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Liu, Y.; Chen, Y.; Lam, S.H.M.; Huang, B.; Romiti, G.F.; Alam, U.; ... ; GLORIA AF Investigators

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Diabetes mellitus and adverse clinical events in patients with atrial fibrillation: A report from the GLORIA-AF registry phase III

Yang Liu MD[1,2] | Yang Chen MD[1] | Steven H. M. Lam PhD[1] | Bi Huang MD[1,3] | Giulio F. Romiti MD[1,4] | Uazman Alam PhD[1,5,6] | Tze Fan Chao MD[7,8] | Brian Olshansky MD[9] | Kui Hong MD[2,10,11] | Menno V. Huisman MD[12] | Gregory Y. H. Lip MD[1,13] | on behalf of the GLORIA-AF Investigators

[1]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University, and Liverpool Heart & Chest Hospital, Liverpool, UK

[2]Department of Cardiovascular Medicine, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China

[3]Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

[4]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy

[5]Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK

[6]Department of Medicine, University Hospital Aintree, Liverpool University Hospitals NHS Foundation Trust, Aintree Hospital, Liverpool, UK

[7]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

[8]Institute of Clinical Medicine, and Cardiovascular Research Centre, National Yang-Ming University, Taipei, Taiwan

[9]Division of Cardiology, The University of Iowa, Iowa City, Iowa, USA

[10]Department of Genetic Medicine, The Second Affiliated Hospital of Nanchang University, Jiangxi Medical College, Nanchang University, Nanchang, China

[11]Jiangxi Key Laboratory of Molecular Medicine, Nanchang, China

[12]Department of Medicine—Thrombosis and Haemostasis, Leiden University Medical Centre, Leiden, The Netherlands

[13]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Correspondence
Gregory Y. H. Lip, Liverpool Centre for Cardiovascular Science, William Henry Duncan Building, 6 West Derby Street Liverpool L7 8TX UK.
Email: gregory.lip@liverpool.ac.uk

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Abstract

Aims: Atrial fibrillation (AF) and diabetes mellitus (DM) are both associated with adverse clinical events, but the associations have not been fully elucidated, particularly with concomitant insulin use. This study aimed to analyse the associations between adverse events and DM, as well as adverse events and sole insulin use.

Materials and Methods: Our analysis included individuals with AF from the prospective Global Registry on Long-Term Oral Anti-Thrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry with 3-year follow-up. Outcomes included all-cause death, major bleeding, cardiovascular (CV) death, myocardial infarction (MI), stroke, thromboembolism and major adverse cardiovascular events (MACE).

Results: A total of 15 861 AF individuals were included (age 70.0 ± 10.2 years; 55% male, 20% Asian), of whom, 3666 had DM (age 70.0 ± 9.5 years ; 59% male, 21% Asian).

Menno V. Huisman and Gregory Y. H. Lip are co-chairs of the GLORIA-AF Registry programme.

After adjustment, those with DM had higher risks of all-cause death (hazard ratio [HR]: 1.46, 95% confidence interval [CI]: 1.28–1.66), CV death (HR: 1.53 95% CI: 1.27–1.86), major bleeding (HR: 1.23, 95% CI: 1.01–1.48), MI (HR: 1.50, 95% CI: 1.17–1.94) and MACE (HR: 1.42, 95% CI: 1.23–1.63). Compared to individuals with DM receiving oral hypoglycaemic agents, those receiving insulin alone were associated with increased risks of all-cause death (HR: 2.16, 95% CI: 1.61–2.91), CV death (HR: 2.24, 95% CI: 1.45–3.47), major bleeding (HR: 1.89, 95% CI: 1. 21–2.95), MI (HR: 2.24, 95% CI: 1.31–3.82) and MACE (HR: 2.11, 95% CI: 1.54–2.88).

Conclusions: DM was independently associated with higher risks of all-cause death, CV death, MI, major bleeding and MACE in AF individuals. Individuals receiving insulin alone were associated with higher risks of all-cause death, CV death, MI, major bleeding and MACE.

KEYWORDS
antidiabetic drug, cardiovascular disease, insulin therapy, real-world evidence

1 | INTRODUCTION

Diabetes mellitus (DM) is an independent risk factor for atrial fibrillation (AF) and AF-related complications.[1,2] Both conditions are associated with prevalent and incident cardiovascular disorders, and if both are present, the risk of adverse clinical events is even greater.

Indeed, cardiovascular disease–related mortality is increased by fourfold in individuals with DM.[3] Several physiologic changes in DM individuals, such as low-grade inflammation, decreased fibrinolytic activity and increased platelet activation, might promote adverse cardiovascular outcomes.[4] Although the individual impact of AF and DM on cardiovascular health has been extensively studied, their combined effect has received less attention, especially with respect to the associations between diabetes therapy and cardiovascular health.

