabetes without insulin therapy, diabetes on insulin therapy).

Results: Out of an overall population of 5,717 patients, 1,288 had diabetes, 22.4% of whom were on insulin. Diabetes on insulin was associated with a significantly increased risk of stroke/systemic embolism at one year versus both no diabetes (5.2% versus 1.9%; HR 2.89, 95% CI 1.67-5.02; P=0.0002) and diabetes without insulin treatment (5.2% versus 1.8%; HR 2.96, 1.49-5.87; P=0.0019). Notably, rates of stroke/embolism were similar in patients with diabetes not receiving insulin versus non-diabetic patients (HR 0.97, 0.58-1.61; P=0.90). The selective predictive role of insulin-requiring diabetes was independent of potential confounders, including diabetes duration, and was maintained in various subpopulations, including the subgroup receiving anticoagulant therapy.

Conclusions. In this cohort of anticoagulated patients with AF, the sole presence of diabetes not requiring insulin does not imply an increased thromboembolic risk. Conversely, insulin-requiring diabetes contributes most, if not exclusively, to the overall increase of thromboembolic risk in AF.

Key words: atrial fibrillation; diabetes; insulin; thromboembolic risk; stroke; systemic embolism; risk prediction.

ABBREVIATIONS:

AF= Atrial fibrillation

CI= Confidence interval

ENGAGE AF-TIMI 48= Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48

HR= Hazard ratio

PAI-1= Plasminogen activator inhibitor type 1

PREFER= Prevention of thromboembolic events - European Registry

tPA= Tissue-plasminogen activator

VKA= Vitamin K antagonists

INTRODUCTION

The evaluation of the thromboembolic risk is crucial in patients with atrial fibrillation (AF) in order to perform an accurate stratification of risk during follow-up and establish optimal therapeutic strategies. Diabetes mellitus has been considered an independent risk factor for thromboembolic events in AF patients (1), and this has led to inclusion of such parameter in the $CHADS_2$ score (2) and the more recent CHA_2DS_2-VASc score (3). Patients with diabetes mellitus have a pro-thrombotic state due to changes in primary (platelet aggregation and vascular function) and secondary (coagulation and fibrinolysis) hemostasis, and this is particularly enhanced in those with long-lasting disease receiving insulin therapy (4). Here, low-grade inflammation, increased levels of coagulation factors, impairment of fibrinolysis, oxidative stress and reduced expression of protective endothelial factors have been indicated as responsible for these prothrombotic changes (4). This is the basis for hypothesizing a stronger predictive role of diabetes requiring insulin therapy compared with less severe forms of diabetes, usually not requiring insulin, on the AF-related thromboembolic risk. To date, no study has explored the differential prognostic weight of diabetes on insulin therapy vs diabetes without insulin therapy on the association between diabetes and thromboembolic events in patients with AF. We have explored this issue in a recent multicenter, European AF registry.

METHODS

We accessed individual patients' data from the Prevention of thromboembolic events - European Registry in Atrial Fibrillation (PREFER in AF Registry) (5). PREFER in AF was a prospective, observational, real-world registry enrolling 7,228 AF patients from 461 hospitals in 7 European countries (Austria, France, Germany, Italy, Spain, Switzerland and United Kingdom). The first patient was enrolled in January 2012, and the last follow-up visit was done in January 2014. Inclusion criteria were: age ≥18 years; written informed consent to participate the study; history of

AF within the preceding 1 year, as demonstrated by an electrocardiogram or by an implanted pacemaker/defibrillator. Patients were included irrespective of the type of AF. In order to reduce selection bias, patients were consecutively enrolled at each site, with no explicit exclusion criteria. The study design consisted of a baseline clinical evaluation at the time of patient enrollment and at 1-year follow-up. Demographic data, clinical characteristics, risk factors and treatment modalities were collected at baseline; at this time the documentation related to previous AF episodes and AF-related antithrombotic therapy within 1 year was also inspected, if needed. The follow-up was performed by office visit at 12±2 months. For the purpose of this study we only included patients with a complete CHA_2DS_2-VASc score evaluation and with both baseline and 1-year follow-up visits. Only documented stroke or systemic embolism were considered as relevant efficacy endpoints, with the date of any event being after the baseline visit.

Individual data were entered into an electronic case report form including various plausibility checks for the considered variables. Furthermore, on-site verification of source data was performed in approximately 5% of the centers. The study management was overseen by a scientific Steering Committee; the registry was sponsored by Daiichi Sankyo Europe GmbH (Munich, Germany) via a contract research organization (SSS International Clinical Research GmbH – Munich, Germany) coordinating various local national contract research organizations.

Definitions and endpoints

For the purpose of this study, diabetic patients were separately considered if they were or were not on insulin therapy (6). Primary study endpoint was the incidence of stroke/systemic embolism at the 1-year follow-up according to the diabetes status (no diabetes, non-insulin requiring diabetes, insulin-requiring diabetes). Stroke and systemic embolism were defined following the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) definitions (7): *Stroke:* abrupt onset of a focal neurologic deficit, generally distributed in the territory of a single brain artery (including the retinal artery), and

that is not attributable to an identifiable nonvascular cause (i.e., brain tumor or trauma). The deficit must either be characterized by symptoms lasting >24 hours or cause death within 24 hours of symptom onset. Stroke definition used in ENGAGE and in our study reflects the *Statement for Healthcare Professionals From the American Heart Association/American Stroke Association* (8), that incorporates the *World Health Organization (WHO)* definition of stroke (9). *Systemic embolic event:* abrupt episode of arterial insufficiency with clinical or radiologic documentation of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation); venous thromboembolism and pulmonary embolism were also included in this outcome measure. Arterial embolic events involving the central nervous system (including the eye) were not considered as systemic embolism.

