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Antithrombotic treatment gap among patients with atrial fibrillation and type 2 diabetes☆

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ABSTRACT

Background: We investigated the use of different antithrombotic therapies at baseline among patients with a history of atrial fibrillation (AF), type 2 diabetes, and established atherosclerotic cardiovascular disease (ASCVD) enrolled in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS).
Methods: TECOS participants with a history of AF were stratified by CHA_2DS_2-VASc score and their antithrombotic use evaluated. Cox proportional hazards models were employed to explore possible associations between history of AF and prespecified clinical outcomes after adjusting for key baseline characteristics.
Results: Of the 14,671 TECOS participants, 1167 (8%) had a history of AF, of whom 51.6% were using vitamin K antagonists (VKA); 31.2% used VKA alone, 16.9% used aspirin plus VKA, 1.8% used clopidogrel plus VKA, and 1.7% used aspirin and clopidogrel plus VKA. Aspirin was used by 56.8%: 30.9% used aspirin alone and 7.3% aspirin plus clopidogrel. Clopidogrel alone was used by 2.9%, and 7.3% were not using any antithrombotic medication. Participants with a history of AF had a higher risk of cardiovascular events, including hospitalization for heart failure and all-cause mortality, than those without AF. White, older men with prior myocardial infarction, heart failure, peripheral artery disease, or prior stroke were more likely to develop new-onset AF than others without these characteristics.
Conclusions: Almost half of high-risk AF patients with diabetes and established ASCVD in TECOS were not treated with anticoagulation therapy despite clear guideline recommendations for such therapy, highlighting the challenge and potential for clinical improvements in managing these patients in clinical practice.
Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00790205.

1. Introduction

Atrial fibrillation (AF) and type 2 diabetes mellitus (T2DM) commonly coexist. Both are associated with higher risk of stroke, heart failure, and mortality. When evaluating the thromboembolic risk for patients with AF, T2DM is included in the $CHADS_2$ [1] and CHA_2DS_2-VASc scores [2]. Anticoagulation therapy is recommended for patients with at least one more risk factor, and should be considered for those who have just AF and T2DM [3,4]. However, little is known about the prevalent use of antithrombotic therapy for patients with AF and T2DM in contemporary international clinical practice. Moreover, the additional impact of AF on adverse outcomes among patients with T2DM with established atherosclerotic cardiovascular disease (ASCVD) deserves further investigation.

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was an international randomized trial that evaluated whether the addition of sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i), to usual care affected rates of major cardiovascular events among participants with T2DM and established ASCVD [5]. Using data from TECOS, we examined those participants with history of AF to a) describe antithrombotic treatment at study entry, overall, and by CHA_2DS_2-VASc score categories; b) assess the relationship between history of AF and clinical outcomes among patients with T2DM and established ASCVD; and c) identify predictors of developing new-onset AF among T2DM patients without prior AF.

☆ Each author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Patients and study design

The design and results of the TECOS trial have been published [5,6]. In summary, TECOS was a randomized, double-blind, placebo-controlled trial that enrolled patients age ≥ 50 years with T2DM, established ASCVD (coronary, cerebrovascular, or peripheral atherosclerotic vascular disease), and a glycated hemoglobin (HbA_{1c}) value of 6.5 to 8.0% on stable treatment with oral antihyperglycemic agents and/or insulin. Patients were excluded if they were treated with a DPP-4i, a glucagon-like peptide-1 receptor agonist, or rosiglitazone in the previous 3 months, had a history of two or more episodes of severe hypoglycemia in the previous year, or had an estimated glomerular filtration rate <30 mL/min/1.73 m^2 at baseline. Patients were randomized to receive either 100 mg of sitagliptin daily (or 50 mg if reduced glomerular filtration rate) or placebo, with dose adjustments during trial follow-up based on glomerular filtration rate. In TECOS, the addition of sitagliptin to usual care in patients with T2DM and established ASCVD was safe with regard to cardiovascular outcomes compared with usual care alone. The TECOS study was approved by the ethics committee for each participating site and monitored by an independent data and safety monitoring board. All participants provided written informed consent for trial participation.

2.2. Outcomes

Clinical outcomes of interest were the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina (primary trial outcome) and its individual components, all-cause mortality, and hospitalization for heart failure. A clinical events classification committee, blinded to study assignment, adjudicated all outcomes according to prespecified criteria. Occurrence of new-onset AF post-randomization was collected in the case report form by clinical investigators. This diagnosis was not adjudicated, and ECGs might have been performed to confirm the occurrence of AF, but these data were not systematically collected.