Oral hypoglycaemic agents (OHA) and insulin are often used to treat diabetes. Treatment with glucagon-like peptide-1 (GLP-1) receptor agonists has beneficial effects on cardiovascular outcomes and mortality in patients with type 2 diabetes.[5] However, insulin treatment was reported to be associated with cardiovascular complications.[6,7] Also, A meta-analysis demonstrated that intensive insulin therapy could increase the risk of hypoglycaemia and confer no overall mortality benefit.[8] The cardiovascular safety of insulin therapy in individuals with AF and DM remains uncertain. However, we do note the results of the United Kingdom Prospective Diabetes Study (UKPDS) which demonstrated, in general, that improved glycaemic control was associated with improved cardiovascular disease outcomes.[9]

This study aimed to analyse the relationship between DM and adverse events in individuals with AF, and explore the impact of different antidiabetic agents on outcomes in individuals with AF and concomitant DM enrolled in the prospective Global Registry on Long-Term Oral Anti-Thrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry.[10]

2 | METHODS

2.1 | Study population and selection criteria

GLORIA-AF is a large global, multicentre registry, involving patients with newly diagnosed (<3 months before baseline visit and <4.5 months for Latin America) nonvalvular AF. The study design has been previously reported.[11] At baseline, demographic data, general signs and history of disease and medication were recorded. In this study, phase III started from January 2014 to December 2016. Follow-up was conducted for 3 years, with scheduled visits at 6, 12, 24 and 36 months.[12] At baseline, data on age, sex, race, body mass index (BMI), type of AF (paroxysmal, persistent, permanent), smoking status, drinking status, CHA_2DS_2-VASc score, comorbidities and pharmacotherapies were collected. During follow-up, major events were recorded.

2.2 | Study groups and clinical end events

In this study, we aimed to investigate the relationship between diabetes and clinical end events (including all-cause death, cardiovascular [CV] death, myocardial infarction [MI], major bleeding, stroke, thromboembolism [TE] and major adverse cardiovascular events [MACE]) in AF patients. We divided the AF population into those with DM and those without DM at baseline. Furthermore, we explored the association between diabetes treatment (including sole OHA, sole insulin and combination of OHA and insulin) and clinical events in the diabetic population. Figure 1 shows the flow chart of this study.

MI was defined as the development of significant Q-waves in at least two adjacent electrocardiogram leads meeting the criteria as reported previously study.[13] Major bleeding was defined according to the International Society of Thrombosis and Haemostasis classification.[14] Stroke was defined as the acute onset of a focal neurological