Statistics

For categorical variables, absolute and percentage frequencies (n, %) are presented. For continuous variables, mean and standard deviation are presented. For the analyses of the time-to-stroke/systemic embolism the Cox proportional hazard regression model was used, with diabetes status as fixed effect. The hazard ratio (HR), the 95% confidence interval (CI) and the corresponding p value are presented. These analyses were repeated for different subgroups of patients based on the demographic/clinical characteristics indicated in **Table 1.** In addition, these characteristics were added as single covariates to the model. Comparisons of all demographic/clinical characteristics for the diabetes status were executed by means of a logistic regression model presenting the odds ratio, the 95% confidence interval and the corresponding p value. All analyses are not confirmatory, but purely descriptive/exploratory. All statistical analyses were performed using SAS version 9.3.

RESULTS

From the overall PREFER in AF population (N=7,228), a total of 816 patients had no one-year follow-up visit; therefore the full analysis set consisted of 6,412 patients, 695 of whom were excluded because of lack of information on stroke/systemic embolic event and/or no availability of CHA_2DS_2-VASc scoring and/or no information on diabetes status (**Figure 1**). Thus, a total of 5,717 patients were included in this sub-analysis. Prevalence of thromboembolic risk factors and different anti-thrombotic therapies in patients included in this analysis was consistent with the overall PREFER in AF population (data not shown). Among those 5,717 patients, a total of 1,288 had diabetes mellitus (22.5%), 288 of whom were on insulin treatment (22.4%). Patients with diabetes, irrespective of the insulin therapy status, had an increased prevalence of systemic hypertension, congestive heart failure, prior transient ischemic attack/stroke/thromboembolism, vascular disease, chronic renal impairment, left atrial enlargement, chronic obstructive pulmonary disease and body mass index >30 kg/m^2 compared to non-diabetic patients (**Table 1**). Patients receiving insulin showed higher percentages of congestive heart failure, vascular disease, chronic renal impairment, chronic obstructive pulmonary disease and body mass index >30 kg/m^2 versus those with non-insulin requiring diabetes. Of note, in our study population only 18 patients had type 1 diabetes, with only one patient experiencing a thromboembolic event during the follow-up.

We also evaluated the prevalence of different antithrombotic strategies in the various subgroups (**Table 1**). Compared with non-diabetic patients, those on insulin treatment had higher use of vitamin K antagonists (VKA) plus antiplatelet therapy (16.7% vs 9.6%, P=0.0002) at baseline and higher utilization of VKAs (71.5% vs 62.9%, P=0.0036) at one year. No antithrombotic therapy was less frequent in diabetic patients on insulin both at baseline and at one year (2.4% vs 6.4% in non-diabetic patients, P=0.0093 and 5.6% vs 9.6%, P=0.0238, respectively). Antithrombotic therapy was similar in diabetic patients with and without insulin, with the exception of a higher prevalence of VKAs plus an antiplatelet agent at baseline in the former (16.7% vs 11.1%, P=0.0120). In the comparison between non-diabetic patients and diabetic patients not receiving insulin, the latter more frequently were given VKAs only at baseline (69.8% vs 66.2%,

P=0.030) and less frequently received antiplatelet treatment and no antithrombotic drug both at baseline and at 1 year.

In the overall population, the incidence of stroke/systemic embolism at 1 year was 2.0 per 100 patients/year. Insulin-requiring diabetes was associated with a higher risk of stroke/systemic embolism versus both no diabetes (5.2 per 100 patients/year vs 1.9 per 100 patients/year; HR 2.89, 95% CI 1.67-5.02; P=0.0002) and non-insulin requiring diabetes (5.2 per 100 patients/year vs 1.8 per 100 patients/year; HR 2.96, 1.49-5.87; P=0.0019) (**Figure 2**). Rates of stroke/systemic embolism were not different in patients with diabetes not receiving insulin and in non-diabetic patients (HR 0.97, 0.58-1.61; P=0.90). Adjustment for potential confounders provided similar results (**Table 2**). After the addition of the various risk factors as covariates to the COX proportional hazard regression model, the correlation between diabetes on insulin therapy and the higher occurrence of thromboembolic events remained always significant, with HRs ranging from 2.60 to 3.52 (**Table 3**).

In the comparison between insulin-requiring diabetes and non-insulin requiring diabetes, out of 15 tested covariates, 2 had statistically significant interactions with the group; in particular, the relative increase of thromboembolic events related to insulin therapy was higher in patients with congestive heart failure (vs those without) and in patients receiving antithrombotic therapy at baseline. Conversely, the HR of the comparison of patients with no diabetes versus patients with non-insulin requiring diabetes remained consistently non-significant (**Table 3**).

The prevalence of sustained (persistent or permanent) AF tended to be higher in patients on insulin treatment (80% vs 76% in diabetic patients not receiving insulin and 67% in patients without diabetes). However, adjustment for the type of AF did not change the overall study results; in particular, the HR of stroke/systemic embolism with insulin-requiring diabetes mellitus vs no diabetes was 2.83, 95% CI 1.60-5.03 (P=0.0004); the HR of stroke/systemic embolism with insulin-requiring diabetes mellitus vs diabetes without insulin therapy was 2.98, 95% CI 1.48-6.02

(P=0.0023); and the HR of stroke/systemic embolism with non-insulin requiring diabetes mellitus vs no diabetes was 0.98, 95% CI 0.59-1.63 (P=0.94).

