Analyses of Results From Cardiovascular Safety Trials With DPP-4 Inhibitors: Cardiovascular Outcomes, Predefined Safety Outcomes, and Pooled Analysis and Meta-analysis

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The U.S. Food and Drug Administration requires that the cardiovascular (CV) safety of all new drugs for diabetes be demonstrated through pooled analyses of phase III studies or specifically designed trials. This requirement prompted several placebo-controlled, noninferiority CV safety trials in high-risk patients; to date, all completed trials showed that dipeptidyl peptidase (DPP)-4 inhibitors do not increase or reduce the risk of major CV events. These results apparently contrast with those of pooled analyses and meta-analyses of previous, smaller trials with metabolic end points, which had suggested a reduction of risk. However, the design of CV trials, which were required to demonstrate safety, is not adequate (for duration, management of concurrent therapies, etc.) for the assessment of potential therapeutic benefits. In addition, CV safety trials enroll patients at high risk of CV events, who are different from those included in earlier trials with metabolic end points. Differences in characteristics of patients enrolled probably account for most of the discrepancy in CV outcomes between CV safety studies and earlier trials. The availability of several large-scale trials with longer duration provides the unique opportunity for assessment of the safety of DPP-4 inhibitors not only with respect to major CV events but also with reference to other safety issues. For example, CV safety trials can be a source of information for pancreatitis, cancer, or hypoglycemia.

In December 2008, the U.S. Food and Drug Administration (FDA) published guidance prompting pooled analyses and meta-analyses of cardiovascular (CV) events (sometimes with post hoc adjudication) observed in trials with metabolic outcomes (1). A shift of emphasis occurred from short-term, HbA_{1c}-centered phase II–III trials in "healthy" patients with type 2 diabetes to CV safety studies in a more vulnerable population (2). Results from the first trials according to the FDA guidance were published in 2013: the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) and the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trials with the dipeptidyl peptidase (DPP)-4 inhibitors saxagliptin and alogliptin, respectively (3,4). The publication of the results of TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) (5) with sitagliptin, the presentation of the ELIXA [Evaluation of Lixisenatide in Acute

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Coronary Syndrome] trial with the glucagon-like peptide 1 (GLP-1) receptor agonist lixisenatide, and the publication of the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial with the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (6) followed in 2015. This wave of information on CV safety of new antidiabetes drugs (ADD) is only the beginning (Fig. 1 and Table 1). Interpretation of the "mountains" of new information provided by these large-scale studies presents new challenges for the treating physician, the scientific world, the pharmaceutical industry, and eventually patients with diabetes themselves (7).

Unexpectedly, in the case of DPP-4 inhibitors the results of earlier trials had suggested a reduction in the incidence of major CV events (8–10), which was not confirmed by the specifically designed CV studies that followed (3–5). The reasons for this discrepancy are controversial and will be discussed in the article.

Primary and Secondary Outcomes: CV Safety Outcomes

CV Outcome Versus CV Safety Trials

The intensification of diabetes treatment appears to improve CV outcomes only in patients with recent-onset diabetes and after a prolonged latency (11,12). The FDA guidance requires the recruitment of patients at high CV risk, often with prolonged diabetes duration, advanced age, and renal failure (1), who are the least likely to benefit from any intervention regarding CV risk factors. In addition, most of those patients already receive multiple treatments for CV disease prevention. In the Steno-2 trial, the use of statins at the end of the intervention in the intensive versus conventional treatment arms was 0 vs. 3% at baseline and 85 vs. 22% at the end of the intervention stage of the trial, respectively (13). In SAVOR-TIMI 53, EXAMINE, and TECOS, statins were used at baseline by 78.3, 90.4, and 79.9% of the trial population, respectively (3–5). The residual CV risk left, in spite of statin treatment, was smaller, and therefore any CV superiority was more difficult to prove.

The FDA requirements for new ADD development programs were to exclude an unacceptable increased relative CV risk with an upper limit of 95% CI of <1.3 (1). For this reason, trials are designed to show noninferiority between treatment arms with respect to CV events while maintaining similar glycemic control (14): investigators are free to modify glucose-lowering medications other than the experimental drug in order to maintain good glycemic control in both treatment groups, and in fact, between-group differences in HbA_{1c}

