

Type 2 diabetes mellitus development programs in the new regulatory environment with cardiovascular safety requirements

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Abstract: For type 2 diabetes mellitus treatment and clinical development, proper evaluation of cardiovascular risk has been required by regulatory agencies (eg, the US Food and Drug Administration) since cardiovascular safety is very important in this patient population. The US Food and Drug Administration issued general guidelines for cardiovascular safety evaluation that outlined the requirements considered adequate for cardiovascular safety evaluation. However, there are multiple options to obtain the data and fulfill these requirements. In this paper, we outline the potential pathways and challenges in various aspects of cardiovascular safety evaluation in type 2 diabetes clinical development, including study design, populations, and endpoints. Specifically, we discuss some challenges in statistical analysis which have implications for the design, implementation, and interpretation of these outcome studies.

Keywords: T2DM, cardiovascular outcome, CV risk, noninferiority, superiority, major adverse cardiac event

Background

Diabetes affects an estimated 347 million people worldwide,¹ with type 2 diabetes mellitus (T2DM) accounting for more than 90% of diabetes cases.² Cardiovascular (CV) events, including myocardial infarctions (MIs) and stroke, are major causes of mortality and morbidity in patients with diabetes. In 2003–2006, after adjusting for population age differences, CV disease death rates were approximately 1.7 times higher among adults aged 18 years or older with diagnosed diabetes than among adults without diagnosed diabetes.³ Thus, the risk that a T2DM therapy might increase the rate of these events is a legitimate concern. Given the availability of alternative treatments for treating type 2 diabetes, the US Food and Drug Administration (FDA) issued a formal guidance document in 2008 suggesting that explicit assessment of CV safety should be done as part of the development of all new drugs for type 2 diabetes regardless of their mechanism of action or preclinical and clinical evidence suggesting a possible increased CV risk.⁴ The key points of these guidelines are outlined below:

- Establishment of an independent CV clinical endpoints committee (CEC) for prospective adjudication of CV events from all Phase II and III trials through a meta-analysis, or from a single large safety trial.
- Events of interest should include CV death, MI, and stroke, and may include hospitalization for acute coronary syndrome (ACS), urgent revascularization procedures, and other major CV clinical endpoints.

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- The patient population should include those at higher risk for a CV event (eg, a longer duration of T2DM, advanced age, renal impairment).
- Studies should be designed and conducted such that a meta-analysis could be performed.
- A protocol describing statistical methods for the proposed meta-analysis should be submitted in which a relative risk (RR) of >1.8 should be ruled out at the time of meta-analysis, with subsequent postmarketing trials to provide definitive evidence of a CV RR <1.3 .
- The selection of the RR thresholds of 1.8 and 1.3 is based on the following rationale:⁵
 - At the initial filing stage, when glycemic control has been established in short-term studies, there is a higher tolerance for additional uncertainty (capped at a 1.8 RR threshold), as lowering glycated hemoglobin (HbA_{1c}) reduces the associated symptoms of hyperglycemia and reduces long-term microvascular complications.
 - The 1.3 RR threshold has been used in other settings for excluding CV risk (eg, for COX-2 inhibitors).
 - The 1.3 RR threshold is feasible, but meeting this criterion preapproval would significantly delay new drug availability.

Aspects needing consideration in development plan design

While the FDA guidelines outlined what kind of evidence/data would be considered appropriate for the initial evaluation and final confirmation of CV safety,⁶ there are many different pathways to obtaining the data/evidence and accordingly multiple ways to analyze the data. When designing the development plan, the following aspects need to be considered:

- Medicine in development (agent)
- Risk factor/biomarker evaluation (biomarkers)
- Patient population selection (cohort)
- Study/program planning (design)
- Safety/clinical outcome (endpoint)
- Completeness of data (follow-up)
- Evaluation of data and statistical analysis (analysis)

In this article, we discuss several challenges in study design, study conduct, and data collection/analysis to obtain sufficient information on CV safety during the development of a T2DM treatment/medication.

Medicine in development (agent) and risk factor/biomarker evaluation (biomarkers)

Before the start of any outcome study, it is essential to have full understanding of the potential biological impact of a

new T2DM medication on CV risk factors (biomarkers), such as lipids or blood pressure. A new medication which causes, for example, an increase in lipids or blood pressure should be evaluated more carefully, and further development should include the initiation of a CV outcome study.⁶ During the study, it is very important to closely monitor CV risk factors/biomarkers, especially if the testing agent is known to increase certain risk factors.