We could collect additional patient-level data on diabetes duration, daily insulin dose, presence/absence of microvascular complications, and use of oral glucose-lowering agents in a subgroup of 344 diabetic patients (i.e., 27% of the overall diabetic study population). The risk profile of these 344 patients providing additional data on diabetes duration was similar to that of the remaining population of diabetic patients (age 73.3±9.2 vs 72.7± 8.6 years, P=0.31; female gender 36% vs 37%, P=0.66; mean CHA_2DS_2-VASc score 4.7±1.6 vs 4.6±1.6, P=0.42). The duration of diabetes was higher in diabetic patients on insulin vs those not receiving insulin (12.8±8.2 yrs vs 9.2±6.7 yrs; P=0.0003), but the HR of stroke/systemic embolism with insulin therapy, adjusted for duration of diabetes, remained significant (HR 8.72, 95% CI 2.89-26.33; P=0.0001).

The total daily insulin dose was similar in patients with vs without stroke/systemic embolism (37.8±9.9 IU vs 38.5±26.2 IU; P=0.22), and no relationship between insulin dose and the occurrence of thromboembolic events was observed (HR 1.00, 95% CI 0.98-1.02; P=0.94). We found a significantly higher risk of stroke/systemic embolism in patients with at least one microvascular complication of diabetes (retinopathy, neuropathy or nephropathy): HR 9.27, 95% CI 2.07-41.41; P=0.0036. We also attempted an analysis of different therapies in non-insulin requiring diabetes (diet vs oral antidiabetic agents, or among various classes of oral antidiabetic drugs), but these analyses were precluded by the overall low rate of thromboembolic events observed in these subgroups.

We also evaluated the risk of stroke/systemic embolism in patients without diabetes, with diabetes not receiving insulin and in those with insulin-requiring diabetes according to different subgroups, including: presence or absence of: female gender, age ≥75 years, congestive heart failure, systemic hypertension, previous transient ischemic attack/stroke, any vascular disease, chronic obstructive pulmonary disease, chronic renal impairment, body mass index >30 kg/m^2,

CHA_2DS_2-VASc score >1, coronary artery disease, peripheral artery disease, use of anticoagulant therapy. The highest incidence of thromboembolic events in patients with diabetes on insulin treatment and the absence of any significant difference in thromboembolic events in patients with diabetes without insulin treatment compared with those without diabetes were maintained across various subpopulations (**Figure 3**). Of note, among patients with diabetes on insulin therapy, the rate of stroke/systemic embolism was even high in those receiving any anticoagulant therapy at baseline (5.1 per 100 patients/year vs 6.1 per 100 patients/year in those without anticoagulation); the increased incidence of thromboembolic complications in diabetic patients receiving insulin was irrespective of the use of anticoagulant therapy (patients receiving any anticoagulant treatment: 5.1 per 100 patients/year in diabetic patients on insulin vs 1.6 per 100 patients/year in diabetic patients without insulin and 1.8 per 100 patients/year in non-diabetics; patients without anticoagulant therapy: 6.1 vs 3.5 vs 1.9 per 100 patients/year).

A total of 4,354 patients had no diabetes or non-insulin requiring diabetes and a CHA_2DS_2-VASc score >1; the occurrence of stroke/systemic embolism at 1 year in such patients was 2.0%. All patients with diabetes on insulin therapy had a CHA_2DS_2-VASc score >1 and showed an annual stroke/embolism rate of 5.2 per 100 patients/year (P=0.0005).

DISCUSSION

In this analysis of individual patients' data from the prospective PREFER in AF registry we found that diabetic patients on insulin therapy have a significantly higher risk of stroke/systemic embolism at 1 year versus both non-diabetic patients and diabetic patients without insulin treatment, but also that diabetes not treated with insulin does not entail a significantly increased risk.

The proportion of patients with diabetes in our population was 22.5%, of whom 22.4% were insulin-treated; this prevalence is similar to that observed in other contemporary registries on AF

patients (10). Of note, a 40% relative increase in the risk of development and progression of AF has been demonstrated in diabetic versus non-diabetic patients (11), and has been related to electrical and structural atrial remodeling, changes in the autonomic response, atrial inflammation and oxidative stress (12).

A wide range (from 3.6% to 8.6%) of annual incidence of thromboembolic events has been reported in diabetic patients with AF (11,13); this large variability reflects differences in study designs, definitions of outcome measures, patients' baseline risk profile, concomitant therapies and types of populations included. Previous large studies have found that AF patients with coexisting diabetes present a significantly higher risk of thromboembolic events compared to those without. In a previous meta-analysis on the topic, including 7 studies and >12,000 patients, a 70% relative increase in risk has been observed in diabetic patient (13). To date, however, no study had separately and independently quantified the annual rates of AF-related thromboembolic events in diabetic patients according to insulin treatment.

The surprising and unexpected finding of our study is the strikingly similar incidence of thromboembolic events at 1 year in patients with diabetes but no insulin treatment compared with non-diabetic patients. The absence of increased risk of events in the former was consistent in the various analyses here performed even after adjustments for both clinical confounders and concomitant antithrombotic therapy. Of note, the events rate was similar in non-diabetic patients and in patients with diabetes not receiving insulin despite the latter having a higher thromboembolic risk profile (i.e., older age, higher prevalence of hypertension, congestive heart failure, previous cerebrovascular events, vascular disease, chronic renal failure). Thus, according to our data, the sole presence of diabetes does not imply an increased thromboembolic risk in AF patients. Conversely, diabetic patients receiving insulin had an approximately 2.5-fold higher risk of stroke or systemic embolism at 1 year compared both to patients without diabetes and to patients with non-insulin requiring diabetes. Of note, this higher risk was more pronounced between 6 months and 1 year of follow-up. A clustering of risk factors likely contributes to this heightened risk, since patients with

diabetes on insulin treatment had a longer diabetes duration, as well as higher prevalence cardiovascular risk factors, congestive heart failure, chronic pulmonary disease and renal impairment than patients without diabetes or those with diabetes not requiring insulin. However, the association between insulin-requiring diabetes and thromboembolic events was independent of the type of AF and of other possible confounding factors here examined; this association was also maintained in various subgroups, including the subpopulation of patients receiving anticoagulant therapy.