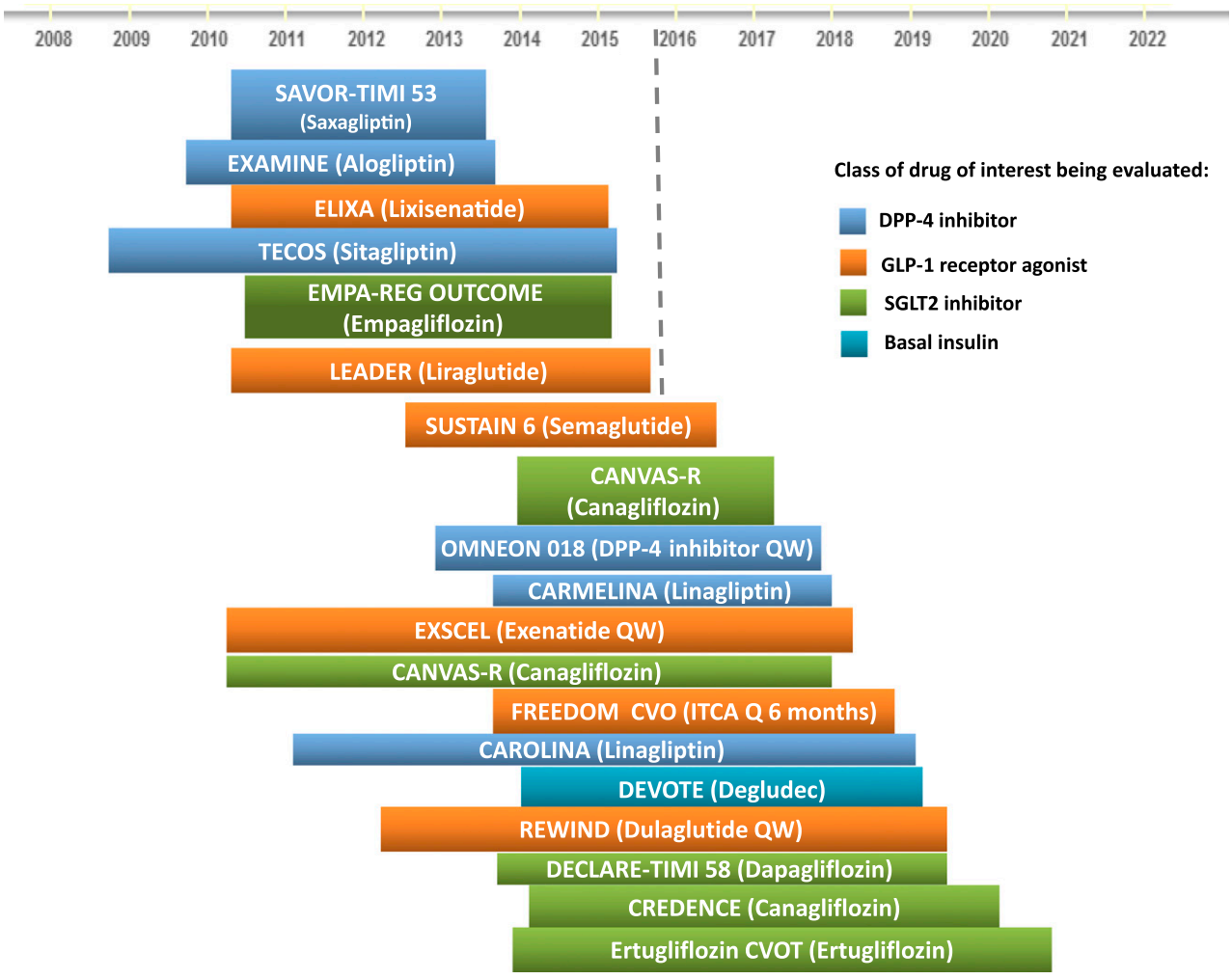

Figure 1—Timing of CV safety trials with drugs for type 2 diabetes.