Patient population selection (cohort)

The target T2DM patient populations for clinical studies to evaluate efficacy and tolerability/safety and to evaluate CV safety may or may not be the same. In most of the Phase III studies which provide full evaluation of efficacy (measured by HbA_{1c}) and tolerability/safety, a wide spectrum of patients is recruited into different trials to evaluate the new medication in various treatment combinations (from drug-naïve patients to those on a combination that includes insulin) and against various comparators (placebo or different active controls). Within each study, patients are usually relatively homogeneous in terms of background medication (eg, metformin only), and a wide age range is represented (eg, 18 to 75 years). In general, the number of patients with high CV risk is limited, even when studies are designed to include those patients.

However, to evaluate CV safety, most outcome studies – including PROactive,⁷ ADVANCE,^{8,9} ADOPT,¹⁰ VADT,^{11,12} ACCORD,¹³ RECORD,¹⁴ BARI 2D,^{15,16} EXAMINE,^{17,18} and SAVOR-TIMI 53^{19,20} (see Table S1) – enrolled elderly patients with higher CV risk defined by either a previous history of CV events or by the presence of two or more CV risk factors. Some of the studies even enrolled patients with a history of ACS. In general, these are not the “typical” patient populations of Phase III T2DM studies. There are at least two factors that need to be considered for patients to be enrolled for a CV outcome study. On one hand, patients with higher CV risk (eg, an ACS population) would yield more CV events during the study, which is critical for study power and duration. On the other hand, if patients enrolled in the study are at high risk with less modifiable CV disease, their CV events or deaths are driven more by the disease itself and may not be treatment related. The results of the study from such a population, especially for a noninferiority trial, may suffer from a lack of “assay sensitivity” and would not be interpretable or generalizable. However, if the results demonstrate superiority of one treatment over another in a population with less modifiable disease, the data would be considered more generalizable and more

Table 1 Options and considerations for patient population selection in an outcome study

	CV event rate	Key consideration	Note
General T2DM population	Low (<1%)	How long/large would it be?	Typical short-term Phase IIIa population, but a larger, longer term study is needed Population for most CV outcome studies
High-risk/multiple-risk-factor population	Moderate (1%–3%)	Generalizability issues?	
ACS population	High (3+%)	Too late to show benefit/detect differences? Generalizability issues?	Selected outcome studies

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; T2DM, type 2 diabetes mellitus.

meaningful. Table 1 outlines some of the considerations for patient population selection.

Study/program planning (design)

The consideration of design(s) for the CV safety evaluation of a medication in T2DM patients includes two aspects: the overall development program design and the specific outcome study design.

There are many different options for an overall development program, ranging from one big outcome study to multiple traditional Phase III studies and various hybrid approaches dependent on study size, timing, and target population. The initial challenge of ruling out a CV RR >1.8 for regulatory approval may require a single large trial or a meta-analysis of several smaller Phase II/IIIa trials. The ultimate requirement of ruling out a CV RR >1.3 definitely will require a large-scale, long-term CV outcome trial. Demonstration of superiority (when desirable) may require an even larger and/or longer term trial and may not be feasible if the drug already

has been approved for use and established as relatively safe. A hybrid approach is the choice for most developers. Figure 1 lists two different hybrid approaches.

It is almost impossible for the traditional approach of multiple Phase III studies to produce a sufficient number of events to provide definitive evidence of CV safety, especially for the RR margin of 1.3. On the other hand, depending on the study design, the single large outcome study approach might not allow researchers to evaluate glycemic control across a broad spectrum of patient populations or against different comparators for risk–benefit evaluations. In addition, the patients included in a single outcome study usually would be patients with high CV risk, differing from general T2DM patients included in the Phase III studies.

There are a number of different hybrid approaches. The options listed in Figure 1 could be considered, with variations as appropriate. Each of them has its own advantages and limitations. Depending on the size of the separate outcome study, the first hybrid option in general would be able to

Approaches	Primary diabetes indication	Initially rule out CV RR >1.8	Later rule out RR of CV >1.3	Demonstrate CV superiority (CV RR <1.0)
Traditional approach: multiple Phase III studies (duration ≤1 year)	<ul style="list-style-type: none"> ▪ Straightforward ▪ Outcome is glycemic control 	<ul style="list-style-type: none"> ▪ Need several Phase III studies ▪ Still need separate outcome study 	<ul style="list-style-type: none"> ▪ May be unachievable ▪ Need separate outcome study 	<ul style="list-style-type: none"> ▪ May be nearly impossible
Hybrid options <ul style="list-style-type: none"> ▪ Traditional Phase III studies + midsize/large outcome study to specifically address CV events ▪ Multiple midterm studies (eg, 2–3 years duration) or meta-analysis across studies with similar designs ▪ May or may not be able to rule out RR of >1.3 				
Large outcome study	<ul style="list-style-type: none"> ▪ May study specific T2DM population ▪ Comparator 	<ul style="list-style-type: none"> ▪ May need interim analysis ▪ May be multiple comparisons 	<ul style="list-style-type: none"> ▪ May need another interim analysis ▪ May be multiple comparisons 	<ul style="list-style-type: none"> ▪ May come from final analysis ▪ May be multiple comparisons

Figure 1 Issues in research program design.