2.3. Statistical analysis

Baseline characteristics were tabulated for participants with a history of AF or no prior AF, and for those with new-onset AF during trial follow-up. Frequencies and percentages are reported for categorical variables, and medians and 25th and 75th percentiles for continuous variables. Antithrombotic treatments are described among patients with previous AF overall, and by their CHA_2DS_2-VASc score categories.

Univariable and multivariable Cox proportional hazards models were used to assess the relationship between history of AF and the prespecified TECOS clinical outcomes. Unadjusted and adjusted hazard ratios (HRs) are reported with respective 95% confidence intervals (CI) and corresponding p values. Adjustment covariables include baseline age, sex, race, ethnicity, HbA1c, New York Heart Association class, current smoking, myocardial infarction, chronic obstructive pulmonary disease, coronary artery disease, stroke, stenosis of carotid artery, insulin, amputation, diabetic neuropathy, foot ulcers, systolic blood pressure, diastolic blood pressure, heart rate, height, body mass index, estimated glomerular filtration rate, randomized treatment, and duration of diabetes. The interaction between randomized treatment, prior AF, and clinical outcomes was also assessed.

A multivariable model was developed using Cox proportional hazards regression to identify predictors of new-onset AF during study follow-up, using backward elimination and alpha <0.05 for retention in the model. All variables in the baseline table were considered candidates with the exceptions of urine albumin-to-creatinine ratio (missing for 65% of patients) and CHA_2DS_2-VASc score (components included in the model). An imputed dataset was used so all patients without prior AF at baseline could be included. Hemoglobin was imputed for 35% of participants and lipid measures for about 25%. All other variables were imputed for <5% of participants. The only candidate variables that were highly correlated (defined here as Spearman correlation >0.6) were low-density lipoprotein cholesterol and total cholesterol. Continuous variables were checked for linearity with the AF event using restricted cubic splines, and the only variable violating the linearity assumption was diastolic blood pressure. Linear splines for diastolic blood pressure above and below 80 mm Hg were considered to accommodate the non-linearity. The proportional hazards assumption was checked for the final model confirming that there were no major violations. As a sensitivity analysis, a parametric model was fit using SAS PROC LIFEREG and a Weibull distribution which yielded similar results. Model discrimination is reported with Harrell's C-index. All tests were 2-sided, and a p value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Of 14,671 patients included in the trial, 1167 (8.0%) had a history of AF at enrollment. Of those without AF, 386 (2.9%) had new-onset AF during trial follow-up (mean 3.01 [±0.95] years). Patients without prior AF were younger and more likely to be female than those with a history of AF, and those with new-onset AF during the trial (Supplementary Table 1). Participants with a history of AF, and those with new-onset AF, were more likely to have a history of coronary heart disease, cerebrovascular disease, hypertension, and heart failure compared with those without prior AF. Patients with prior AF had lower estimated glomerular filtration rate compared with those without AF, as well as those with new-onset AF.

3.2. Antithrombotic treatments

Among patients with a history of AF, 7.3% were not receiving any antithrombotic therapy, 56.8% were treated with aspirin, 13.7% with clopidogrel, and 51.6% with vitamin K antagonists (VKA) (Table 1). Monotherapy was used in 65.0% of patients with prior AF (VKA in 31.2%, aspirin in 30.9%, and clopidogrel in 2.9%). The combination of aspirin plus VKA was used in 16.9% of patients with prior AF; aspirin plus clopidogrel was used in 7.3%, and clopidogrel plus VKA in 1.8%. Triple therapy with aspirin, clopidogrel, and VKA was used in 1.7% of patients with prior AF. Use of VKA modestly increased with higher CHA_2DS_2-VASc scores: 41.9% in patients with a score of 2–3, 50.2% with a score of 4–5, and 58.3% with a score ≥ 6. Among those without AF, 12.8% were not using any antithrombotic therapy, and 80.4% were using aspirin.