Table 1—Completed and ongoing CV safety trials with ADDs

Group of ADD and trial	Tested drug (comparator if not placebo)	Patients (*N*)	Main CV inclusion criteria	HbA_{1c} inclusion criteria (%)	Background ADDs	Start–actual/planned completion, mean duration of follow-up	Primary outcome (number of target events)
DPP-4 inhibitors							
SAVOR-TIMI 53	Saxagliptin	16,492	≥50 y.o + established CVD or ≥55 (M) or ≥60 (F) y.o + CVD risk factors	6.5–12 during the last 6 months	All other than incretin based	5/2010–5/2013, 2.1 years	CV death, nonfatal MI, nonfatal stroke (1,040)
EXAMINE	Alogliptin	5,380	ACS within 15–90 days	6.5–11	All other than incretin based	10/2009–6/2013, 1.5 years	CV death, nonfatal MI, nonfatal stroke (550)
TECOS	Sitagliptin	14,724	Preexisting CVD	6.5–8	Mono- or dual therapy: metformin, SU, pioglitazone, insulin	12/2008–6/2013, 3.0 years	CV death, nonfatal MI or stroke, hospitalization for UAP (1,300)
CAROLINA	Linagliptin (glimepride)	6,000	CVD history, end-organ damage, ≥70 y.o, or CVD risk factors	6.5–8.5 or 6.5–7.5 if with SU/glinides	Drug naïve or mono- or dual therapy: metformin, SU, AGI	10/2010–9/2018	CV death, nonfatal MI or stroke, hospitalization for UAP (631)
CARMELINA	Linagliptin	8,300	Albuminuria + CVD or RF + specific albuminuria	6.5–10.0	All other than incretin based and SGLT2 Inh	7/2013–1/2018	CV death, nonfatal MI or stroke, hospitalization for UAP
OMNEON 018	MK 3102 (once weekly)	4,000	Preexisting CVD	6.5–10 or 7–10 (insulin, SU, glinides)	All other than incretin based	10/2012–10/2017	CV death, nonfatal MI or stroke, hospitalization for UAP
GLP-1 receptor agonists							
ELIXA	Lixisenatide	6,068	ACS <180 days	5.5–11.0	All other than incretin based	6/2010–2/2015, 25.7 months	CV death, nonfatal MI or stroke, hospitalization for UAP (844)
LEADER	Liraglutide	9,340	≥50 y.o + prior CVD events/PAD/CRF/ CHF or ≥60 y.o + CVD risk factors	>7.0	All other than incretin based	9/2010–10/2015, all patients at least 3.5 years	CV death, nonfatal MI, or nonfatal stroke (611)
SUSTAIN 6	Semaglutide QW	3,297	≥50 y.o + prior CVD or ≥60 y.o + subclinical CVD	>7.0	Drug naïve or mono- or dual oral therapy, long-acting or premix insulin	2/2013–1/2016, up to 148 weeks	CV death, nonfatal MI, or nonfatal stroke
EXSCEL	Exenatide QW	14,000	none	6.5–10	0–3 oral ADDs (including DPP-4 Inh), insulin + 0–2 oral ADDs	6/2010–1/2018, up to 7.5 years	CV death, nonfatal MI, or nonfatal stroke
FREEDOM CVO	ITCA 650 exenatide Q 3–6 months	4,000	History of CAD, cerebrovascular disease, or PAD	>6.5	All other than incretin based	3/2013–7/2018, 2 years	CV death, nonfatal MI or stroke, hospitalization for UAP
REWIND	Dulaglutide QW	9,622	≥50 y.o + established CVD, ≥55 y.o + subclinical vascular disease, or ≥60 y.o + ≥2 CVD risk factors	≤9.5	0–2 oral ADDs ± basal insulin ± GLP-1 RA	7/2011–4/2019, up to 8 years (expected mean of 6.5 years)	CV death, nonfatal MI, or nonfatal stroke
Albiglutide CV safety trial	Albiglutide QW	9,400	≥40 y.o + established CVD	>7	All other than GLP-1 RA	7/2015–5/2019	CV death, nonfatal MI, or nonfatal stroke
SGLT2 inhibitors							
EMPA-REG OUTCOME	Empagliflozin (2 [10 mg, 25 mg]:1)	7,034	>18 y.o, established CVD	7–10 (7–9 if ADD naïve)	ADD-naïve patients, all ADDs, or their combination	7/2010–4/2015	CV death, nonfatal MI, or nonfatal stroke (≥691)
CANVAS	Canagliflozin (2 [100 mg, 300 mg]:1)	4,407	>30 y.o with established CVD or >50 y.o and ≥2 CV risk factors	7–10.5	All ADDs	12/2009–6/2017	CV death, nonfatal MI, or nonfatal stroke
CANVAS-R	Canagliflozin	5,865	Established vascular complication or ≥2 CV risk factors	7–10.5	ADD-naïve patients, all ADDs, or their combination	1/2014–1/2017	Number of patients with progression of albuminuria

