Journal of Diabetes and Its Complications 30 (2016) 1378–1384

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Safety and efficacy of linagliptin in patients with type 2 diabetes mellitus and coronary artery disease: Analysis of pooled events from 19 clinical trials

Michael Lehrke [a], Lawrence A. Leiter [b], Uwe Hehnke [c], Sandra Thiemann [c], Amit Bhandari [d], Thomas Meinicke [e], Odd Erik Johansen [f,*]

[a] University Hospital Aachen, Aachen, Germany
[b] Keenan Research Centre in the Li Ka Shing Research Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada
[c] Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
[d] Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA
[e] Boehringer Ingelheim Corporation, Biberach, Germany
[f] Boehringer Ingelheim Norway KS, Asker, Norway

ARTICLE INFO

Article history:
Received 28 April 2016
Received in revised form 13 June 2016
Accepted 15 June 2016
Available online 16 June 2016

Keywords:
Linagliptin
Dipeptidyl peptidase-4 inhibitor
Type 2 diabetes mellitus
Coronary artery disease
Drug safety
Heart failure

ABSTRACT

Aims: To examine the safety and efficacy of linagliptin in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) using pooled data from the global clinical trials program.
Methods: Patient-level data were pooled from randomized, placebo-controlled clinical trials of linagliptin (5 mg, monotherapy or combination therapy). Safety/efficacy analyses were conducted for patients with CAD and ≥12 and ≥24 weeks of treatment, respectively.
Results: The safety analysis included 19 trials (linagliptin, $n = 451$; placebo, $n = 272$) and the efficacy analysis, 12 trials (linagliptin, $n = 328$; placebo, $n = 198$); mean (± standard deviation) exposure to study treatment was 212 (144) days linagliptin and 245 (171) days placebo. Occurrence of cardiac adverse events (AEs) was similar for linagliptin- and placebo-treated patients (9.1% and 9.2%, respectively); exposure-adjusted incidence rates (per 100 patient-years) were 16.6 and 14.0, respectively. Overall incidence of AEs was numerically lower with linagliptin than placebo. After 24 weeks, mean adjusted change (standard error) from baseline glycosylated hemoglobin was −0.64% (0.04) with linagliptin vs. –0.08% (0.05) with placebo ($P < .001$).
Conclusions: This comprehensive pooled analysis showed that addition of linagliptin to treatment regimens of patients with T2DM and CAD was not associated with an increased incidence of cardiac AEs, was well tolerated, and was effective.

1. Introduction

Coronary artery disease (CAD) is a prevalent condition in patients with type 2 diabetes mellitus (T2DM) (Go, Mozaffarian, Roger, et al., 2014; Huxley, Barzi, & Woodward, 2006); compared with individuals without diabetes, patients with T2DM have a two- to fourfold increased risk of cardiovascular (CV) disease (Beckman, Creager, & Libby, 2002; Haffner, Lehto, Rönnemaa, Pyörälä, & Laakso, 1998; Preis, Hwang, Coady, et al., 2009). For patients with T2DM, the presence of CAD results in poorer clinical outcomes compared with those without CAD (Beckman et al., 2002; Franco, Steyerberg, Hu, Mackenbach, & Nusselder, 2007; Miettinen, Lehto, Salomaa, et al., 1998). The pathophysiology of diabetic vascular disease is complex, and patients with T2DM may also have additional risk factors which increase the risk of atherosclerosis, including hypertension, dyslipidemia, obesity, smoking and insulin resistance. The importance of controlling these risk factors through medication and lifestyle changes is well established (Beckman et al., 2002). In particular, the control of hyperglycemia has been shown to reduce the risk of microvascular endpoints. Data from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated, over a 10-year follow-up period, that intensive glycemic control was associated with a reduction of

Conflict of Interest: ML has acted as an advisor to BMS, Astra-Zeneca, Roche, GSK, MSD, Amgen, Sanofi, and a speaker for BMS, Astra-Zeneca, Roche, GSK, Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Amgen. LAL has received research funding from, has provided CME on behalf of, and/or has acted as an advisor to: AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Merck, Pfizer, Sanofi, and Sevier. UH, ST, OEJ, AB and TM are all employees of Boehringer Ingelheim.