We observed no relationship of daily insulin dose and thromboembolic risk. We cannot exclude a type II error in these results, and it is possible that the daily doses of insulin – marking a diabetes of particular severity – could be related to outcomes in larger cohorts or with a longer follow-up. Of note, diabetic patients with microvascular complications (retinopathy, neuropathy or nephropathy) featured a significantly increased incidence of thromboembolic events. Importantly, however, the selectively increased thromboembolic risk of patients receiving insulin – with no apparent increase in risk in the other set of diabetic patients – was independent of all potential confounders from parameters collected in the PREFER in AF Registry here assessed, also including duration of diabetes (14).

Similar data supporting a differential prognostic role of diabetes with vs without insulin therapy have been described in at least one other setting; in particular, an analysis from the SHIFT trial on patients with chronic systolic heart failure (15) showed no increased incidence of cardiovascular death or hospitalization for worsening heart failure in diabetic patients not receiving insulin compared to non-diabetic patients, and a significant 33% higher risk of this outcome measure in diabetic patients on insulin compared to those not on insulin.

Therefore, according to our data, diabetes needing insulin therapy, rather than the presence of diabetes per se, appears to be an independent factor affecting the occurrence of AF-related stroke/systemic embolism during follow-up. Results of this study may thus expand and strengthen

observational data from certain investigations suggesting no overall increase of thromboembolic risk in diabetic patients (16-20); a different prevalence of patients receiving insulin (generally not reported in most studies) may at least in part explain the important variability in the reported annual rates of thromboembolic events among diabetic patients and the variable degree of increase in the thromboembolic risk by diabetes mellitus in the various studies.

Several pathophysiological mechanisms may explain the findings of this study. In patients with diabetes mellitus there is a hypercoagulable state, and this is particularly evident and pronounced in those with long-lasting disease receiving insulin therapy. In the latter, an increase in platelet reactivity and platelet turnover has been described, with a consequently more pronounced platelet activation (21). Moreover, a high inflammatory status and oxidative stress cause endothelial dysfunction, with higher expression of adhesion molecules, reduced release of nitric oxide/prostacyclin and increased production of endothelin-1 (4,22-24). Diabetic patients on insulin treatment also show increased levels and/or activity of various coagulation factors, including tissue factor, factor VII, von Willebrand factor and fibrinogen, as well as enhanced thrombin generation (21,25,26). Finally, lower tissue-plasminogen activator (tPA) activity, higher levels of type 1 plasminogen activator inhibitor (PAI-1) (27,28) and higher levels of incorporation of the C3 complement component in the clot (29) have been demonstrated in such patients, leading to impaired fibrin clot lysis. The presence of insulin treatment is therefore certainly a marker for more advanced disease. Insulin may however also called into play as triggering by itself some of the disease features, including atherosclerosis (30). While the precise mechanisms triggering changes in coagulation in diabetic patients receiving insulin therapy are not completely known, chronic exposure to high glucose levels, increased levels of advanced glycosylation end products, and also direct effects of exogenous insulin, providing pathologically high levels of insulin in the setting of insulin resistance, as occurring in all type 2 diabetic patients receiving insulin, are all possibly involved (30,31).

This work has strengths in being a prospective analysis on AF patients who received a complete baseline assessment and underwent a planned follow-up visit at 1 year with accurate evaluation of the outcome measures. Limitations are that we could not establish the thromboembolic risk of the untreated population included, or the risk in relation to specific antithrombotic therapies. However, the crude increase in thromboembolic risk occurred in the presence of insulin-requiring diabetes is probably even higher than that detected in our investigation: in fact, patients on insulin had a higher prevalence of VKA use and less frequently received no antithrombotic drug than those without diabetes, while they more often were given VKAs plus antiplatelet drugs than those with diabetes without insulin. Thus, it is unlikely that we overestimated the risk of insulin-requiring diabetic patients in our study. Furthermore, residual confounding cannot be excluded and, due to the size of the population, we could not stratify the thromboembolic risk of diabetic patients on insulin therapy according to different CHA_2DS_2-VASc scores (score 1 versus >1). The issue of whether the relationship between the type of diabetes and thromboembolic risk was irrespective of the duration of diabetes was evaluated in approximately ¼ of the diabetic population within PREFER in AF (344 patients, 27%), representative of the entire original cohort of diabetic patients; in this subset, the HR of stroke/systemic embolism in patients with insulin therapy, compared with patients not on insulin, when adjusted for the duration of diabetes, remained significant. Therefore, main results of this sensitivity analysis continue to support one main conclusion of the paper, that insulin-requiring diabetes is a much worse condition than non-insulin requiring diabetes. Importantly, the risk profile of those 344 patients providing additional data on diabetes duration was similar to that of the remaining population of diabetic patients. We can therefore reasonably assume that the results of this further analysis were not affected by the selection of patients, and no bias was introduced in this secondary analysis. Finally, a non-uniform definition of diabetes mellitus might have been used in the study population according to local practices, and – more important – we have no data on the specific criteria for initiating insulin therapy and on glycemic control during follow-up. However, we consider unlikely

that use of non-uniform definitions of diabetes and criteria for initiating insulin therapy may have affected the study results, inasmuch as the physicians in the Western European countries participating in PREFER in AF are generally accustomed to contemporary, international guidelines for defining diabetes and initiating insulin treatment. Any such limitations should not however affect the main finding of our study, which is not only the higher risk of the insulin-requiring diabetes, likely clustering with a higher severity of diabetes, but rather the very low risk of non-insulin-requiring diabetes. This indicates for the first time a quite dichotomous behavior of the diabetic AF population as to thromboembolic risk according to the use or lack of use of insulin. Of note, results of our investigation apply essentially to patients with type 2 diabetes, who represented 98.6% of the diabetic population included, and it may be that insulin provision in type 1 diabetes, in the absence of insulin resistance, is not associated with increased thromboembolic risk.