Abbreviations: CV, cardiovascular; RR, relative risk; T2DM, type 2 diabetes mellitus.

rule out RRs of both >1.8 and >1.3 , and even demonstrate superiority. However, with this option, one may encounter the challenge of early data release/publication (see the section “Evaluation of data and statistical analysis [analysis]”). Depending on the study population and sample size, use of the second hybrid option may not accumulate enough events for full evaluation, especially for ruling out an RR of >1.3 .

As for the large outcome study design, Table 2 outlines several current ongoing or completed outcome studies that were initiated after the 2008 FDA guidelines.⁶ Some of the studies were initiated before the end of the main Phase III programs and some of them were initiated after FDA approval. In both of these situations, the patients enrolled in the CV outcome studies were generally different from those in the main Phase III program, with higher CV risk and prior CV events. As an extreme example, the EXAMINE study enrolled diabetic patients with recent ACS.^{17,18} These patients are usually excluded from Phase III studies in T2DM.

The most important aspects of the design of a specific CV outcome study are the objectives of the study and the choice of comparator. Is safety the only study objective (ie, to rule out a CV RR of >1.3) or is a second objective to demonstrate CV superiority (ie, a clinically meaningful benefit)? Different objectives have different impacts on both the sample size and patient population selection. For example, it might be harder to demonstrate superiority in the ACS patient population, as those patients might not be considered to have CV disease that can be modified by T2DM medication. It also takes much longer to complete a superiority study if the intervention effect size is moderate, which is often the case. As for the selection of comparators, most of the studies^{17–27} outlined in Table 2 used a placebo added to standard care as the comparator, while the CAROLINA study²³ used glimepiride. However, the sponsor of the CAROLINA study also started a separate placebo-controlled study (ie, the CARMELINA study²⁴ of linagliptin versus placebo).

Table 2 Selected type 2 diabetes mellitus CV outcome studies

Agent, study	Background medications	Population	Comparator	N	Initiated before FDA approval
Alogliptin, EXAMINE ^{17,18}	OADs/insulin (no GLP-1RA/DPP-4-I)	≥ 18 years old with ACS within 15–90 days before randomization; HbA _{1c} 6.5%–11%	PBO	5,400	Yes
Saxagliptin, SAVOR-TIMI 53 ^{19,20}	OADs/insulin (no GLP-1RA/DPP-4-I)	≥ 40 years old with CVD or ≥ 55 –60 years with multiple CV risk factors; HbA _{1c} 6.5%–12%	PBO	16,500	No
Dulaglutide, REWIND ²¹	Drug naïve or two or fewer OADs \pm GLP-1RA or basal insulin or basal insulin alone	≥ 50 years old with CVD, ≥ 55 years old with subclinical CVD, ≥ 60 years old with two or more CV risk factors; HbA _{1c} $\leq 9.5\%$	PBO	9,622	Yes
Exenatide QW, EXSC ²²	Three or fewer OADs	≥ 18 years old with CVD (60%) and CV risk factors (40%); HbA _{1c} 7%–10%	PBO	9,500	No
Linagliptin, CAROLINA ²³	Drug naïve/OADs (no GLP-1RA/DPP-4-I/TZD/insulin)	40–85 years old with CVD or two or more specified CV risk factors; HbA _{1c} 6.5%–8.5%	Glimepiride	6,000	Yes
Linagliptin, CARMELINA ²⁴	Drug naïve/any background except GLP-1RA/DPP-4-I/SGLT-2 inhibitor)	≥ 18 years old with high risk of CV events; HbA _{1c} 6.5%–10.0%	PBO	8,300	Yes
Liraglutide, LEADER ²⁵	OADs/insulin (no GLP-1RA/DPP-4-I)	≥ 50 years old with CVD or ≥ 60 years old with CV risk factors; HbA _{1c} $>7\%$	PBO	8,800	No
Lixisenatide, ELIXA ²⁶	Any antidiabetic treatment (except for GLP-1RA/DPP-4-I)	≥ 30 years old with ACS event (ie, STEMI, NSTEMI, UA) leading to hospitalization up to 6 months before screening; HbA _{1c} 5.5%–11%	PBO	6,000	Yes
Sitagliptin, TECOS ²⁷	Met/SU/PIO/insulin	≥ 50 years old with CVD; HbA _{1c} 6.5%–8%	PBO	14,000	No

Note: *Completed studies.

