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COMMENTARY

# Cardiovascular safety trials of incretin-based drugs: What do they mean?

**Incretin-based dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists are newer choices of antidiabetic medications that are now most widely used worldwide. Preclinical study results suggest that the two drugs potentially exert benefits to prevent onsets and/or progressions of diabetes-related complications, such as myocardial infarctions and strokes. Outcomes of five clinical trials to evaluate the cardiovascular (CV) safety of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonist have been recently reported. The heart failure findings of the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI53) are unexpected and very concerning; results of the Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care (EXAMINE), the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) and the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) encourage neutral CV safety profiles of incretin-based drugs in individuals with type 2 diabetes and established CV diseases or multiple CV risks. Furthermore, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) results show the benefits of liraglutide in preventing CV events in a similar study population. Despite the many preclinical studies showing the beneficial effects of incretin-related drugs, most CV safety trials of incretin-based drugs, except for LEADER, did not show benefits for CV events. It is important to recognize that CV safety trials were carried out to meet the US Food and Drug Administration guidance to assess CV safety of all new antidiabetic drugs; they were not designed to assess their benefits for CV events. Therefore, the long-term potential benefit, as well as even the safety, of incretin-based drugs for certain CV outcomes has not been definitively established, and requires evaluation in more specific and more relevant trials. If the need for CV safety trials would be determined based on an individual drug's safety data during its earlier development as well as its mechanism of action, resources could be saved for carrying out such clinical trials.**

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Chronic hyperglycemia, in collaboration with hypertension and dyslipidemia, can cause diabetes-associated microvascular complications (e.g., neuropathy, nephropathy and retinopathy) and macrovascular complications (e.g., myocardial infarctions, strokes and peripheral arterial diseases) in individuals with diabetes. Lines of evidence show that amelioration of glycemia with appropriate controls of bodyweight, blood pressures, and lipid levels prevents onset and/or progression of such complications. To date, several glucose-lowering drugs have been developed to normalize glycemia in individuals with type 2 diabetes. Among such drugs, incretin-based dipeptidyl peptidase-4 inhibitors (DPP-4is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are newer choices of such antidiabetic medications. The two drugs are now most widely used worldwide, in part because they have low risks of hypoglycemia and bodyweight gain despite their ability to ameliorate glycemia through enhancement of insulin secretion, unlike sulfonylureas and glinides[1]. DPP-4is improve glycemic control in individuals with type 2 diabetes by preventing degradation of the two incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide. GLP-1RAs does so by binding to the GLP-1 receptor and activating GLP-1 receptor signaling. GLP-1 and glucose-dependent insulinotropic polypeptide are secreted from the intestine on ingestion of various nutrients and enhance insulin secretion from pancreatic β-cells glucose-dependently. Preclinical studies in animal models have shown diverse biological functions of both incretins in addition to their glucose-dependent insulinotropic action[2]. Thus, it has been expected that the incretin-related drugs potentially exert benefits to prevent onsets and/or progressions of diabetes-related complications, such as myocardial infarctions (MI) and strokes. However, the effects of incretin-based drugs on diabetes-related complications need to be examined in clinical trials with adequately powered, prospective, controlled relevant endpoints. For these reasons, outcomes of five clinical trials to evaluate the cardiovascular (CV) safety of individual incretin-based drugs have gained much attention.

Three trials, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI53), the Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care (EXAMINE) and