In conclusion, our findings robustly indicate that insulin-requiring diabetes, essentially type 2 diabetes, largely contributes to the overall increase of thromboembolic risk in AF; while the mere presence of diabetes without insulin treatment does not apparently convey a negative prognostic value. Such findings have implications in the assessment of thromboembolic risk in the AF population with diabetes and might have therapeutic implications, which need however to be explored in further dedicated intervention studies.

Disclosures:

GP: speaker/consultant/advisory board for Bayer, Boehringer-Ingelheim, BMS-Pfizer, Daiichi Sankyo, Eli Lilly, Astra Zeneca and MSD. GR: speaker/consultant/advisory board for Boehringer-Ingelheim, Daiichi-Sankyo and Bayer. RDC: fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, MSD. ML is currently an employee of Daiichi Sankyo Europe. FR is currently an employee of Daiichi Sankyo Italy. J-YLH: consultant/conferences/advisory board for Sanofi-Aventis, BMS/Pfizer, Meda,

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FIGURE LEGENDS

Figure 1. Flow diagram indicating patients' disposition in the present study, leading to the final number of 5,717 patients here included.

Figure 2. Kaplan-Meier curves for incidence of stroke/systemic embolism according to diabetes status. DM= Diabetes mellitus; SEE= Systemic embolic events

Figure 3. Stroke or systemic embolism by subpopulations. CHA_2DS_2-VASc score ≤1 is 'female gender-corrected' (i.e. CHA_2DS_2-VASc ≤1 for males and CHA_2DS_2-VASc ≤2 for females).

AP= Antiplatelet; BL= Baseline; BMI= Body mass index; CHD= Coronary heart disease; CHF= Congestive heart failure; COPD= Chronic obstructive pulmonary disease; CRI= Chronic renal impairment; Hyp= Systemic hypertension; NOAC= Non-vitamin K antagonist oral anticoagulants; PAD= Peripheral artery disease; SEE= Systemic embolic events; TIA= Transient ischemic attack; VKA= vitamin K antagonists

Table 1. Main demographic/clinical characteristics in the study population according to diabetes status.

Variable	No DM N=4,429	Non-insulin requiring DM N=1,000	Insulin-requiring DM N=288	P value No DM vs non-insulin requiring DM	P value No DM vs insulin-requiring DM	P value Non-insulin requiring DM vs insulin-requiring DM
Age 65-74 yrs	1,431 (32.3)	384 (38.4)	97 (33.7)	0.0002	0.63	0.15
Age ≥75 yrs	1,941 (43.8)	453 (45.3)	137 (47.6)	0.40	0.22	0.50
Female gender	1,782 (40.2)	373 (37.3)	104 (36.1)	0.09	0.17	0.71
BMI >30 kg/m^2	1,089 (25.3)	377 (38.2)	133 (47.0)	<0.0001	<0.0001	0.0079
Systemic hypertension	2,998 (67.7)	852 (85.2)	255 (88.5%)	<0.0001	<0.0001	0.15
Congestive heart failure	1,146 (25.9)	342 (34.2)	164 (56.9)	<0.0001	<0.0001	<0.0001
Prior TIA/stroke/thromboembolism	635 (14.3)	192 (19.2)	67 (23.3)	0.0001	<0.0001	0.13
Vascular disease	846 (19.1)	295 (29.5)	133 (46.2)	<0.0001	<0.0001	<0.0001
Chronic renal impairment (Cr Cl <30 mL/min/1.73 m^2)	484 (11.1)	173 (17.7)	100 (36.4)	0.0001	<0.0001	<0.0001
Left atrial enlargement (antero-posterior diameter >40 mm)	2,529 (69.2)	650 (78.2)	190 (79.2)	<0.0001	0.0013	0.7532
Chronic obstructive pulmonary disease	434 (9.9)	131 (13.3)	62 (21.7)	0.0016	<0.0001	0.0005
Antithrombotic therapies at baseline						

NOAC	281 (6.3)	77 (7.7)	13 (4.5)	0.1192	0.2154	0.0648
VKA only	2933 (66.2)	698 (69.8)	194 (67.4)	0.0300	0.6943	0.4295
Antiplatelet only	505 (11.4)	82 (8.2)	26 (9.0)	0.0034	0.2183	0.6553
VKA plus antiplatelet	427 (9.6)	111 (11.1)	48 (16.7)	0.1634	0.0002	0.0120
No therapy	283 (6.4)	32 (3.2)	7 (2.4)	0.0001	0.0093	0.5036
Antithrombotic therapies at one year						
NOAC	576 (13.0)	152 (15.2)	32 (11.1)	0.0661	0.3533	0.0821
VKA only	2788 (62.9)	662 (66.2)	206 (71.5)	0.0538	0.0036	0.0897
Antiplatelet only	384 (8.7)	54 (5.4)	9 (3.1)	0.0007	0.0017	0.1193
VKA plus antiplatelet	255 (5.8)	62 (6.2)	25 (8.7)	0.5900	0.0435	0.1413
No therapy	426 (9.6)	70 (7.0)	16 (5.6)	0.0098	0.0238	0.3881

Values are given as N (%). BMI= Body mass index; DM= Diabetes mellitus; NOAC= non-vitamin K antagonist oral anticoagulants; TIA= Transient ischemic attack; VKA= vitamin K antagonists