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Table 1—Continued

Group of ADD and trial	Tested drug (comparator if not placebo)	Patients (*N*)	Main CV inclusion criteria	HbA_{1c} inclusion criteria (%)	Background ADDs	Start–actual/planned completion, mean duration of follow-up	Primary outcome (number of target events)
CREDENCE	Canagliflozin	3,627	>30 y.o, urinary ACR 300–2,000 mg/g, eGFR 90–30 mL/min/BSA. Stable maximum tolerated dose of ACEI or ARB	6.5–12	All ADDs	2/2014–1/2020	ESRD, doubling of serum creatinine, renal or CV death
DECLARE-TIMI 58	Dapagliflozin	17,150	≥50 y.o + established CVD or ≥55 (M) or ≥60 (F) y.o + CVD risk factors	6.5–12	All ADDs other than pioglitazone	4/2013–4/2019	CV death, nonfatal MI, or nonfatal stroke
Ertugliflozin CVOT	Ertugliflozin [2 (5 mg, 15 mg):1]	3,900	>40 y.o with established CVD	7–10.5	Naïve or all ADDs (specific substudies)	11/2013–6/2020	CV death, nonfatal MI, or nonfatal stroke
Other drugs							
DEVOTE	Insulin degludec vs. insulin glargine	7,637	≥50 y.o + established CVD or renal disease or ≥60 y.o + CVD risk factors	≥7 or <7 if >20 units insulin/day	One or more oral or injectable ADDs	10/2013–12/2016	CV death, nonfatal MI, or nonfatal stroke
TOSCA.IT	Pioglitazone vs. SU (open label)	3,371	50–75 y.o, >2 years' diabetes duration	7–9	>2 months, metformin >2 g	9/2008–12//2018	All-cause mortality, nonfatal MI, or nonfatal stroke, unplanned coronary revascularization

ACEI, ACE inhibitor; ACR, albumin-to-creatinine ratio; AGI, α-glucosidase inhibitors; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CANVAS, CANagliflozin cardioVascular Assessment Study; CANVAS-R, A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus; CARMELINA, CArdiovascular and Renal Microvascular outcomE study with LINAgliptin in patients with type 2 diabetes mellitus; CAROLINA, CARdiovascular Outcome Study of LINAgliptin Versus Glimepiride in Patients with Type 2 Diabetes; CHF, congestive heart failure; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CRF, chronic renal failure; CVD, CV disease; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovasculAR Events; DEVOTE, Degludec Cardiovascular Outcomes Trial; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; EXSCEL, EXenatide Study of Cardiovascular Event Lowering; F, female; Inh, inhibitor; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results—A Long Term Evaluation; M, male; MI, myocardial infarction; PAD, peripheral arterial disease; RA, receptor agonist; REWIND, Researching Cardiovascular Events With a Weekly INcretin in Diabetes; RF, renal failure; TOSCA.IT, Thiazolidinediones or Sulphonylureas and Cardiovascular Accidents Intervention Trial; UAP, unstable angina pectoris; y.o, years old.

are small (3–5). Conversely, in superiority trials the study is designed to highlight the benefits of drug treatment: for example, in lipid trials additional lipid-lowering therapies could not be modified during the study, creating a sizable difference in the surrogate marker (e.g., LDL cholesterol) that would hopefully lead to improved CV outcome.

The FDA required the CV safety trials to extend for a minimum of 2 years. A longer trial duration increases the risk for missing data (6), possibly affecting the magnitude and even the direction of results (15). The short duration of CV trials is also driven by market issues, such as patent duration, the extravagant cost of large clinical trials (the three currently available trials with DPP-4 inhibitors alone, taken together, accumulated >85,000 patient-years of follow-up), and competition between pharmaceutical companies.

In summary, these trials should be called "CV safety trials" and not "CV outcome trials" owing to the trial goals and design, the patient population chosen, the minimization of glycemic differences between treatment arms, and the relatively short duration. The recent finding of a significant benefit of empagliflozin in a similarly designed CV safety trial (6) was completely unexpected; despite this unpredictable result, the design of those trials remains inadequate for exploring treatment benefits.

Choosing the Primary Outcome: MACE Versus MACE Plus—Is There a Difference?

The FDA guidance specifies that CV end points should be prospectively and blindly adjudicated by an independent committee in all trials of clinical development of new drugs. The CV end points that must be adjudicated are CV mortality, myocardial infarction (MI), and stroke, combined in the composite end point, major adverse CV events (MACEs). Other CV end points specifically mentioned in the FDA guidance that can also be adjudicated are hospitalization for acute coronary syndrome (ACS), urgent revascularization procedures, "and possibly other endpoints" (1). Some of the companies have chosen to add hospitalization for unstable angina, urgent coronary revascularization, and/or hospitalization for heart failure (hHF) to the definition of MACE (Table 1), although these end points are less "clear-cut" and more difficult to define; this

increases overall event rates, thus reducing required sample size, but it limits the reliability of results, augmenting background noise and biasing results in favor of "no difference" between treatment arms (16).