Compared with those with a history of AF and not receiving VKA at study entry, patients with AF on VKA at study entry were more frequently men (76.9% vs 71.5%; $p = 0.035$) and Hispanic (11.1% vs 7.3%; $p = 0.022$), had less history of coronary disease (77.2% vs 83.7%; $p = 0.005$) and more history of cerebrovascular disease (35.2% vs 23.0%; $p <$

Table 1
Baseline antithrombotic treatments in patients with type 2 diabetes and atherosclerotic cardiovascular disease with and without history of atrial fibrillation.

Antithrombotic treatments	No history of AF (N = 13,504)	History of AF (N = 1167)	CHA_2DS_2-VASc score		
			2–3 (N = 167)	4–5 (N = 584)	≥6 (N = 379)
None	1732 (12.8)	85 (7.3)	12 (7.2)	47 (8.0)	23 (6.1)
Any antithrombotic medication	11,772 (87.2)	1082 (92.7)	155 (92.8)	537 (92.0)	356 (93.9)
Aspirin	10,855 (80.4)	663 (56.8)	112 (67.1)	353 (60.4)	180 (47.5)
Clopidogrel	3027 (22.4)	160 (13.7)	24 (14.4)	85 (14.6)	45 (11.9)
Vitamin K antagonist	398 (2.9)	602 (51.6)	70 (41.9)	293 (50.2)	221 (58.3)
Two or more antithrombotic medications	2482 (18.4)	323 (27.7)	48 (28.7)	182 (31.2)	86 (22.7)
Combinations					
Aspirin only	8380 (62.1)	361 (30.9)	67 (40.1)	183 (31.3)	100 (26.4)
Clopidogrel only	694 (5.1)	34 (2.9)	2 (1.2)	15 (2.6)	14 (3.7)
Vitamin K antagonist only	216 (1.6)	364 (31.2)	38 (22.8)	157 (26.9)	156 (41.2)
Aspirin and clopidogrel	2300 (17.0)	85 (7.3)	16 (9.6)	46 (7.9)	21 (5.5)
Aspirin and vitamin K antagonist	149 (1.1)	197 (16.9)	26 (15.6)	112 (19.2)	55 (14.5)
Clopidogrel and vitamin K antagonist	7 (0.1)	21 (1.8)	3 (1.8)	12 (2.1)	6 (1.6)
Aspirin, clopidogrel, and vitamin K antagonist	26 (0.2)	20 (1.7)	3 (1.8)	12 (2.1)	4 (1.1)

Data are n (%).

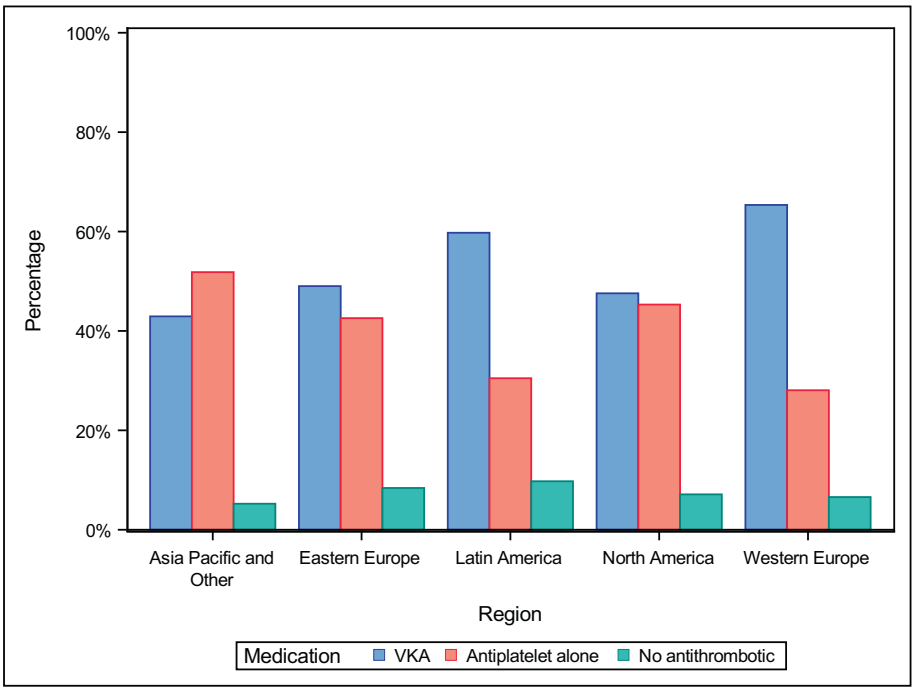

Fig. 1. Use of antiplatelet agents, vitamin K antagonist, or no antithrombotic agent by geographic region.