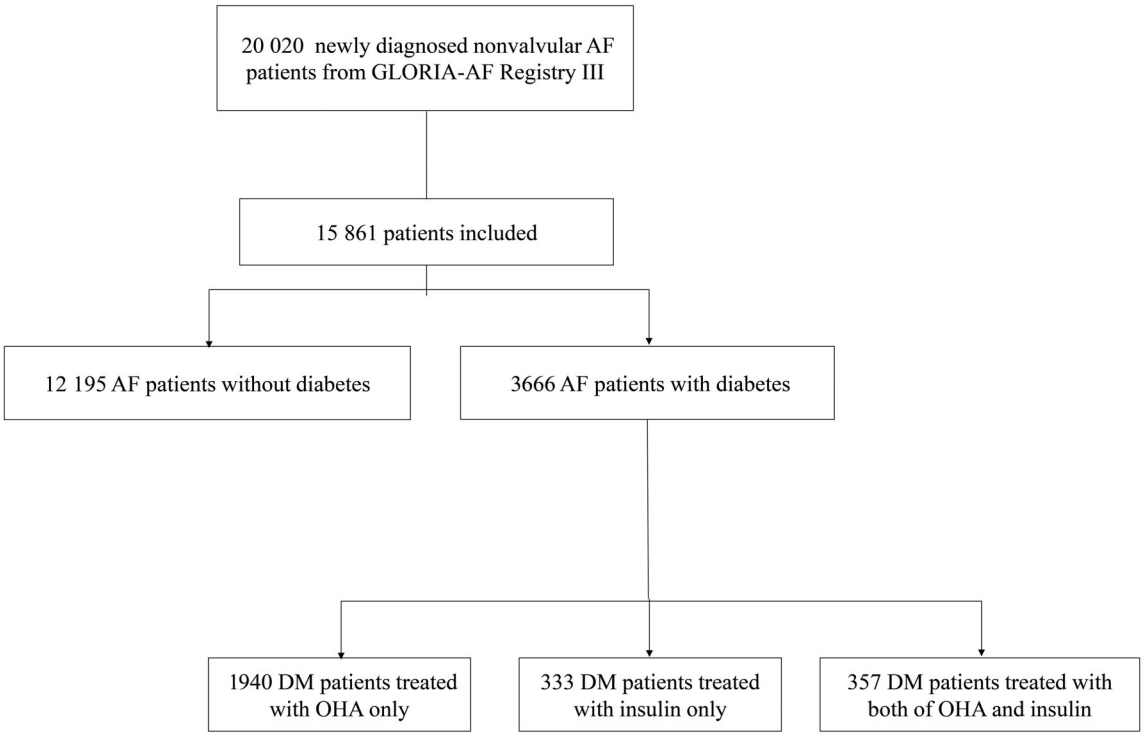

FIGURE 1 Flow chart. GLORIA-AF, Global Registry on Long-Term Oral Anti-Thrombotic Treatment in Patients with Atrial Fibrillation; AF, atrial fibrillation; DM, diabetes mellites; OHAs, oral hypoglycaemic agents.

deficit of presumed vascular origin lasting 24 h or more, or resulting in death, including ischaemic stroke, haemorrhagic stroke and uncertain classification. For other composite outcomes, TE was defined as the sum of stoke, transient ischemic attack and non–central nervous system atrial embolism. MACE was defined as the composite events of MI, stroke and CV death.

2.3 | Statistical analysis

Continuous variables were represented by mean (±standard deviation [SD]) and median (interquartile range [IQR]) as appropriate and compared using *t*-test or Kruskal–Wallis test for normal and parametric indices, respectively. Categorical variables were represented as frequencies (%) and were compared by Pearson's chi-squared test.

Kaplan–Meier curves were constructed to estimate the cumulative incidence of clinical events and were tested by log-rank test. Univariable and multivariable Cox regression models were utilized to evaluate the association between (1) DM and clinical end events, and (2) DM treatment and clinical end events, using hazard ratio (HR) and 95% confidence interval (CI).

In the Cox regression models, we established four models to eliminate confounding factors. Model 1 was univariable model; model 2 was adjusted by basic information, including age, sex, BMI, race, alcohol and smoking status and type of AF (paroxysmal, persistent, permanent); model 3 was further adjusted by comorbidities and history of adverse events, including hypertension, hyperlipidaemia, coronary artery disease (CAD), chronic heart failure (CHF), history of TE and history of major bleeding. Model 4 was further adjusted for baseline pharmacotherapy, including angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), beta-blocker, statin, antiarrhythmic drug (AAD), aspirin and oral anticoagulants (OAC). Additionally, subgroup analyses were conducted to determine whether the effects were consistent across different populations. For sensitivity analysis, propensity score (PS) matching was conducted using the confounding factors mentioned above to further control for confounders that may affect the prescription choice. Based on PS, patients with AF were matched into the two groups: (1) individuals with diabetes and those without diabetes (1:1 matched); (2) DM patients receiving OHAs and those receiving insulin (1:1 matched); DM patients receiving OHAs and those receiving both insulin and OHAs (1:1 matched) using the nearest-neighbour method. Standardized mean differences (SMD) were calculated to compare the distributions of covariates between the two groups.

All analyses were performed by R (version 4.2.1). The value of $p < 0.05$ was considered as statistically significant.

3 | RESULTS

3.1 | Analysis of DM and non-DM

3.1.1 | Diabetes and clinical events in individuals with AF

Table 1 shows the baseline characteristics of the study cohort. In total, 15 861 individuals with AF were included (mean age

TABLE 1 Baseline characteristics of atrial fibrillation (AF) patients with diabetes or without diabetes.

