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A post hoc analysis of saxagliptin efficacy and safety in patients with type 2 diabetes stratified by UKPDS 10-year cardiovascular risk score

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Abstract *Background and aims:* To assess the efficacy and safety of saxagliptin 2.5 and 5 mg/d in patients with type 2 diabetes mellitus (T2DM) and high risk of coronary heart disease (CHD) or stroke as estimated by the United Kingdom Prospective Diabetes Study (UKPDS) risk engine.
Methods and results: Post hoc analysis of data pooled from 5 previously reported phase 3, randomized, placebo-controlled, 24-week studies was conducted. Patients were stratified into subgroups by UKPDS 10-year CHD and/or stroke risk ≥20% and CHD and stroke risk <20%. End points were adjusted mean change from baseline in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), 120-min postprandial glucose (PPG), and body weight and the proportion of patients achieving HbA1c <7% and ≤8% at week 24. Pooled safety data were analyzed for adverse events (AEs) and hypoglycemia. Both doses of saxagliptin reduced HbA1c, FPG, and PPG to a greater extent than placebo regardless of UKPDS risk score. The proportions of patients achieving HbA1c <7% and ≤8% were greater with saxagliptin than placebo and consistent across risk score groups. AE profile and hypoglycemia incidence were similar for saxagliptin and placebo across UKPDS risk score groups.
Conclusion: Saxagliptin was well tolerated and improved glycemic control in patients with T2DM regardless of their CHD and stroke UKPDS risk score.
Clinical trial registration numbers: Clinicaltrials.gov NCT00121641, NCT00316082, NCT00121667, NCT00313313, and NCT00295633.

Introduction

Cardiovascular disease (CVD) is a common cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) and accounts for up to 70% of deaths in individuals with diabetes aged 65 years or older [1]. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend a patient-centered approach to the management of hyperglycemia in patients with T2DM and identified CVD as an

Abbreviations: ADA, American Diabetes Association; AEs, adverse events; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; PPG, 120-min postprandial glucose; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; UKPDS, United Kingdom Prospective Diabetes Study.

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important factor in modifying treatment goals. ADA/EASD suggest that their generally recommended glycated hemoglobin (HbA1c) level of <7% be modified to a less aggressive (e.g., 7–8%) target in patients with significant CVD [2]. A main reason for this higher HbA1c level is the significant increase in the risk of hypoglycemia when HbA1c target is particularly low, and the understanding that low blood glucose may exacerbate myocardial ischemia or cause dysrhythmias [2,3]. However, not all antidiabetic medications cause hypoglycemia when used in monotherapy and with some of them the risk of hypoglycemia is negligible even when pursuing very ambitious HbA1c targets.

The armamentarium of antidiabetic medications currently includes seven classes of commonly used drugs, i.e., biguanides (metformin), sulfonylureas/glinides, α-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 receptors agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 inhibitors. A number of meta-analyses reported that the efficacy of drugs of these classes is quite similar [4–6]. These meta-analyses, generally based upon pooling of phase 2 and 3 randomized controlled trials with end points set after 6 months of treatment, did not focus on special populations. In fact, little attention was dedicated to patients with increased CVD risk. These patients might have different antidiabetic medication efficacy and safety profiles due to concomitance of several risk factors (e.g., smoking, hypertension, dyslipidemia, older age, longer history of diabetes) [7–10] and/or the concurrent use of several medications (e.g., antihypertensive or hypolipidemic drugs) [11–14] which might affect the dominant pathogenetic disturbances underlying hyperglycemia (i.e., insulin resistance and β-cell dysfunction).

Saxagliptin is a potent, selective DPP-4 inhibitor that improves glycemic control and is well tolerated when used as monotherapy or as add-on therapy to commonly used oral antihyperglycemic drugs and insulin [15–19]. In the present study, we analyzed the efficacy and safety of saxagliptin in patients with T2DM stratified by CHD or stroke risk estimated using the United Kingdom Prospective Diabetes Study (UKPDS) risk engine [20,21]. The UKPDS risk engine is a T2DM-specific risk calculator with terms for HbA1c and diabetes duration [21]. It is considered preferable to other risk estimators that treat diabetes as a categorical variable [22].

Methods

Study design

This was a post hoc analysis of data pooled from 5 previously reported phase 3, randomized, placebo-controlled, 24-week studies, including 2 studies of saxagliptin as monotherapy in drug-naïve patients (NCT00121641 and NCT00316082) [17,19] and 1 study each of saxagliptin as add-on therapy to metformin (NCT00121667) [16], saxagliptin add-on to glyburide versus uptitrated glyburide (NCT00313313) [15], and saxagliptin add-on to thiazolidinedione (TZD) (NCT00295633) [18]. The analyses were limited to doses of saxagliptin 2.5 and 5 mg/d; the saxagliptin 2.5- to 5-mg titration arm of Frederich et al. [17] was not included in the analysis.

Study population

Institutional review boards or ethics committees at each study site approved the protocol, and all patients gave written informed consent. Inclusion and exclusion criteria for the 5 studies have been previously reported in detail [15–19]. Briefly, eligible patients were aged 18–77 years with T2DM and HbA1c level of 7–10% [16,17,19], 7.5–10% [15], or 7–10.5% [18], body mass index ≤40 or ≤45 kg/m^2 (study dependent), and a fasting C-peptide level ≥1 ng/mL. At study entry, patients were either drug-naïve or were receiving a stable dose of metformin (1500–2550 mg/d for ≥8 weeks prior to screening), TZD (≥12 weeks prior to screening), or a submaximal dose of sulfonylurea (≥8 weeks prior to screening).

Exclusion criteria that were common to all studies included poorly controlled diabetes; a significant CV event within 6 months; heart failure (New York Heart Association class III and IV or left ventricular ejection fraction ≤40%); significant history of renal or hepatic disease; history of substance abuse in the previous year; immunocompromised state; and use of potent cytochrome P450 3A4 inhibitors or inducers. For this analysis, patients with existing CVD were excluded.

Analyses

Data from patients who received saxagliptin 2.5 or 5 mg/d or placebo in the 5 clinical trials were pooled and analyzed using the UKPDS risk engine version 2.01 to estimate risk for CHD and stroke [20,21]. Patients were stratified into subgroups by estimated (1) UKPDS 10-year stroke and/or CHD risk ≥20% [23] and (2) 10-year stroke and CHD risk <20%. A UKPDS score ≥20% was considered high risk based on the judgment of the authors and as reported in other studies [24–26].

End points were adjusted mean change from baseline HbA1c level, fasting plasma glucose (FPG) concentration, 120-min postprandial glucose (PPG) concentration, and body weight. We also calculated the proportion of patients achieving HbA1c levels of <7% and ≤8% at week 24. Pooled safety data were analyzed for adverse events (AEs) and all reported and confirmed (fingerstick blood glucose concentration ≤ 2.8 mmol/L [50 mg/dL] with associated symptoms) hypoglycemia.

Change from baseline HbA1c, FPG, and PPG levels at week 24 were analyzed in the pooled patient populations using analysis of covariance with terms for treatment, study, subgroup, and treatment by subgroup, and with baseline value as a covariate. *P* values for treatment-by-subgroup interactions were assessed to detect inconsistency of treatment effect across groups, with $P<0.1$ considered statistically significant. The Mantel-Haenszel proportion difference estimate was used to compare the