0.001), more frequently had heart failure (46.7% vs 40.0%; p = 0.022), and were less likely to be taking aspirin (36.0% vs 78.9%; p < 0.001).

The use of antiplatelet agents, VKA, or no antithrombotic agent by geographic region is presented in Fig. 1. Latin America and Western Europe were the regions where the use of VKA was more prevalent. Additionally, these regions had the lowest prevalence of antiplatelet use.

3.3. Clinical outcomes

Kaplan-Meier curves for the primary outcome in patients with and without a history of AF are presented in Fig. 2. Over a mean follow-up of 2.90 (1.05) years, patients with a history of AF had a higher risk for the composite outcome (HR 1.81, 95% CI 1.57–2.09), cardiovascular death (HR 2.26, 95% CI 1.84–2.76), myocardial infarction (HR 1.73, 95% CI 1.36–2.19), stroke (HR 2.04, 95% CI 1.53–2.73), all-cause mortality (HR 2.29, 95% CI 1.95–2.71), and hospitalization for heart failure (HR 3.50, 95% CI 2.81–4.37) compared with those without a history of AF. The risk for hospitalization for unstable angina was not different between patients with prior AF and those without AF (HR 1.32, 95% CI 0.88–1.99).

After adjustment, patients with a history of AF had higher risk for all clinical outcomes compared with those without AF, with the exception of hospitalization for unstable angina (Fig. 3). No interaction between treatment and history of AF was observed for any of the outcomes analyzed (all interaction *p* values >0.15).

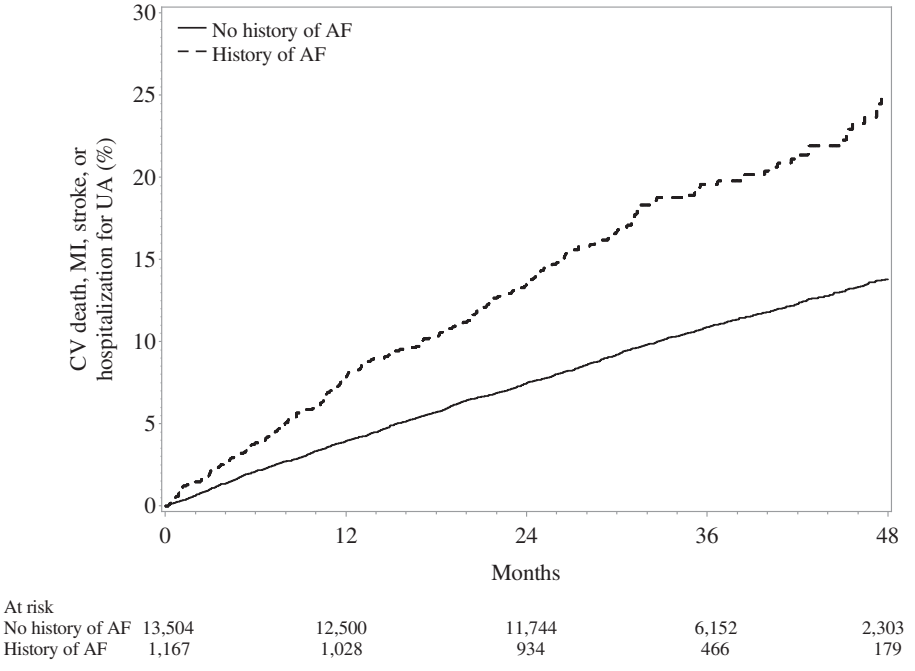

Fig. 2. Kaplan-Meier curves for the primary outcome in patients with and without history of atrial fibrillation (AF). CV, cardiovascular; MI, myocardial infarction; UA, unstable angina.