Characteristic	Overall, $N = 15\,861$	No diabetes $N = 12\,195$	Diabetes $N = 3666$	*p*-Value
Age				0.4
Mean (SD)	70.0 (10.2)	69.90 (10.4)	70.0 (9.5)	
Median (25%, 75%)	71.0 (64.0, 77.0)	71.0 (64.0, 77.0)	71.0 (64.0, 77.0)	
Sex				<0.001
Male	8708 (55%)	6541 (54%)	2167 (59%)	
Female	7153 (45%)	5654 (46%)	1499 (41%)	
Race				<0.001
White	11 766 (74%)	9110 (75%)	2656 (72%)	
Arab or Middle East	24 (0.2%)	19 (0.2%)	5 (0.1%)	
Asian	3234 (20%)	2472 (20%)	762 (21%)	
Black or Afro-Caribbean	279 (1.8%)	184 (1.5%)	95 (2.6%)	
Others	558 (3.5%)	410 (3.4%)	148 (4.0%)	
Smoking status				<0.001
Never smoked	9299 (59%)	7259 (60%)	2040 (56%)	
Ex-smoker	5019 (32%)	3742 (31%)	1277 (35%)	
Current smoker	1543 (9.7%)	1194 (9.8%)	349 (9.5%)	
Alcohol status				<0.001
No alcohol	7250 (46%)	5382 (44%)	1868 (51%)	
<1 drink/week	4012 (25%)	3060 (25%)	952 (26%)	
1–7 drinks/week	3436 (22%)	2777 (23%)	659 (18%)	
≥8 drinks/week	1163 (7.3%)	976 (8.0%)	187 (5.1%)	
BMI				<0.001
Mean (SD)	28.7 (6.4)	28.0 (5.9)	30.8 (7.2)	
Median (25%, 75%)	27.6 (24.5, 31.6)	27.1 (24.2, 30.8)	29.4 (25.9, 34.3)	
Type of AF				0.2
Paroxysmal AF	9164 (58%)	7081 (58%)	2083 (57%)	
Persistent AF	5238 (33%)	4019 (33%)	1219 (33%)	
Permanent AF	1459 (9.2%)	1095 (9.0%)	364 (9.9%)	
CHA2DS2-VASc score				< 0.001
Mean (SD)	3 (1)	3 (1)	4 (1)	
Median (P25, P75)	3 (2, 4)	3 (2, 4)	4 (3, 5)	
CHA2DS2-VASc score class, *n* (%)				<0.001
High (Score ≥2)	13 479 (85%)	9901 (81%)	3578 (98%)	
Moderate (Score = 1)	2382 (15%)	2294 (19%)	88 (2.4%)	
Previous disease, *n* (%)				
Hypertension	11 853 (75%)	8736 (72%)	3117 (85%)	<0.001
Hyperlipidaemia	6493 (41%)	4431 (36%)	2061 (56%)	<0.001
Coronary artery disease	3060 (19%)	2064 (17%)	996 (27%)	<0.001
Congestive heart failure	3342 (21%)	2407 (20%)	935 (26%)	<0.001
Thromboembolism	2239 (14%)	1709 (14%)	530 (14%)	0.5
Previous bleeding	876 (5.5%)	661 (5.4%)	215 (5.9%)	0.3
Oral anticoagulation, *n* (%)				
No OAC	2844 (18%)	2278 (19%)	586 (15%)	<0.001
VKA	3566 (22%)	2648 (22%)	918 (25%)	
Apixaban	3353 (21%)	2567 (21%)	786 (21%)	

TABLE 1 (Continued)

Characteristic	Overall, $N = 15\,861$	No diabetes $N = 12\,195$	Diabetes $N = 3666$	*p*-Value
Dabigatran	2878 (18%)	2271 (19%)	607 (17%)	
Rivaroxaban	2991 (19%)	2255 (18%)	736 (20%)	
Edoxaban	229 (1.4%)	176 (1.4%)	53 (1.4%)	
Pharmacotherapy, *n* (%)				
Antiarrhythmic drugs	3847 (24%)	3001 (25%)	846 (23%)	0.058
Any antiplatelet drug use	4212 (27%)	3081 (25%)	1131 (31%)	<0.001
ACEI use	4706 (30%)	3445 (28%)	1261 (34%)	<0.001
ARB use	4105 (26%)	2937 (24%)	1168 (32%)	<0.001
Beta-blocker use	10 004 (63%)	7600 (62%)	2404 (66%)	<0.001
Statin	7379 (47%)	5125 (42%)	2254 (61%)	<0.001
Aspirin use	3786 (24%)	2785 (23%)	1001 (27%)	<0.001
Follow-up duration, mean (SD)	1034.8 (186.0)	1039.1 (179.4)	1020.5 (205.9)	<0.001
Antidiabetic treatment				
OHA only	1940 (73.8%)	-	1940 (73.8%)	
Insulin only	333 (12.7%)	-	333 (12.7%)	
Both of OHA and insulin	357 (13.6)	-	357 (13.6)	

Note: Continuous variables were presented by mean (SD) and median (IQR). Catalogue variables were presented by frequency and percentage (*n*%).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; IQR, interquartile range; OAC, oral anticoagulation; OHA, oral hypoglycaemic agents; SD, standard deviation; VKA, vitamin K antagonists.

TABLE 2 Three-year cumulative incidence rate of clinical events in patients with diabetes and without diabetes.

	No diabetes (3-year cumulative incidence rate %)	Diabetes (3-year cumulative incidence rate %)	*p*-Value
All-cause death	815 (6.7%)	375 (10.0%)	<0.001
Cardiovascular death	353 (2.9%)	179 (4.9%)	<0.001
Major bleeding	404 (3.3%)	166 (4.5%)	<0.001
Myocardial infarction	188 (1.5%)	104 (2.8%)	<0.001
Stroke	301 (2.5%)	115 (3.1%)	0.026
Thromboembolism	317 (2.6%)	118 (3.2%)	0.044
MACE	696 (5.7%)	328 (8.9%)	<0.001

Note: MACE is the composite event of myocardial infarction, stroke or cardiovascular death.
Abbreviation: MACE, major adverse cardiovascular events.