Choosing the Trial Population and Its Effect on Study Conduct and Results

In the FDA 2008 guidance (1), patients with "higher CV risk" to be included in CV safety analysis were defined as "patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment." Pharmaceutical companies and researchers followed these instructions yet chose different inclusion and exclusion criteria in different CV safety trials (Table 1). Patients in EXAMINE and ELIXA (4) had experienced recent ACS, whereas those in TECOS had previous CV disease (5). Conversely, in the SAVOR-TIMI 53 trial 21.7% of enrolled patients had no prior CV events but showed at least two risk factors (17). The selection of a higher-risk population increases CV event rate, thus reducing the sample size and/or the duration of the trial. For example, if the expected annual event rate is 3% instead of 2%, with a 5-year follow-up, the sample needed to prove CV safety according to the FDA requirement is 5,400 patients instead of 8,000 (16). However, the downside of using such a specific high–CV risk population is the external validity of trial results. Alogliptin was shown to be safe in patients with ACS during the last 90 days (4), but the inference of those results to patients with stable CV disease, or with high CV risk without prior events is of uncertain validity.

Other CV Safety Issues: hHF

Unexpectedly, in the SAVOR-TIMI 53 trial, saxagliptin was associated with an increased rate of hHF (3.5 vs. 2.8%; hazard ratio [HR] 1.27 [95% CI 1.07–1.51]; P = 0.007) (3,18). This phenomenon occurred during the first year, with no significant difference thereafter. In EXAMINE, in which hHF was a component of a prespecified exploratory extended MACE end point, there was no statistically significant increase in the risk of first event of hHF with alogliptin versus placebo (3.1 vs. 2.9%; 1.07 [0.79–1.46]) (19). However, these results are still not sufficient to exclude a small increase in risk (20). In TECOS, in which hHF was a secondary outcome, the rate of hHF in the sitagliptin arm (228 [3.1%]) was not statistically or numerically different from that in the placebo arm (229 [3.1%]) (HR 1.00 [95% CI 0.83–1.2] P = 0.98) (5). The results of saxagliptin on hHF in the SAVOR-TIMI 53 trial could be a play of chance, a specific effect of that drug, or an effect of the class of drugs on specific (and still unidentified) subpopulations of patients. In fact, the TECOS and SAVOR-TIMI 53 populations, although similar in age (66 vs. 65.1 years) and diabetes duration (9.4 vs. 10.3 years), differ in other features: for example, inclusion of patients without prior CV disease (0 vs. 21.6%), HbA_{1c} (7.2 vs. 8.0%), ethnicity (whites 67.9 vs. 75.3%), renal impairment (estimated glomerular filtration rate $<$50 mL/min [9.3 vs. 15.6%]), and/or use of insulin at baseline (23.2 vs. 41.4%).

None of the major CV safety trials with DPP-4 inhibitors were specifically designed to assess the effect of these drugs on heart failure, which was a secondary end point or part of a composite end point. This is a typical case in which a meta-analysis can add relevant information (see below).

Other Predefined Safety Outcomes: Hypoglycemia, Weight Changes, Cancer, Pancreatitis, and Fractures

Common adverse events (AEs) can be easily identified in phase II/III trials; conversely, rare AEs can be missed by those studies due to insufficient sample size and/or duration of observation (21). In addition, most early trials with diabetes drugs include only relatively healthy populations, who may be at lower risk of AEs (22). Large-scale trials designed for CV end points may yield important results for other safety issues.

Hypoglycemia

Targeting intensive glycemic control significantly increases the risk of severe hypoglycemia (23), which may increase CV disease risk (24).

However, there is a consistent heterogeneity in the incidence of severe hypoglycemia among trials, which could be attributable to various factors such as frailty, age, duration of disease, HbA_{1c} targets, and therapeutic strategies. Severe hypoglycemia tends to be positively associated with baseline HbA_{1c}; the higher the starting HbA_{1c} value of the patient, the higher the event rate of severe hypoglycemia.

Notably, incretin-based therapy should be void of hypoglycemic risk owing to the ability of these drugs to stimulate insulin secretion with a glucose-dependent effect. However, in SAVOR-TIMI 53, episodes of severe hypoglycemia were significantly more frequent in the saxagliptin arm (2.1 vs. 1.7%, P = 0.047) (3), whereas any hypoglycemic events were more frequent only in patients with a baseline HbA_{1c} $<$7%. Almost all episodes were observed in patients treated with sulfonylureas (SUs), especially in those with HbA_{1c} $<$7%. In EXAMINE (4) and TECOS (5), no increase in rates of hypoglycemia was reported with alogliptin and sitagliptin, respectively.