the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), assessed CV safety of the DPP-4is saxagliptin, alogliptin and sitagliptin in individuals with type 2 diabetes at risk for CV events, respectively. SAVOR-TIMI53 was carried out globally using a total of 16,492 patients with a history of CV disease (approximately 80% of the study population) or with multiple CV risks (approximately 20%) (Table 1)[3]. The median observation period was 2.1 years; glycated hemoglobin (HbA1c) changes from baseline were just 0.3% greater in those receiving saxagliptin compared with a placebo. The primary composite end-point of CV death, non-fatal MI and non-fatal ischemic stroke occurred in patients receiving saxagliptin similarly to those receiving a placebo (hazard ratio [HR] 1.00, 95% confidence interval [CI] 0.89–1.12, $P = 0.99$). EXAMINE was carried out globally using a total of 5,380 patients, all of whom had acute coronary syndrome[4]. The median observation period was 1.6 years; HbA1c changes from baseline were 0.4% greater in those receiving alogliptin. The primary composite end-point of CV death, non-fatal MI and non-fatal stroke occurred in patients receiving alogliptin similarly to those receiving a placebo (HR 0.96, upper 99% CI: <1.16, $P = 0.32$). TECOS was carried out globally using a total of 14,671 patients with a history of CV disease (approximately 75%), ischemic stroke (approximately 25%) and/or peripheral artery diseases (approximately 20%)[5]. The median observation period was 3.0 years; HbA1c changes from baseline were 0.3% greater in those receiving sitagliptin. The primary composite end-point of CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina was 0.98 (95% CI: 0.89–1.08, $P = 0.65$). These results can be taken to show that DPP-4is have neutral CV safety profiles in individuals with type 2 diabetes and high risks for CV events, particularly MI, stroke and CV death. Unexpectedly, saxagliptin use was associated with a significant increase in hospitalization for heart failure compared with a placebo (HR 1.27, 95% CI: 1.07–1.51, $P = 0.007$). EXAMINE and TECOS did not find significant associations of heart failure with use of alogliptin and sitagliptin, suggesting that the effects of saxagliptin on heart failure might be a drug effect rather than a class effect. Rigorous post-hoc analyses on SAVOR-TIMI53 failed to identify obvious causal mechanisms for heart failure with saxagliptin; further investigations are warranted to evaluate changes in cardiac function in individuals with type 2 diabetes receiving saxagliptin.

Two clinical trials, the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) and the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), assessed the CV safety of the GLP-1RAs lixisenatide and liraglutide in individuals with type 2 diabetes at risk for CV events, respectively. ELIXA was carried out globally using a total of 6,068 patients with a recent experience of acute coronary syndrome (Table 1)[6]. The median observation period was 2.1 years; HbA1c changes from baseline were approximately 0.3% greater in those receiving lixisenatide compared with a placebo. The primary composite end-point of CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina occurred in patients receiving lixisenatide similarly to those receiving placebo (HR 1.02, 95% CI: 0.89–1.17, $P = 0.81$). LEDER was carried out globally using a total of 9,340 patients with high risks for CV events[7]. The median observation period was 3.8 years; HbA1c changes from baseline were approximately 0.4% greater in those receiving liraglutide compared with a placebo. The primary composite end-point of CV death, non-fatal MI and non-fatal stroke occurred in significantly fewer patients receiving liraglutide (HR 0.87, 95% CI: 0.78–0.97, $P < 0.001$ for non-inferiority and $P = 0.01$ for superiority). Although the differing outcomes of ELIXA and LEADER are still unexplained, differences in baseline characteristics of the enrolled patients, such as HbA1c (LEADER ≈8.7%/ELIXA ≈7.7%) and body mass index (LEADER ≈32/ELIXA ≈30), might have implications in accord with differences in the mode of action (i.e., short-acting vs long-acting)[8]. Further investigations are required to understand the factors responsible for the differing outcomes of ELIXA and LEADER. Nevertheless, it is important to consider that hospitalization for heart failure was not affected by lixisenatide use (HR 0.96, 95% CI: 0.75–1.23, $P = 0.75$) or by liraglutide use (HR 0.87, 95% CI: 0.73–1.05, $P = 0.14$).

The heart failure findings of SAVOR-TIMI53 are unexpected and very concerning; the results of EXAMINE, TECOS and ELIXA encourage neutral CV safety profiles of incretin-based drugs in individuals with type 2 diabetes and established CV diseases or multiple CV risks. Furthermore, LEADER results show benefits of liraglutide for preventing CV events in a similar study population. Because of the existence of the many preclinical studies showing the beneficial effects of incretins and incretin-related drugs, obvious questions arise as to why most CV safety trials of incretin-based drugs, except for liraglutide, did not show benefits for CV events. In this regard, it is important to recognize that CV safety trials were carried out to meet the US Food and Drug Administration guidance implemented in 2008 to assess the CV safety of all new antidiabetic drugs; they were not designed to assess their benefits for CV events. CV safety trials require a large study population in multiple countries to obtain CV events sufficient for statistical analysis. Monitoring such large study populations globally requires substantial costs and efforts; thus encouraging enrollment of patients with established CV diseases who are likely to experience a CV event within a limited time-period. These patients are already taking aspirin, statin and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers along with multiple antidiabetic drugs (Table 1); the results obtained should be evaluated taking these patient characteristics into consideration. Therefore, the long-term potential benefit, as well as even the safety, of incretin-based drugs for certain CV outcomes has