69.97 years ± SD 10.21 years; 55% male), and 3666 (23.11%) had DM. Compared with patients without DM, patients with DM were more likely to be male (59% vs. 54%), with higher BMI (30.80 ± 7.17 kg/cm^2 vs. 28.04 ± 5.94 kg/cm^2), CHA_2DS_2-VASc score (4.04 ± 1.48 vs. 2.86 ± 1.39) and had more comorbidities, including hypertension (85% vs. 72%), hyperlipidaemia (56% vs. 36%), CAD (27% vs. 17%) and CHF (26% vs. 20%). DM patients had greater use of antiplatelet drugs (31% vs. 25%), ACEI (34% vs. 28%), ARB (32% vs. 24%), beta-blockers (66% vs. 62%) and statins (61% vs. 42%).

3.1.2 | Incidence rate of clinical events during follow-up

Table 2 shows the cumulative incidence rate of outcomes during the 3-year follow-up. Event rates were higher in individuals with DM: all-cause death (10% vs. 6.7%, $p < 0.001$), CV death (4.9% vs. 2.9%, $p < 0.001$), major bleeding (4.5% vs. 3.3%, $p < 0.001$), MI (2.8% vs. 1.5%, $p < 0.001$), stroke (10% vs. 6.7%, $p = 0.026$), TE (3.2% vs. 2.6%, $p = 0.044$) and MACE (8.9% vs. 5.7%, $p < 0.001$). Kaplan–Meier curves show that AF patients with DM had higher cumulative hazards of all-cause death ($p < 0.001$), CV death ($p < 0.001$), major bleeding ($p < 0.001$), MI ($p < 0.001$), stoke ($p = 0.018$), TE ($p = 0.032$) and MACE ($p < 0.001$) (Figure 2A–F).

3.1.3 | Univariate and multivariate analyses

Figure 3 shows the associations between DM and clinical events. The univariable Cox regression model (model 1) indicated that DM was associated with a higher risk of all-cause death (HR: 1.56, 95% CI: 1.38–1.77), CV death (HR: 1.72, 95% CI: 1.44–2.06), major bleeding (HR: 1.4, 95% CI: 1.17–1.67), stroke (HR: 1.29, 95% CI: 1.04–1.61), TE (HR: 1.26, 95% CI: 1.02–1.56), MI (HR: 1.88, 95% CI: 1.48–2.39) and MACE (HR: 1.61, 95% CI: 1.41–1.84).

Using multivariable Cox models that adjusted for age, sex, race, BMI and smoking/alcohol status, model 2 yielded similar results. After adjustment for comorbidities (model 3) and pharmacotherapies (model 4), only DM was associated with all-cause death (HR: 1.46, 95% CI: 1.28–1.66), major bleeding (HR: 1.23, 95% CI: 1.01–1.48), MI