Table 2. Adjusted risk of stroke/systemic embolic events at one year *

Comparison	HR	95% CI	P value
Insulin-requiring diabetes vs no diabetes	2.19	1.21-3.94	0.009
Insulin-requiring diabetes vs non-insulin requiring diabetes	2.61	1.26-5.43	0.01
Non-insulin requiring diabetes vs no diabetes	0.93	0.55-1.58	0.80

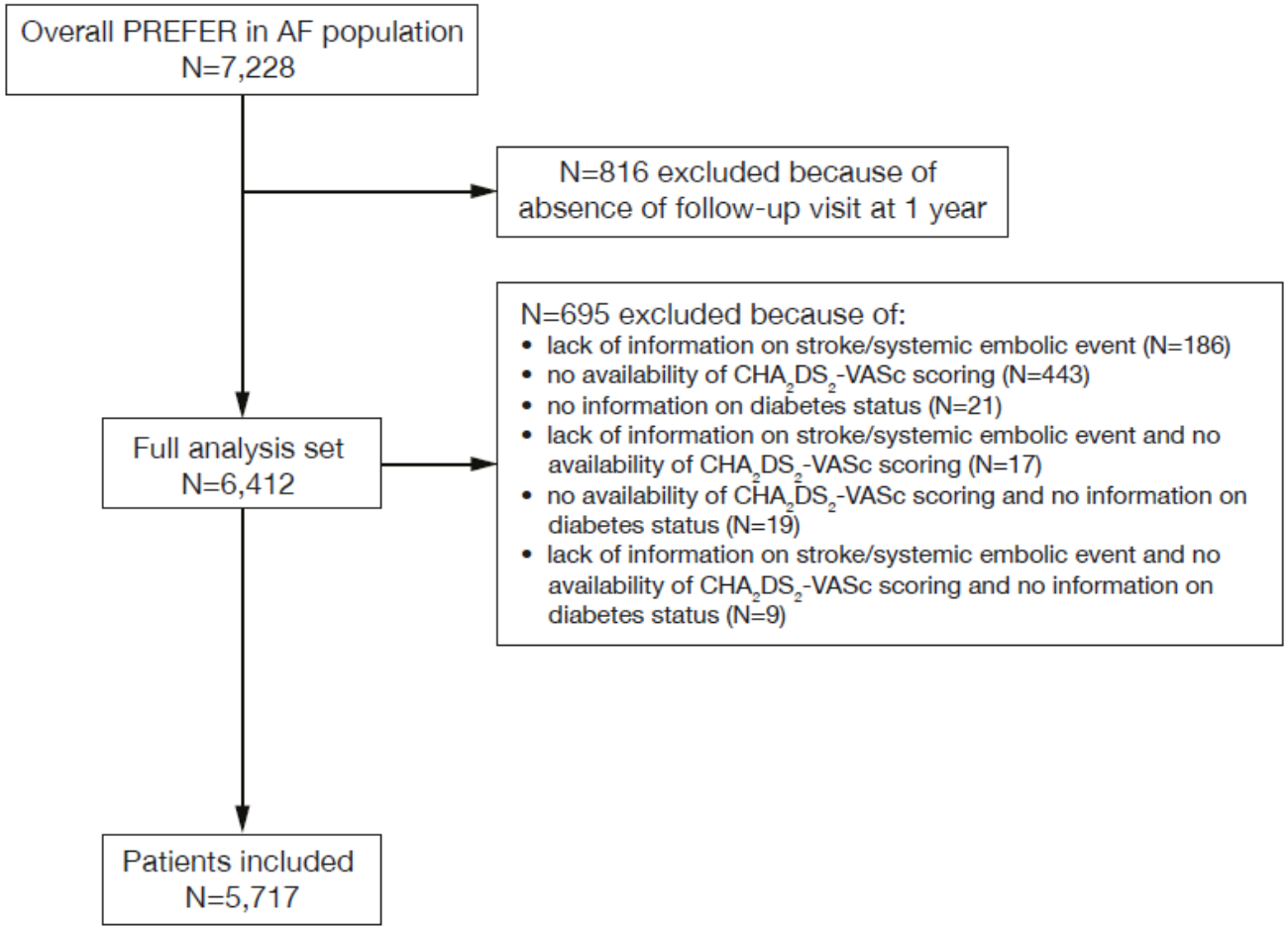
*Adjusted for congestive heart failure, systemic hypertension, age ≥75 yrs, prior stroke/transient ischemic attack/thromboembolism, vascular disease, female gender, chronic obstructive pulmonary disease, chronic renal impairment, body mass index >30 kg/m^2, CHA_2DS_2-VASc score 0-1, type of atrial fibrillation, vitamin K antagonist therapy, use of non-vitamin K antagonist oral anticoagulants, vitamin K antagonist plus antiplatelet therapy