Prior Publication: The data in this manuscript have been previously presented in posters at the American Diabetes Association 75th Scientific Sessions, Boston, MA, USA, June 5–9, 2015 (Poster 1246-P), and at the 51st Annual Meeting of the European Association for the Study of Diabetes, Stockholm, Sweden, 14–18 September, 2015 (Poster 814).

* Corresponding author at: Boehringer Ingelheim Drengsrudbekken 8, 1373 Asker, Oslo, Norway.
E-mail address: odd_erik.johansen@boehringer-ingelheim.com (O.E. Johansen).

http://dx.doi.org/10.1016/j.jdiacomp.2016.06.015

microvascular endpoints, as well as risk reduction for myocardial infarction (MI) and death from any cause (Holman, Paul, Bethel, Matthews, & Neil, 2008). Similarly, in the Kumamoto study, intensive glycemic control was shown to delay the onset and progression of early diabetic microvascular complications after an 8-year follow-up of Japanese patients with T2DM (Shichiri, Kishikawa, Ohkubo, & Wake, 2000). In contrast, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was prematurely terminated following a recommendation by the data and safety monitoring committee due to a 22% relative increase in risk of mortality and a 38% relative increase in CV death among patients receiving an intensive strategy to reduce glycosylated hemoglobin (HbA1c) levels, compared with those with a less stringent HbA1c target, although the groups did not differ with respect to the composite outcome measure of non-fatal MI, non-fatal stroke or CV death (in fact, non-fatal MI was significantly reduced) (Gerstein, Miller, Byington, et al., 2008). Subsequent reports from the ACCORD Study Group on long-term effects, following 3.7 years of intensive glucose lowering, include reports on outcomes after 5 years of follow-up (Gerstein, Miller, Genuth, et al., 2011) as well as 9-year outcomes (in the ACCORD International Ongoing [ACCORDION] Study) (The ACCORD Study Group Writing Committee, 2016), which demonstrated persistence of the original findings, in addition to an attenuation of the overall mortality risk, shown in ACCORDION.

However, the use of intensive glucose control showed no benefit on macrovascular events for patients with T2DM in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study. Although intensive glucose control was associated with a significant 10% relative reduction in the combined outcome of major macrovascular and microvascular events during a median 5-year follow-up period, this was mainly as a result of a 21% relative reduction in the incidence of nephropathy ($P = .006$), with no risk reduction in the incidence of major macrovascular events or death from CV causes (Patel, MacMahon, Chalmers, et al., 2008). In the extended follow-up of this trial (median, 5.4 years' post-trial follow-up), intensive glucose control during the trial did not lead to long-term benefits with respect to mortality or macrovascular events (Zoungas, Chalmers, Neal, et al., 2014). Similarly, a study of American veterans with T2DM, the Veterans Affairs Diabetes Trial (VADT), showed no significant effect of intensive glycemic control on the incidence of major CV events or on the risk of death from any cause, after a median follow-up period of 5.6 years (Duckworth, Abraira, Moritz, et al., 2009). However, after extended follow-up of the VADT population to 9.8 years after the start of the study, patients who received intensive glucose control for the first 5.6 years were found to have a significant 17% reduction of the primary endpoint of macrovascular disease but no improvement in cardiovascular- or overall survival (Hayward, Reaven, Wiitala, et al., 2015).

In addition to uncertainties about the effectiveness of tight glycemic control in reducing the risk of macrovascular events, this approach can be associated with an increased risk of severe hypoglycemic episodes, which can offset some of the CV benefits of therapy (Boussageon, Bejan-Angoulvant, Saadatian-Elahi, et al., 2011; Mannucci, Monami, Lamanna, Gori, & Marchionni, 2009). Subgroup analyses of UKPDS, ACCORD, ADVANCE and VADT suggest that patients with T2DM of shorter duration and without established CV disease (CVD) are more likely to benefit from intensive glycemic control, compared with those having more established disease for whom the risks might outweigh the potential CV benefits of intensive therapy (Skyler, Bergenstal, Bonow, et al., 2009).