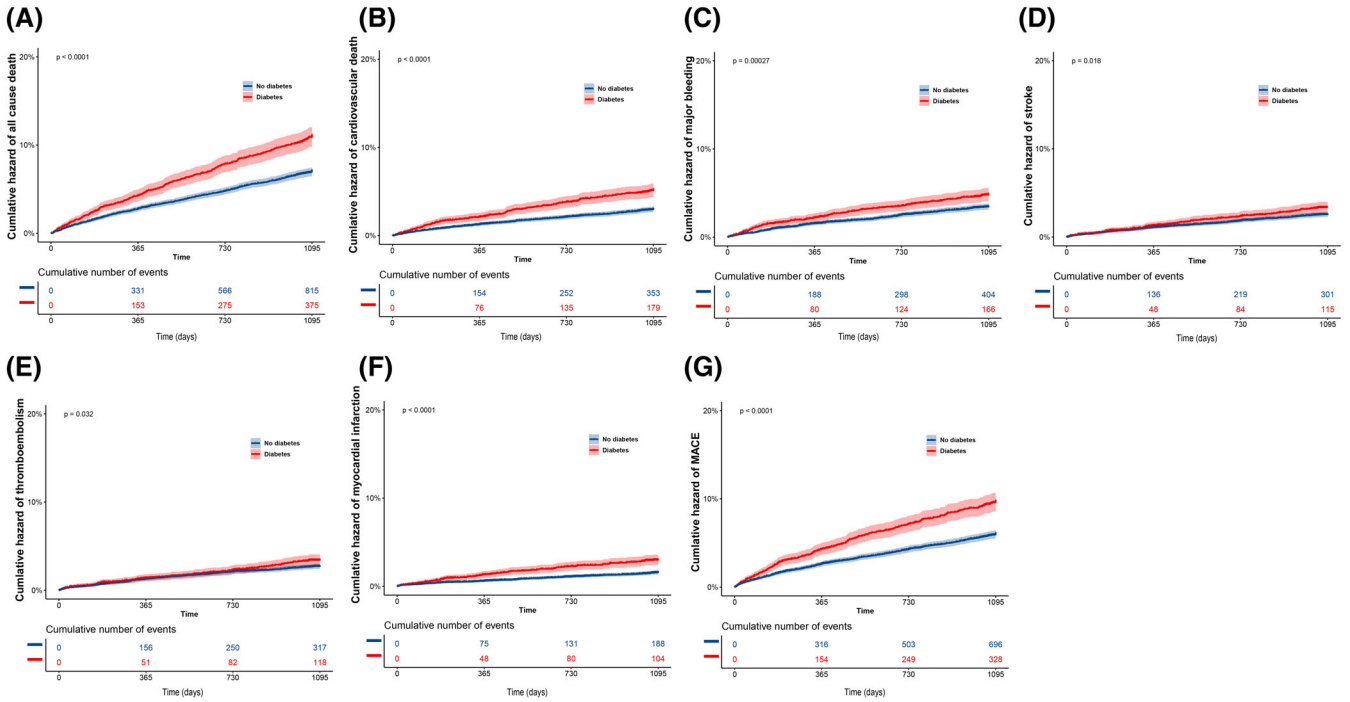

FIGURE 2 MACE is the composite of myocardial infarction, stroke and cardiovascular death. A-G: cumlative hazard of clinical adverse events, including all-cause death (A), cardiovascular death (B), major bleeding (C), stroke (D), thromboembolism (E), myocardial infarction (F) and MACE (G). Abbrevation: MACE: major adverse cardiovascular events.

(HR: 1.50, 95% CI: 1.17–1.94), CV death (HR: 1.53, 95% CI: 1.27–1.86) and MACE (HR: 1.42, 95% CI: 1.23–1.63).

3.1.4 | Sensitivity analysis

Subgroup analyses are shown in supplementary Table S1, including sex, age, region, race, OAC therapy and type of AF. No significant interactions were noted between DM and outcomes in all subgroups (all $p_{interaction}$ >0.05).

Individuals with DM and non-DM were matched by age, sex, race, BMI, smoking/alcohol status, comorbidities and pharmacotherapies (all SMD <0.01, Supplementary Table S2). After PSM, individuals with DM were associated with higher risk of all-cause death, CV death, MI and MACE (Supplementary Figure S1).

3.2 | Analysis of DM treatment

3.2.1 | Incidence rate of clinical end events in patients both with AF and DM

In individuals with AF and DM, 333 (12.7%) took only insulin, 1940 (73.8%) took OHA only and 357 (13.6%) received OHA and insulin to treat their DM (Supplementary Table S3). Compared to individuals receiving OHA, individuals with DM solely managed with insulin had higher incidence rates of all-cause death (20% vs. 8.1%; $p < 0.001$), CV death (9.9% vs. 3.5%; $p < 0.001$), major bleeding (8.4% vs. 4.2%; $p = 0.003$), MI (6.3% vs. 2.4%; $p < 0.001$) and MACE (18% vs. 7.6%; $p < 0.001$).

3.2.2 | Multivariable analysis

Supplementary Figure S2 shows the associations between clinical outcomes and DM treatment. After adjustment for sex, age, race, BMI, alcohol/smoking status, type of AF, comorbidities and pharmacotherapy, compared with patients with only OHAs, patients solely managed with insulin to treat DM had increased risks of all-cause death (HR: 2.16, 95% CI: 1.61–2.91), CV death (HR: 2.24, 95% CI: 1.45–3.47), major bleeding (HR: 1.89, 95% CI: 1.21–2.95), MI (HR: 2.24, 95% CI: 1.31–3.82) and MACE (HR: 2.11, 95% CI: 1.54–2.88).

Patients receiving both OHA and insulin had higher risks of all-cause death (HR: 1.74, 95% CI: 1.25–2.41) and CV death (HR: 1.74, 95% CI: 1.07–2.84) compared to patients receiving only insulin, but with lower HRs.

3.2.3 | Sensitivity analysis

Sensitivity analyses were performed using subgroup analysis and PSM. There was no interaction between the type of AF (paroxysmal/non-paroxysmal AF) and diabetes treatment for all