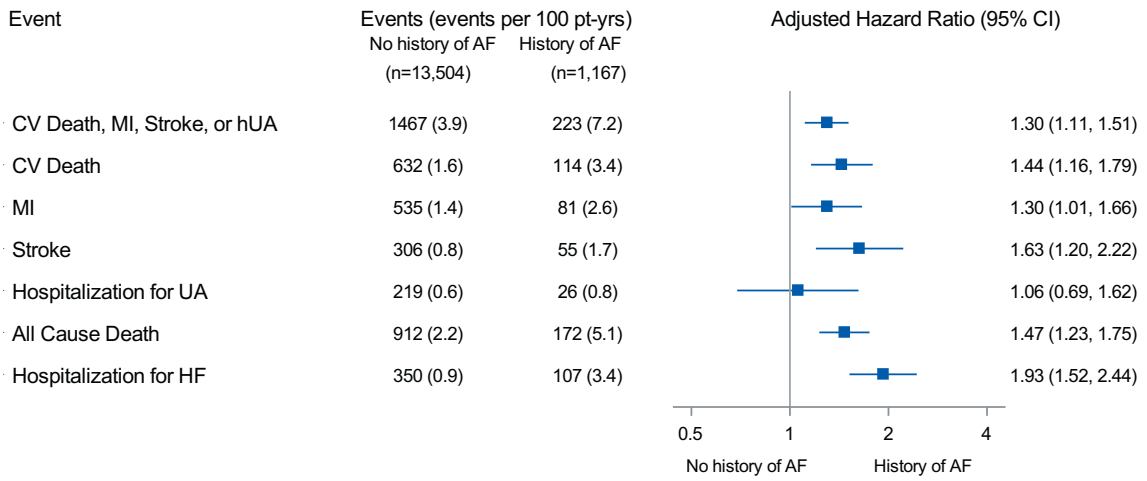

Fig. 3. Clinical outcomes in patients with type 2 diabetes according to history of atrial fibrillation (AF). CV, cardiovascular; HF, heart failure; hUA, hospitalization for unstable angina; MI, myocardial infarction; UA, unstable angina.

3.4. Predictors of new-onset AF

Several clinical factors were independently associated with new-onset AF among patients with T2DM and ASCVD without prior AF (Supplementary Table 2). White, older men with prior myocardial infarction, heart failure, peripheral artery disease, or prior stroke were more likely to develop new-onset AF than others without these characteristics. Patients from North America were also more likely to develop new-onset AF than those from other regions. The C-index for the model is 0.73 (95% CI: 0.70–0.75).

4. Discussion

Our study provides insights into the antithrombotic strategies used for patients with AF, T2DM, and established ASCVD, as well as the additional associations between AF and adverse outcomes among these patients. The main findings of our study are the following: 1) only half of the patients with AF and T2DM were treated with anticoagulation at study entry, whereas a third of them were receiving monotherapy with aspirin; 2) patients with prior AF had higher adjusted risk for cardiovascular outcomes compared with those without a history of AF; and 3) several clinical factors such as white race, increasing age, male sex, prior myocardial infarction, heart failure, peripheral artery disease, or prior stroke were associated with the occurrence of new-onset AF during trial follow-up.

T2DM is a well-known risk factor for stroke among patients with AF. In the context of AF and T2DM, all patients should at least be considered for anticoagulation therapy, provided there are no contraindications. Even when the only risk factor for stroke among younger men without comorbidities is the presence of T2DM, it has been shown that T2DM carries a higher risk for thromboembolic events than other risk factors, such as vascular disease and hypertension [7]. Patients with prior AF included in TECOS had T2DM and a median age of 69 years, >90% had hypertension, and all of them had ASCVD as enrichment criteria for entering in the trial. Therefore, all AF patients in TECOS had a CHA_2DS_2-VASc score ≥ 2 points, with 85.2% of patients having a score ≥ 4 points.

VKA was used by only half of patients with prior AF at baseline, despite the indication for oral anticoagulation. The use of VKA modestly increased with higher CHA_2DS_2-VASc scores, but was still lower than 60% for patients with CHA_2DS_2-VASc ≥6. In the Outcomes for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry, around 75% of patients with AF and diabetes were being treated with VKA, and this rate was greater than that of patients without diabetes [8]. Since ORBIT-AF is a quality improvement program specifically designed to include and follow patients with AF, the observed anticoagulation rates might not reflect routine clinical practice in different settings. Despite antiplatelet monotherapy being a class III recommendation for stroke prevention in AF [4], aspirin was used as monotherapy by a third of the patients with prior AF enrolled in TECOS. Treatment of patients with multiple comorbidities is often a challenge in clinical practice. In TECOS, as all patients had T2DM and established ASCVD, it is possible that health care providers focused more on antihyperglycemic therapies for DM than on the high risk of stroke associated with AF. This fact, coupled with the risk of bleeding, could at least partially explain the underuse of anticoagulants and the overuse of aspirin in this population.