Developing optimal treatment strategies in patients with T2DM and CAD remains a challenge in this high-risk population, where individuals often present with multiple risk factors, which substantially increase the risk for morbidity and mortality (Turner, Millns, Neil, et al., 1998). In view of the need for polypharmacy, frequent hospitalization and the risk of potential side effects or contraindications to some drugs, selecting the appropriate glucose-lowering treatment for these patients is uniquely challenging. The latest Diabetes Management Guidelines from the American Association of Clinical Endocrinologists (AACE) (Garber, Abrahamson, Barzilay, et al., 2016) and the joint Position Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Inzucchi, Bergenstal, Buse, et al., 2015) recommend a patient-centered approach to management, with treatment individualized to take account of risk factors, including comorbid conditions such as CAD. Current uncertainty about the long-term CV safety of specific glucose-lowering drugs (Selvin, Bolen, Yeh, et al., 2008), has led to the recommendation by the U.S. Food and Drug Administration (U.S. FDA) that the CV risk is evaluated for all compounds, except insulins, that are being developed as therapies for T2DM (U.S. FDA, 2008). As a result, many trials have been designed to assess the long-term CV outcomes of recently developed drugs for the management of T2DM, and there remains a clinical need for approaches to glycemic control that do not further increase CV risk (Cavender, Steg, Smith, et al., 2015).

Linagliptin is a dipeptidyl-peptidase (DPP)-4 inhibitor approved for the treatment of T2DM. The overall safety and tolerability of linagliptin have been established in a large clinical trial program and further demonstrated in a pooled analysis of 22 placebo-controlled trials of linagliptin (Lehrke, Marx, Patel, et al., 2014). The findings of this analysis supported previous findings of a low incidence of AEs and good overall tolerability of linagliptin in a broad range of patients with T2DM. The CV safety of linagliptin has been evaluated in a comprehensive patient-level pooled analysis of prospectively adjudicated CV events from the clinical trial program (Rosenstock, Marx, Neubacher, et al., 2015). This analysis of 19 trials of at least 12 weeks' duration, in which linagliptin was evaluated in comparison with placebo or one or more active comparators, showed that linagliptin was not associated with increased CV risk in patients with T2DM. A post-hoc pooled analysis of linagliptin as add-on to insulin therapy in T2DM also demonstrated a neutral effect of linagliptin on the occurrence of major CV AEs (Zinman et al., 2016). Two CV outcome trials are underway with the aim of further evaluating the CV safety of linagliptin. The CARdiovascular Outcome Study of LINAgliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA®) (NCT01243424) has randomized 6041 patients with early T2DM who are at high CV risk to receive therapy with linagliptin or the sulfonylurea (SU) glimepiride (Marx, Rosenstock, Kahn, et al., 2015; Rosenstock, Marx, Kahn, et al., 2013). The CArdiovascular and Renal Microvascular OutcomE Study With LINAgliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA®) (NCT01897532) trial will compare the CV and renal safety of linagliptin vs. placebo, added to standard care in patients with T2DM who are at high risk of vascular complications. While the outcomes of dedicated CV safety trials of linagliptin are awaited, analysis of available data from completed clinical trials can provide some insights into the role of this agent in patients with CAD or at high risk of CV events. The aim of this analysis was to examine the safety and efficacy of linagliptin in patients with CAD using pooled data from a global clinical trials program.

2. Materials and methods

Patient-level data were pooled for this analysis from randomized, placebo-controlled clinical trials of linagliptin 5 mg, of at least 12 weeks' duration. The trials included linagliptin administered either as monotherapy or in combination with other glucose-lowering drugs. All trials were conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Eligibility criteria across the included trials were similar and included a diagnosis of T2DM, age ≥18 years, HbA1c 7%–10% entrance criterion in most studies, and a body mass index (BMI) of 20–45 kg/m^2. In all