Weight Changes

The observed adherence to oral hypoglycemic drugs in patients with type 2 diabetes varies from 48.5 to 72.5% (25). Drug-induced weight gain is a well-known predictor of nonadherence (25). In addition, the increase in body weight induced by some glucose-lowering drugs may have an adverse effect on quality of life and on some CV risk factors (26). Weight gain induced by treatment intensification is influenced by the amount of HbA_{1c} reduction, background therapy, and treatment strategy. When insulin is added to background metformin and SUs, weight gain is almost 3 kg; when TZDs are added the observed weight gain is $>$4 kg (27). In a meta-analysis of 40 randomized controlled trials, the use of secretagogues (SUs plus meglitinides) added to background metformin was associated with a weight gain of 1.9 kg (28).

Conversely, the use of DPP-4 inhibitors is not associated with weight gain: in SAVOR-TIMI 53, EXAMINE, and TECOS, no significant weight changes were observed. The main reasons for this may be related to lesser degrees of serious hypoglycemic events, to a delay in gastric emptying, and/or to a sense of satiety secondary to a direct hypothalamic effect (29).

Cancer and Pancreatitis

Type 2 diabetes may be associated with increased risk of malignancies (30); in addition, it is possible that some glucose-lowering drugs increase the risk for all cancers or specific forms of cancer. Such a concern has been raised also for GLP-1 receptor agonists and DPP-4 inhibitors. GLP-1 receptor activation directly promotes cell proliferation and enhances cell survival in several tissues

(31). It has been observed that GLP-1–based therapies can induce histological changes suggestive of pancreatic damage in rodents (32). An analysis of AEs reported to the FDA suggested that GLP-1 receptor agonists and DPP-4 inhibitors could be associated with pancreatitis and pancreatic cancer (33), but that result could have been heavily affected by underreporting and reporting bias. In fact, cohort studies failed to detect any signal of risk either for pancreatitis or for pancreatic cancer (34).

Reassuring findings are also available from SAVOR-TIMI 53, EXAMINE, and TECOS, which did not report any significant increase in risk of either pancreatitis or pancreatic cancer, although a modest trend toward an increased incidence of pancreatitis was reported in TECOS (3–5).

Finally, it has been observed in preclinical studies that the incidence of thyroid C-cell tumors is increased in rodents treated with GLP-1 analogs (35). Notably, in mouse and rat thyroid gland C cells, GLP-1 receptor densities are much higher than in humans and primates (36). The available CV safety trials confirm the safety of DPP-4 inhibitors in this respect; in fact, no case of thyroid medullary carcinoma was reported in SAVOR-TIMI 53, EXAMINE, or TECOS (3–5).

Pooled Analyses and Meta-analyses: Combining CV Outcome Studies and Trials With Other Outcomes

Meta-analyses are typically performed when there is a multiplicity of available studies that either provide inconsistent results or lack adequate statistical power because of insufficient sample size. CV trials performed with molecules of the same class, which can be assumed to have a similar profile of action on CV risk, can be combined in a meta-analysis, thus increasing their power to detect even small differences between treatment groups. However, it is unlikely that such a meta-analysis would provide any relevant additional information on the effect of DPP-4 inhibitors on major CV events, in which the sample size was calculated to have an adequate power to explore the principal end point (i.e., MACE).

On the other hand, a meta-analysis of CV trials could be useful for the exploration of secondary end points or of individual components of the principal end points, for which each trial is underpowered. A typical example is hHF, which was significantly increased with saxagliptin in the SAVOR-TIMI 53 trial (3). In the CV trial with alogliptin, the difference between treatment groups for hHF was not statistically significant, but this could have been the consequence of a smaller overall number of events, with a lower statistical power (19); on the other hand, no such effect was detected with sitagliptin in TECOS (5). A meta-analysis of all available trials with DPP-4 inhibitors (including those with a non-CV end point, but not TECOS, which was unavailable at the time) confirmed an increased risk for heart failure (37). However, when trials with a non-CV end point (i.e., phase II–III studies) were considered separately, no signal of risk was detected, with no significant difference across molecules (37). This result is consistent with the hypothesis that the increased risk observed with saxagliptin in SAVOR-TIMI 53 may have been related to the characteristics of the patients enrolled. In the case of heart failure with DPP-4 inhibitors, the number of available large-scale trials is insufficient to draw definitive conclusions through meta-analysis. Further insight may be provided by a pooled analysis of patient-level data from the CV safety trials (SAVOR-TIMI 53, EXAMINE, and TECOS), exploring the effect of DPP-4 inhibitor treatment on different subgroups of patients categorized for their baseline characteristics, with the molecule used as a categorical covariate. However, such an analysis would pose many technical and organizational challenges, considering differences in protocols across studies.