Prior bleeding and high bleeding risk are common reasons to hold anticoagulation in patients with AF [9]. In recent years, non-vitamin K antagonist oral anticoagulants (NOACs) have been increasingly used for stroke prevention in AF, with no need for laboratory monitoring and a better safety profile compared with VKA. Secondary analyses of the major trials testing NOACs against VKA in patients with AF have shown consistent effects in patients with T2DM [10–13]. TECOS enrolled patients from 2008 to 2012, a period when not all NOACs were approved for clinical use in many countries. In TECOS, only six patients were using NOACs at baseline. Our observation that anticoagulants are underused by patients at high risk for thromboembolic events highlights important gaps in treatment of patients with AF and concomitant T2DM. The increasing use of NOACs may help overcome some of these gaps [14].

In our study, patients with prior AF had higher adjusted risk for cardiovascular outcomes compared with those without history of AF. These findings were consistent with a secondary analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) study that included 11,140 patients with T2DM and additional cardiovascular risk factors, of whom 7.6% had AF at baseline [15]. The presence of AF was independently associated with an increased risk for all-cause death, cardiovascular death, cerebrovascular events, and heart failure over a mean follow-up of 4.3 years. Focusing on lifestyle changes, glycemic control, and stroke prevention strategies are important goals in the treatment of this high-risk population.

Treatment with a DPP-4i, such as sitagliptin, promotes beneficial metabolic effects in patients with T2DM [16,17]. It was unknown whether these agents had a role in preventing the occurrence of new-onset AF in patients with T2DM. In the multivariable model, treatment with sitagliptin was not shown to have a protective effect against the development of new-onset AF. Other variables such as age, white race, male sex, and prior cardiovascular disease were independently associated with the occurrence of new-onset AF among T2DM patients.

Another study has also found that older age and history of heart failure were associated with new-onset AF in patients with T2DM [18].

Our findings should be interpreted in light of several limitations. First, as a post-hoc analysis, unmeasured confounding is always present, and our results should be interpreted as hypothesis-generating. Second, new-onset AF during trial follow-up was reported by local investigators in the case report form and was not centrally adjudicated. Third, since there was no information on international normalized ratio control, the HAS-BLED bleeding score could not be calculated. Fourth, data on the type and duration of AF were not recorded at baseline or during follow-up. Therefore, we could not determine when patients had the diagnosis of AF before entering in the trial. Finally, since the TECOS study was performed some years ago, the use of anticoagulants in patients with AF and T2DM might have been lower than in the current clinical era when NOACs are widely prescribed.

5. Conclusions

Patients with AF, T2DM, and established ASCVD are at high risk of adverse clinical outcomes, but only half of such patients enrolled in TECOS were receiving anticoagulation therapy despite clear guideline recommendations. Our study identified important gaps in the antithrombotic treatment of this population, highlighting the challenge in managing these patients in routine clinical practice.

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Conflict of interest disclosures

Dr. Peterson has received grant support from Janssen, Merck, Sanofi, AstraZeneca, Genentech, and Amgen; and has consulting associations with Bayer, Merck, Sanofi, and Janssen. Dr. Lokhnygina has received grants from Merck, Janssen Research & Development, AstraZeneca, GlaxoSmithKline, and Bayer HealthCare AG. Dr. Green has received grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Sanofi; personal fees from AstraZeneca, Merck, Boehringer-Ingelheim, and NovoNordisk. Dr. McGuire has provided clinical trial leadership for AstraZeneca, Sanofi Aventis, Janssen, Boehringer Ingelheim, Merck & Co, Novo Nordisk, Lexicon, Eisai, GlaxoSmithKline, Esperion, and consultancy for AstraZeneca, Sanofi Aventis, Lilly US, Boehringer Ingelheim, Merck & Co, Pfizer, Novo Nordisk, Applied Therapeutics, and Metavant. Dr. Holman has received grants from AstraZeneca, Bayer AG, and Merck Sharp & Dohme, as well as personal fees from Amgen, Bayer AG, Boehringer Ingelheim, Novo Nordisk, and Servier. Dr. Lopes has received research grants from Bristol Myers Squibb, GlaxoSmithKline, Medtronic, and Pfizer; consulting fees from Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, and Portola Pharmaceutical. The other authors have no disclosures to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.085.

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