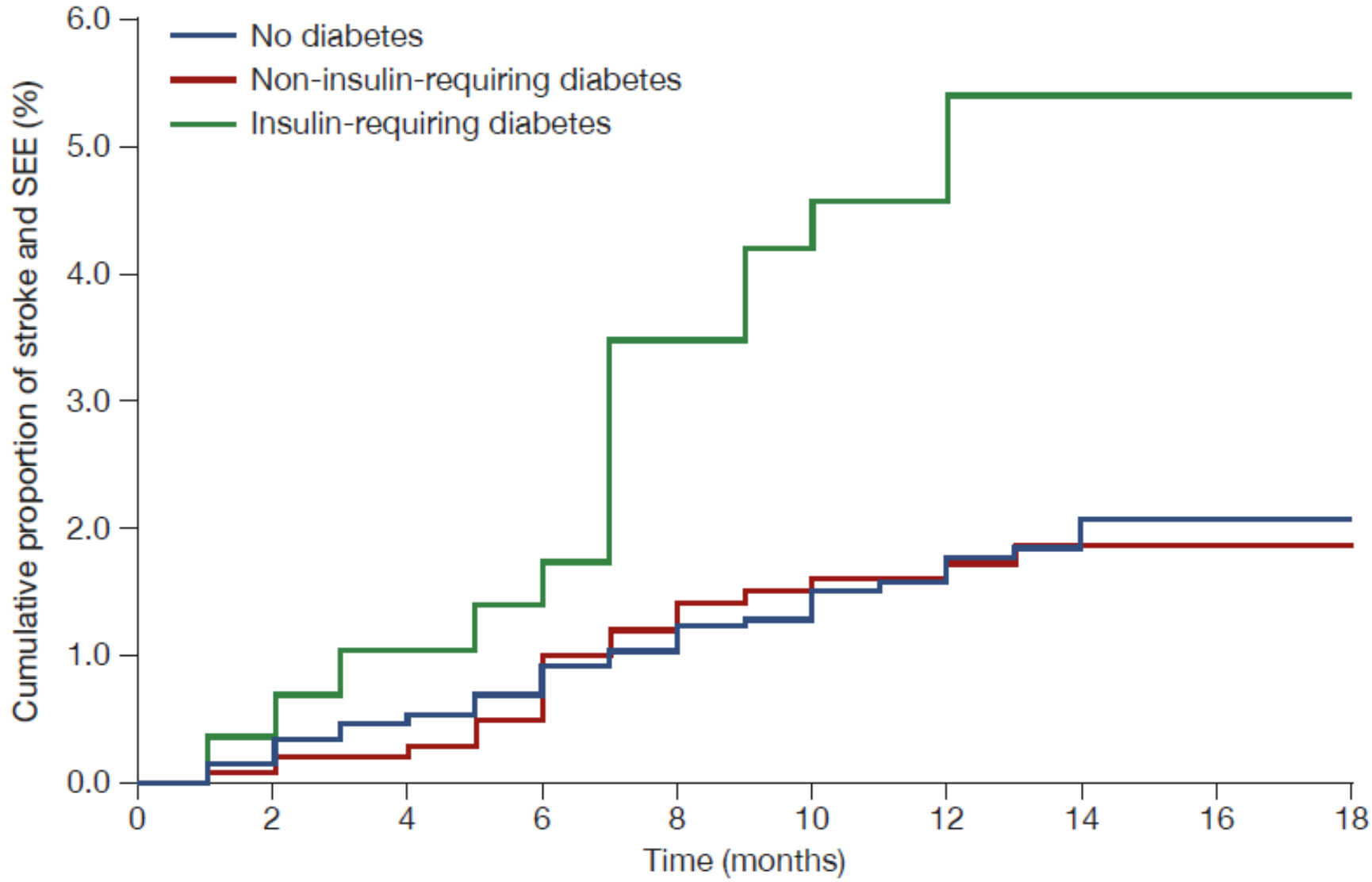
.

Table 3. COX Proportional Hazard Regression Model including various clinical characteristics as covariates.