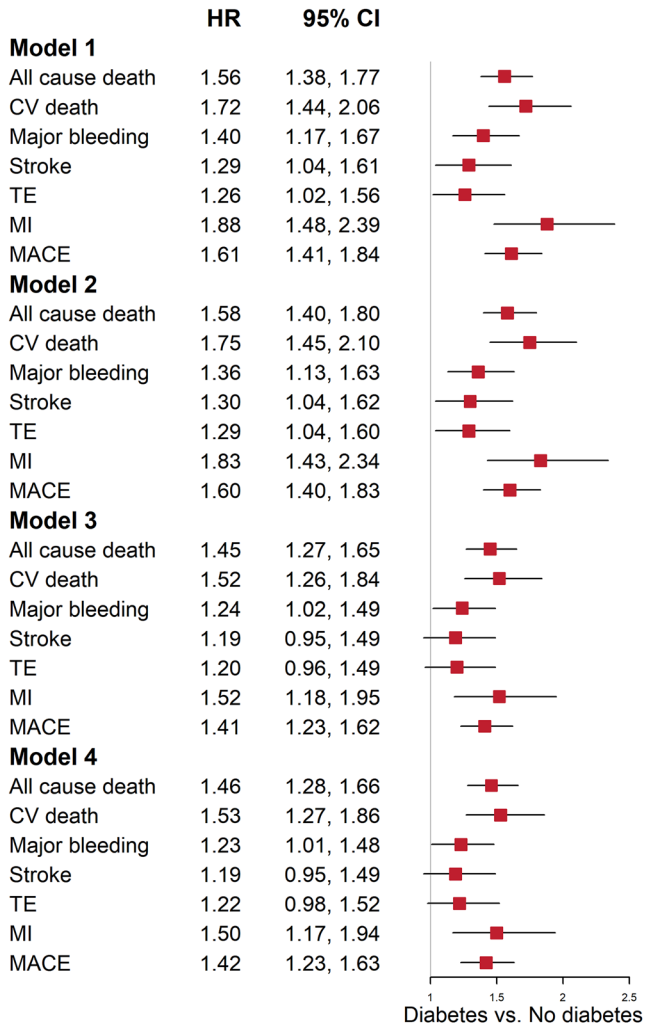

FIGURE 3 Forest plot of analysis of risk of clinical end events in AF patients by multivariable cox regression comparing diabetes and no diabetes (reference). Model 1: Univariable model. Model 2: Adjusted by age (≥75 years old), sex, body mass index (BMI), alcohol status, smoking status, race (Asian/not Asian) and type of AF. Model 3: Model 2 and hypertension, hyperlipidaemia, coronary artery disease, chronic heart failure, TE and previous bleeding. Model 4: Model 3 and angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), beta-blocker, statin, aspirin, oral anticoagulation and arrhythmic drugs. TE is a composite event of any stroke, TIA or non-CNS arterial embolism. MACE is a composite event of MI, stroke or CV death. AF, atrial fibrillation; CI, confidence interval; CNS, central nervous system; CV death, cardiovascular death; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; TE, thromboembolism; TIA, transient ischaemic attack.

outcomes (all $p_{interaction}$ >0.05) (Supplementary Table S4). After PSM, patients receiving insulin alone had increased risks of all-cause death, CV death, major bleeding, MI and MACE, compared to those receiving OHAs, which is similar with the results of the multivariable analysis (Supplementary Figure S3; Supplementary Table S5).

4 | DISCUSSION

This study demonstrates significant associations between DM and increased risks of mortality and cardiovascular events in patients with AF. Consistent with prior research, our findings underscore the independent risk posed by DM, even after adjustment of patient characteristics, comorbidities and pharmacotherapy. Of note, in patients with both AF and DM, sole insulin use, when compared with those without DM treatment, was associated with adverse outcomes, including all-cause mortality, CV death, MI, major bleeding and MACE.

Previous studies have demonstrated a direct association between AF and diabetes.[2,15,16] DM is an independent risk factor for AF and is included in the CHA_2DS_2-VASc score.[1] This study, using a global prospective multicentre registry, confirms that DM increases the risk for poor prognosis, including all-cause mortality and cardiovascular events. Consistent with our study, the ACCORD trial reported an increased risk of all-cause death (HR: 2.36, 95% CI: 1.8–3.86) and MI (HR: 2.1, 95% CI: 1.33–3.31) in AF patients with DM compared to those without DM.[17] Similarly, the multicentre Swizz-AF study suggested that the presence of diabetes was also associated with MI (odds ratio: 1.55, 95% CI: 1.18–2.03) and heart failure (odds ratio: 1.99, 95% CI: 1.57–2.51).[18]

In our study, univariate regression analysis found that DM is a risk factor for stroke. However, after adjustment for comorbidities (including previous stroke), diabetes was no longer independently associated with stroke or TE. First, a history of stroke or comorbidities also have a significant association with the risk of subsequent stroke ("stroke begets stroke"), and stroke already accounts for 2 points in the CHA_2DS_2-VASc score. In addition, the percentage of patients receiving oral anticoagulation was high, which might alleviate the risk of stroke. By contrast, one study with 44 451 AF patients found that both pre-diabetes and diabetes were independently associated with an increased risk of stroke after multivariable adjustment[19]; however, the overall use of oral anticoagulant was much lower (40%) in that study compared to GLORIA-AF (80%), which might explain the different findings.