**Table 1** | Summary of selected outcomes and baseline characteristics of United Kingdom Prospective Diabetes Study and cardiovascular safety clinical trials of incretin-based drugs

| | UKPDS33 | SAVOR-TIMI53 | EXAMINE | TECOS | ELIXA | LEADER |
|---|---|---|---|---|---|---|
| *n* | I 2,729/C 1,138 | D 8,280/P 8,212 | D 2,701/P 2,679 | D 7,332/P 7,339 | D 3,034/P3,034 | D 4,668/P 4,672 |
| Follow up (years)† | 10.0 | 2.1 | 1.6 | 3.0 | 2.1 | 3.8 |
| Primary end-point | Any diabetes-related end-points | CV death, non-fatal MI and non-fatal ischemic stroke | CV death, non-fatal MI and non-fatal stroke | CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina | CV death, non-fatal MI, nonfatal stroke and hospitalization for unstable angina | CV death, non-fatal MI and non-fatal stroke |
| | HR 0.88 (0.79–0.99) $P = 0.029$ | HR 1.00 (0.89–1.12) $P = 0.99$ $P < 0.001$ for non-inferiority $P = 0.99$ for superiority | HR 0.96 (upper boundary of the one-sided repeated CI: 1.16) $P < 0.001$ for non-inferiority $P = 0.32$ for superiority | HR 0.98 (0.88–1.09) $P < 0.001$ for non-inferiority HR 0.98 (0.89–1.08) $P = 0.65$ for superiority | HR 1.02 (0.89–1.17) $P < 0.001$ for non-inferiority $P = 0.81$ for superiority | HR 0.87 (0.78–0.97) $P < 0.001$ for non-inferiority $P = 0.01$ for superiority |
| Death from CV cause | ND | HR 1.03 (0.87–1.22) $P = 0.72$ | HR 0.79 (0.60–1.04) $P = 0.10$ | HR 1.03 (0.89–1.19) $P = 0.71$ | HR 0.98 (0.78–1.22) $P = 0.85$ | HR 0.78 (0.66–0.93) $P = 0.007$ |
| MI | HR 0.84 (0.71–1.00) $P = 0.052$ | HR 0.95 (0.80–1.12) $P = 0.52$ | HR 1.08 (0.88–1.33) $P = 0.47$ (non-fatal) | HR 0.95 (0.81–1.11) $P = 0.49$ (fatal or non-fatal) | HR 1.03 (0.87–1.22) $P = 0.71$ (fatal or non-fatal) | HR 0.86 (0.73–1.00) $P = 0.046$ (fatal or non-fatal) |
| Stroke | HR 1.11 (0.81–1.51) $P = 0.52$ | HR 1.11 (0.88–1.39) $P = 0.38$ (ischemic) | HR 0.91 (0.55–1.50) $P = 0.71$ (non-fatal) | HR 0.97 (0.79–1.19) $P = 0.76$ (fatal or non-fatal) | HR 1.12 (0.79–1.58) $P = 0.54$ (fatal or non-fatal) | HR 0.86 (0.71–1.06) $P = 0.16$ (fatal or non-fatal) |
| Hospitalization for HF | ND | HR 1.27 (1.07–1.51) $P = 0.007$ | HR 1.07 (0.79–1.46) $P = 0.657$ | HR 1.00 (0.83–1.20) $P = 0.98$ | HR 0.96 (0.75–1.23) $P = 0.75$ | HR 0.87 (0.73–1.05) $P = 0.14$ |
| Age (years)‡ | I 53.2 ± 8.6/C 53.4 ± 8.6 | D 65.1 ± 8.5/P 65.0 ± 8.6 | D 61.0/P 61.0 | D 65.4 ± 7.9/ P 65.5 ± 8.0 | D 59.9 ± 9.7/ P 60.6 ± 9.6 | D 64.2 ± 7.2/P 64.4 ± 7.2 |
| Sex, male (%) | I 60.6/C 61.9 | D 66.6/P 67.3 | D 67.7/P 68.0 | D 70.9/P 70.5 | D 69.6/P 69.1 | D 64.5/P 64.0 |
| Ethnicity, white (%) | I 81/C 81 | D 75.4/P75.1 | D 72.8/P72.5 | D 67.6/P 68.2 | D 74.4/P 76.4 | D 77.5/P 77.5 |
| CV disease (%) | – | D 78.4/P 78.7 | D 100/P100 | D 73.6/P 74.5 | D 100/P 100 | D 82.1/P 80.6 |
| Duration of diabetes (years)§ | Newly diagnosed | D 10.3 (5.2–16.7)/P 10.3 (5.3–16.6) | D 7.1 (2.6–13.8)/ P 7.3 (2.8–13.7) | D 11.6 ± 8.1/ P 11.6 ± 8.1 | D 9.2 ± 8.2/ P 9.4 ± 8.3 | D 12.8 ± 8.0/P 12.9 ± 8.1 |
| HbA1c (%) | I 7.09 ± 1.54/C 7.05 ± 1.42 | D 8.0 ± 1.4/P 8.0 ± 1.4 | D 8.0 ± 1.1/P 8.0 ± 1.1 | D 7.2 ± 0.5/ P 7.2 ± 0.5 | D 7.7 ± 1.3/ P 7.6 ± 1.3 | D 8.7 ± 1.6/P 8.7 ± 1.5 |
| BMI¶ | I 27.5 ± 5.1/C 27.8 ± 5.5 | D 31.1 ± 5.5/P 31.2 ± 5.7 | D 28.7 (15.7–55.9)/ P 28.7 (15.6–68.3) | D 30.2 ± 5.6/ P 30.2 ± 5.7 | D 30.1 ± 5.6/ P 30.2 ± 5.8 | D 32.5 ± 6.3/P 32.5± 6.3 |
| Metformin (%) | I 0/C 0 | D 69.9/P 69.2 | D 65.0/P 67.4 | D 81.0/P 82.2 | D 67.2/P 65.4 | D 75.8/P 77.0 |
| Sulfonylurea (%) | I 0/C 0 | D 40.5/P 40.0 | D 46.9/P 46.2 | D 45.6/P 45.0 | D 32.6/P 33.5 | D 50.6/P 50.5 |
| Insulin (%) | I 0/C 0 | D 41.6/P 41.2 | D 29.4/P 30.3 | D 23.5/P 22.9 | D 39.2/P 39.0 | D 43.6/P 45.5 |
| Aspirin (%)†† | I 1.7/C 1.5 | D 75.5/P 75.0 | D 90.6/P 90.8 | D 78.6/P 78.4 | D 97.6/P97.4 | D 68.6/P66.8 |
| Statin (%)‡‡ | I 0.3/C 0.3 | D 78.3/P 78.4 | D 90.6/P 90.3 | D 79.8/P 80.0 | D 93.3/P92.2 | D 72.7/P71.4 |