Information on CV events provided by meta-analyses and pooled analyses is particularly relevant when no CV outcome study is yet available. Under current regulations, most new drugs are marketed on the basis of a clinical program composed of studies with metabolic end points, with a large-scale, noninferiority CV study performed only after marketing, to confirm the safety of the drug. While long-term studies are ongoing, combined analyses of shorter-term trials can provide some insights on possible CV actions of new treatments. In the case of DPP-4 inhibitors, pooled analyses of CV events in randomized phase II–III studies have been published for all molecules (38–42); all these analyses yielded risk estimates <1, although differences from comparator groups were not statistically significant (Table 2). Data from different analyses are not comparable, because the definition of events and the trial entry criteria are heterogeneous. In addition, in some of the analyses CV events had not been adjudicated (38).

Pooled analyses, which combine patient-level data, can be performed only by companies that hold the property of data collected during clinical development of new drugs. Independent researchers, without access to patient-level data, can only pool trial-level results from studies in a post hoc meta-analysis, which allows the combination of trials with different drugs from the same class, estimating an overall class effect. Since some of the trials submitted to regulatory authorities remain unpublished, it is important that all disclosed trials, including those not published in medical journals, are included in the meta-analysis. Notably, in such analysis only the crude number of events is available, whereas time to event remains unknown; this produces an imprecision in risk

Table 2—Pooled analyses of major CV events based on patient-level data from phase II–III trials with DPP-4 inhibitors

Reference	Drug	# Studies	# Patients (drug/comparator)	# Events (drug/comparator)	Adjudicated	Risk estimate (HR [95% CI])
Engel et al. (38), 2013	Sitagliptin	25	7,726/6,885	40/38	No	0.83 [0.53–1.30]
Iqbal et al. (39), 2014	Saxagliptin	20	5,701/3,455	43/31	Yes	0.75 [0.46–1.21]
Rosenstock et al. (40), 2015	Linagliptin	19	5,847/3,612	60/62	Yes	0.78 [0.55–1.12]
Schweizer et al. (41), 2010	Vildagliptin	25	7,509/6,061	81/91	Yes	0.84 [0.62–1.14]
White et al. (4), 2013	Alogliptin	11	4,162/1,855	13/10	Yes	0.63 [0.00–1.41]

estimates, which is negligible in short-term studies but which can be relevant if the duration of treatment is very long. The lack of adjudication of events and the short duration of treatment are also major limitations for post hoc meta-analyses. Furthermore, it is possible that some trials with unfavorable results for experimental drugs remain undisclosed or that CV outcomes are only partially reported, thus producing a systematic bias. All these methodological issues suggest caution in the interpretation of results from post hoc meta-analyses. However, it is notable that all post hoc analyses (8–10,43) reported a significant reduction in the incidence of major CV events, with risk estimates ranging from 0.36 to 0.71 (Table 3); the only exception is a meta-analysis that included two CV studies (SAVOR-TIMI 53 and EXAMINE) along with earlier trials, with the former largely driving the overall result (44). One of the largest of those meta-analyses (8) also reported a significant reduction of all-cause mortality—the only end point unaffected by event adjudication.

Table 3—Post hoc meta-analyses of major CV events based on trial-level data with DPP-4 inhibitors

Reference	# Studies	# Patients (drug/comp)	# Events (drug/comp)	Risk estimate (HR [95% CI])
Not including CV safety trials				
Monami et al. (37), 2014	63	23,562/16,509	263/232	0.71 (0.59–0.86)
Patil et al. (43), 2012	18	4,998/3,546	45/56	0.48 (0.61–0.75)
Wu et al. (9), 2014	8[a]	7,778	6/18[a]	0.36 (0.15–0.85)[a]
	50[b]		10/12[b]	0.54 (0.25–1.19)[b]
Zhang et al. (10), 2014	12	5,505/5,477	25/43[c]	0.53 (0.32–0.87)[c]
Including CV safety trials				
Agarwal et al. (44), 2014	80	40,749/32,592	NR	0.95 (0.86–1.04)

NR, not reported. [a]Versus metformin, monotherapy; [b]versus placebo, add-on to metformin; [c]versus SUs.

Why Are the Results of Pooled Analyses and Meta-analyses of Early Trials Different From Those of Studies With a CV End Point?