In our AF cohorts, patients receiving insulin alone were associated with an increased risk of adverse clinical events compared to DM patients not receiving OHAs or insulin. Consistent with our findings, insulin treatment has been associated with a higher risk of MI, stroke and TE events compared to noninsulin treatment in patients with AF and diabetes.[20–22] A study by Gamble et al. reported that higher insulin exposure was associated with increased mortality.[23] These potential adverse effects of insulin could be attributed to many mechanisms, including endothelial dysfunction, inflammation and oxidative stress and atherogenic progression.[24–26] Importantly, exogenously administered insulin has a different (and perhaps suboptimal) metabolic profile compared to endogenous secretion. Indeed, high concentrations of peripherally delivered insulin bypass hepatic first-past metabolism leading to relatively unrestrained hepatic glucose production, whereas over-insulinisation of peripheral tissue increases the risk of clinically significant hypoglycaemia.[27] However, insulin use

may also reflect the phenotype of patients with more advanced diabetes and greater β-cell failure. This would be more likely associated with greater diabetes complications (macro- and microvascular disease), which would be a risk factor for poor outcomes.

Interestingly, we found that the combination of insulin and OHA was associated with relatively lower risks of adverse events than sole insulin. This suggests that OHA could alleviate the adverse effect of sole insulin use. Indeed, some oral antidiabetic drugs have been shown to significantly reduce cardiovascular events; for example, Sattar et al. reported that GLP-1 receptor agonists reduced all-cause mortality by 12% (HR: 0.88, 95% CI: 0.82–0.94) and hospital admission for heart failure by 11% (HR: 0.89, 95% CI: 0.82–0.98).[28] Another meta-analysis showed that sodium/glucose cotransporter 2 (SGLT2) inhibitors reduced the risk of cardiovascular death or hospitalisation for heart failure by 23% (HR: 0.77, 95% CI: 0.71–0.84).[24] Thus, OHAs, especially GLP-1 receptor agonists or SGLT2 inhibitors, are preferably recommended by current guidelines due to their CV death benefits.[29]

4.1 | Strengths and limitations

Our study has several strengths. First, this study, based on the global GLORIA-AF registry, prospectively included a large number of AF patients with detailed follow-up records. Second, a high percentage of patients in our study received anticoagulation (>80%), and 60% used non-vitamin K oral anticoagulants. These findings underscore the importance of implementing personalized management strategies in AF patients with DM to mitigate their heightened risk of cardiovascular complications and mortality. This aligns with the current holistic or integrated care approach for AF management, including proactive comorbidities management.[30,31] This is important given the multimorbidity, frailty and polypharmacy commonly seen in patients with AF with or without DM, with implications for treatments and outcomes.[32–34]

Our study also has limitations. Unfortunately, detailed measures of DM were lacking in the GLORIA-AF registry, including severity, glycated haemoglobin, DM aetiology and duration, hypoglycaemic events and the dosing of OHA and insulin which may have confounded our results, especially for the associations between treatment and outcomes. Second, precise analyses of the impact of other factors associated with DM treatment would require more data, such as DM duration and glycaemic control.[35,36] Finally, the impact of other novel diabetes treatments, including SGLT2,[37] remains unexplored.

5 | CONCLUSION

DM was independently associated with a higher risk of all-cause death, CV death, MI, major bleeding and MACE in patients with AF. A higher risk of all-cause death, MI, major bleeding, stroke, and MACE was associated with patients with AF and DM receiving insulin alone. For patients receiving both insulin and OHAs, no significant associations with these adverse outcomes were found.

AUTHOR CONTRIBUTIONS

Yang Liu, Yang Chen and Gregory Y.H. Lip designed the study. Yang Liu did analysis and wrote the draft with Yang Chen and Steven H.M. Lam, who contributed to the interpretation of the data. Bi Huang, Giulio F. Romiti, Uazman Alam, Tze F. Chao, Brian Olshansky, Kui Hong, Menno V. Huisman and Gregory Y.H. Lip contributed to substantive revision. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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Gregory Y.H. Lip is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Anthos. No fees are received personally. He is a senior investigator at National Institute for Health and Care Research (NIHR) and co-PI of the AFFIRMO project on multimorbidity in AF (grant agreement number: 899871), TARGET project on digital twins for personalized management of atrial fibrillation and stroke (grant agreement number: 101136244) and ARISTOTELES project on artificial intelligence for management of chronic long-term conditions (grant agreement number: 101080189), which are all funded by the EU's Horizon Europe Research & Innovation programme. Other authors declare no competing interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15950.

DATA AVAILABILITY STATEMENT

Data supporting this study by the data contributors Boehringer Ingelheim and were made and are available through Vivli, Inc. Access was provided after a proposal was approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement.

ORCID

Yang Liu https://orcid.org/0000-0003-4430-3452
Giulio F. Romiti https://orcid.org/0000-0002-3788-8942
Gregory Y. H. Lip https://orcid.org/0000-0002-7566-1626

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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