**Table 1** (*Continued*)

| | UKPDS33 | SAVOR-TIMI53 | EXAMINE | TECOS | ELIXA | LEADER |
|---|---|---|---|---|---|---|
| β-Blocker (%) | I 12/C 12 | D 61.6/P 61.6 | D 81.7/P 82.2 | D 63.4/P 63.7 | D 83.6/P85.3 | D 56.7/P54.0 |
| ARB (%) | | D 28.2/P 27.6 | D 81.5/P 82.5 | D 20.1/P 21.1 | D 84.9/P 85.0 | D 31.8/P 31.8 |
| ACEI (%) | | D 53.6/P 54.9 | | D 58.2/P 58.1 | | D 51.7/P 50.3 |

†Median. ‡Mean ± standard deviation except for median in the Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care (EXAMINE). §Mean ± standard deviation except for median with range in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI53) and EXAMINE. ¶Mean ± standard deviation except for median with range in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). ††Use of antiplatelet agent (%) instead of aspirin in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER). ‡‡Use of lipid-lowering drugs, instead of statin in the United Kingdom Prospective Diabetes Study (UKPDS). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II-receptor blockers; BMI, body mass index; C, conventional therapy; CV, cardiovascular; D, drug of interest; HbA1c, glycated hemoglobin; HF, heart failure; HR, hazard ratio; I, intensive therapy; ND, not determined; P, placebo.

not been definitively established and requires evaluation of individuals without CV diseases, similar to what was done in the United Kingdom Prospective Diabetes Study (UKPDS)[9], making full use of appropriate surrogate markers (e.g., intima-media thickness on the carotid ultrasonography). In this respect, the question remains whether the US Food and Drug Administration guidance for assessing CV safety through large CV safety trials of every new antidiabetes drug is appropriate. If the need for CV safety trials would be determined based on an individual drug's safety data during its earlier development as well as its mechanism of action, resources could be saved for carrying out more specific and more relevant trials (e.g., prevention of onset and/or progression of diabetes-related micro- and macrovascular complications) or trials to find effective therapeutics for reducing CV death and improving long-term healthy survival.

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