The difference in results between pooled analyses and meta-analyses of early studies, on one side, and CV trials, on the other, is quite substantial. The methodological limitation of pooled analyses and meta-analyses summarized above, although relevant, does not seem sufficient for inducing such a large distortion. It has been suggested that differences in results could be determined by the duration of trials, with DPP-4 inhibitors producing a benefit in the short-term, which is lost with longer-term treatment (45). This view is not confirmed by CV trials, in which no evidence of a temporary benefit is present in the first few months after randomization; in addition, a significant reduction of major CV events is observed in non–CV outcome trials with DPP-4 inhibitors with duration of treatment >52 weeks (46). Another possible explanation for the observed difference is the diversity in the characteristics of enrolled patients. Subjects recruited in CV studies, who are selected for high CV risk, are typically older with longer duration of diabetes, greater impairment of renal function, higher comorbidity, and higher number of concomitant treatments than those participating in earlier trials with metabolic end points. It is possible that DPP-4 inhibitors produce a CV benefit in relatively low-risk patients, whereas they are neutral in subjects at very high risk or with prior CV events.

The enrollment of subjects at high CV risk is a practical strategy for yielding a high number of events with a limited sample size and duration of observation. It is also reasonable to verify safety in those patients who are at greatest risk of adverse outcomes. On the other hand, patients enrolled in CV trials with DPP-4 inhibitors are scarcely/hardly representative of those actually receiving a prescription of those drugs in clinical practice.

Conclusions

The results of the first CV trials with DPP-4 inhibitors (3–5) did not meet the expectations of many clinicians, who hoped for a demonstration of a CV benefit, as suggested by meta-analyses of previous, shorter-term studies (8–10,43). However, CV trials provided exactly the result that they had been designed for: noninferiority versus placebo. CV trials in diabetes simply demonstrate that drugs do not catastrophically increase CV risk. The unexpected finding of a significantly beneficial effect of the active drug, as with empagliflozin (6), given the design of those studies, is almost a case of serendipity.

The explanation of differences in CV outcomes between earlier studies and CV safety trials is complex. Our opinion is that methodological issues are not sufficient to account for such difference and that the more favorable result of an earlier trial is the effect of the enrollment of younger, healthier patients with fewer complications, with a lower proportion of subjects receiving other medications for the reduction of CV risk. However, available data are not sufficient to confirm such a hypothesis, which could be proven only through a specifically designed CV outcome trial in patients with diabetes at low risk—which is very unlikely to be ever performed.

CV trials provide a huge amount of safety data. Large-scale trials of appropriate duration, although designed for major CV events, yield relevant information on other safety end points (for example, with DPP-4 inhibitors, pancreatitis). Exposure of several thousand patient-years to an experimental drug also warrants the detection of relatively infrequent AEs. However, in this latter case, unless results are consistent across trials with molecules of the same class, the interpretation of results can be overwhelmingly difficult. This is what happened for the unexpected (and problematic) finding of increased hHF with saxagliptin in SAVOR-TIMI 53.

Although the results of CV safety studies could underestimate the actual benefit of DPP-4 inhibitors on CV outcomes, a recent study with a similar design did show a significant reduction of CV morbidity and mortality with the SGLT2 inhibitor empagliflozin (6). Although the characteristics of patients enrolled in this latter trial (5) are not exactly the same as in trials with DPP-4 inhibitors (3–5), the fact that results with empagliflozin in patients with prior CV events were much improved compared with than those observed with saxagliptin,

alogliptin, or sitagliptin should be clearly recognized.

Inevitably, information on safety is excellent for newer agents but largely missing for older drugs. This creates an information disequilibrium, for which safety issues have a greater probability of being raised for newer drugs, while they may remain unnoticed, or underestimated, for older agents. Another problem with the current approach is that populations enrolled in CV trials can be quite different from those that, on average, receive a prescription for a drug in the real-world. This can lead to an overestimation of safety issues with newer agents.

Finally, the most important drawback of CV safety trials is their excruciatingly high cost, which has an impact on the price, and therefore the widespread availability, of newer agents. Furthermore, pharmaceutical companies, being forced to invest huge budgets on placebo-controlled CV trials, tend to shrink their development programs on the side of phase III active-comparator controlled trials, which are probably more useful for clinical decision making and which could be more cost-efficient.

The decision of the FDA to require safety data from large-scale, specifically designed trials had the merit of focusing the attention of the scientific community on the relevance of CV safety of glucose-lowering drugs. At the same time, the unintended negative consequences of this decision may outweigh the benefits. As an alternative, CV safety could be assessed through pooled analyses of patient-level data from wider programs of active comparator-controlled phase III trials of appropriate duration, provided that a relevant fraction of patients at high CV risk is included and that MACEs are appropriately adjudicated. This would probably require a safety criterion less stringent than the present 1.3 for upper confidence limit (1); however, additional real-world data could be obtained through specific programs for postmarketing surveillance, thus avoiding specific CV safety trials.

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