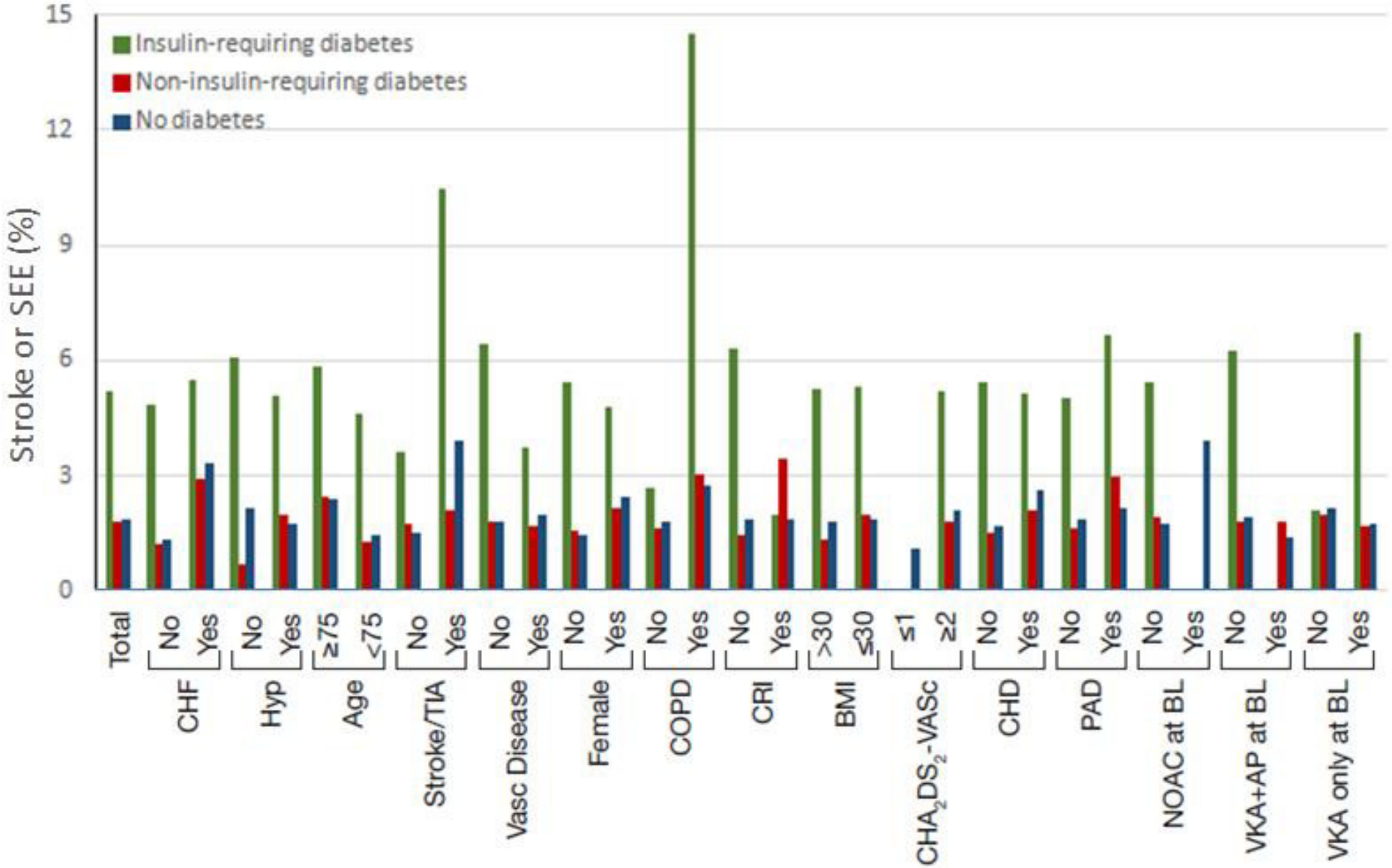
	HR	95% CI	P value	Interaction P value
Insulin-requiring diabetes vs non-insulin requiring diabetes	2.96	1.49-5.87	0.0019	
Congestive heart failure	2.60	1.28-5.25	0.0079	0.13
Systemic hypertension	2.92	1.47-5.81	0.0022	0.47
Age ≥75 yrs	2.92	1.47-5.80	0.0022	0.18
Previous transient ischemic attack/stroke/thromboembolism	2.87	1.45-5.70	0.0026	0.08
Vascular disease	3.11	1.55-6.23	0.0014	0.42
Age 65-74 yrs	2.92	1.47-5.80	0.0022	0.46
Female gender	2.96	1.49-5.88	0.0019	0.76
Left atrial enlargement	3.52	1.63-7.58	0.0014	0.11
Chronic obstructive pulmonary disease	2.60	1.30-5.19	0.0068	0.0008
Chronic renal impairment	2.82	1.40-5.66	0.0036	0.72
BMI >30 kg/m^2	3.19	1.59-6.40	0.0011	0.58
No anti-thrombotic therapy at baseline	3.05	1.54-6.06	0.0015	0.0027
VKA therapy at baseline	2.98	1.50-5.92	0.0018	0.37
Antiplatelet therapy at baseline	2.97	1.50-5.89	0.0019	0.60
VKA + antiplatelet therapy at baseline	3.07	1.54-6.10	0.0014	0.21
Non-insulin requiring diabetes vs no diabetes	0.97	0.58-1.61	0.90	
Congestive heart failure	0.89	0.53-1.48	0.65	<0.0001
Systemic hypertension	0.99	0.59-1.66	0.97	0.55
Age ≥75 yrs	0.96	0.58-1.60	0.88	0.011
Previous transient ischemic attack/stroke/thromboembolism	0.92	0.55-1.54	0.75	0.0002
Vascular disease	0.96	0.58-1.60	0.88	0.80
Age 65-74 yrs	0.99	0.59-1.64	0.95	0.14
Female gender	0.98	0.59-1.63	0.94	0.02
Left atrial enlargement	0.82	0.45-1.48	0.50	0.33
Chronic obstructive pulmonary disease	0.95	0.57-1.59	0.86	0.07
Chronic renal impairment	0.96	0.58-1.60	0.87	0.41
BMI >30 kg/m^2	0.94	0.56-1.60	0.83	0.68
No anti-thrombotic therapy at baseline	0.97	0.58-1.62	0.92	0.65
VKA therapy at baseline	0.97	0.59-1.62	0.92	0.33
Antiplatelet therapy at baseline	0.97	0.58-1.62	0.91	0.72
VKA + antiplatelet therapy at baseline	0.97	0.58-1.62	0.91	0.48

BMI= Body mass index; VKA= Vitamin K antagonist


Overall PREFER in AF population
N=7,228
N=816 excluded because of absence of follow-up visit at 1 year
N=695 excluded because of:
• lack of information on stroke/systemic embolic event (N=186)
• no availability of CHA2DS2-VASc scoring (N=443)
• no information on diabetes status (N=21)
• lack of information on stroke/systemic embolic event and no availability of CHA2DS2-VASc scoring (N=17)
• no availability of CHA2DS2-VASc scoring and no information on diabetes status (N=19)
• lack of information on stroke/systemic embolic event and no availability of CHA2DS2-VASc scoring and no information on diabetes status (N=9)
Full analysis set
N=6,412
Patients included
N=5,717



No diabetes	4429	4409	4384	4365	4326	4280	3854	1642	148	27
Non-insulin DM	1000	998	994	987	973	963	868	320	33	5
Insulin DM	288	287	285	284	270	260	230	72	5	1


Insulin-requiring diabetes
Non-insulin-requiring diabetes
No diabetes
Stroke or SEE (%)
15
12
9
6
3
0
Total
No
Yes
CHF
No
Yes
Hyp
≥75
<75
Age
No
Yes
Stroke/TIA
No
Yes
Vasc Disease
No
Yes
Female
No
Yes
COPD
No
Yes
CRI
>30
≤30
BMI
≤1
≥2
CHA2DS2-VASc
No
Yes
CHD
No
Yes
PAD
No
Yes
NOAC at BL
No
Yes
VKA+AP at BL
No
Yes
VKA only at BL