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; DPP-4-I, dipeptidyl peptidase-4 inhibitor; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide 1 receptor agonists; Met, metformin; NSTEMI, non-ST elevation myocardial infarction; OAD, oral antidiabetic drug; PBO, placebo; PIO, pioglitazone; QW, weekly; SGLT-2, sodium glucose cotransporter 2; STEMI, ST elevation myocardial infarction; SU, sulfonylurea; TZD, thiazolidinedione; UA, unstable angina.

Another important part of study planning is about clinical management of patients which will affect incidence of major CV events. The prospective randomized clinical trials have failed to establish a correlation between patients with tight glycemic control and CV outcomes – eg, ADVANCE and ACCORD.^{8,9,13} Therefore, more attention should be paid to alterations beyond hyperglycemia, eg, a reduction of endoplasmic reticulum stress, oxidative stress, and/or inflammation through pharmacological or lifestyle interventions seems promising as, given the extensive crosstalk between these three alterations, reducing one can potentially reduce the others.²⁸ With improvement of clinical management of patients, the incidence of major adverse cardiac events (MACE) may be lower than estimated at study design period. The incidence rate should be carefully monitored during the trial so that number of patients or duration of the study could be adjusted accordingly.

Safety/clinical outcome (endpoint)

Traditionally, an adjudicated “MACE” is considered as a fully validated clinical outcome for CV outcome studies, where MACE is defined as CV death, MI, or stroke. In the 2008 FDA guidelines for evaluating CV risk in the diabetes population, additional CV-related events (referred to as MACE+ in some literature) also could be considered for adjudication by the CEC.⁶ Note that the general guidance provided by the FDA later indicated that even though the adjudication could include events beyond MACE (such as congestive heart failure), the recommended MACE+ endpoint should be defined as MACE plus hospitalization due to unstable angina. All events need to be adjudicated by an independent and blinded CEC (see Table S2).

While the most important aspect of clinical endpoint selection is clinical meaningfulness, statistically it is important to understand the appropriateness of the selection: Is the endpoint so narrow that it may not cover the CV safety aspect of the targeted patient population? Or is it so wide that it would not allow the detection of safety signal? That is, a narrow outcome might miss key results that the intervention might negatively affect. A very wide outcome might include results that would never be affected by the intervention and thus could obscure the components that are affected, resulting in an overall safety signal not being detected.

Completeness of data (follow-up)

In all outcome studies, completeness of data and follow-up are critical for final data analysis and interpretation. A study with too many patients being lost to follow-up limits and may

distort inferences about the population, especially if the loss may be related to adverse events or a life event that would impact the primary analysis. Most analysis methods assume that the missing data are independent of the disease process or underlying risk. However, there are examples where the loss to follow-up, or failing to follow patients when they stop taking their medication, appears related to the underlying risk and thus is a process referred to as informative censoring, eg, the APPROVe and APPROVe+1 studies.^{29,30}

Even if the loss to follow-up is not considered related to the endpoint, the amount of lost information does not allow proper comparison of the new intervention with the comparator. Such loss could introduce bias “if the unavailability of data is associated with the likelihood of outcome events” or reduce power “because the effective sample size is reduced”.³¹ Decreased power may have an impact on the interpretation of noninferiority study outcomes.

Recognizing the importance of data completeness, studies should consider proper rescue procedures which would allow patients to remain for follow-up. Even if patients withdraw from active treatment, they still can be followed up in the study for safety information. As T2DM progresses, patients need either to switch to or add on new antidiabetic medications (ie, rescue medications) in order to follow general diabetes treatment guidelines. Proper specification of rescue procedures provides good glycemic control throughout the study, allowing more complete follow-up and therefore also allowing a proper evaluation of CV effects without the confounding factor of a glycemic difference, especially in placebo-controlled studies.

Evaluation of data and statistical analysis (analysis)

Like other clinical studies, data and statistical analysis are involved in every aspect of a CV safety evaluation. Notably, there also are some special statistical challenges throughout the planning and analysis of CV safety data in T2DM drug development. Among them is the practical consideration of study conduct and integrity in the implementation of a step-wise sequential approach for two noninferiority hypotheses, using 1.8 and 1.3 as the RR safety margins. The role of the independent data monitoring committee (IDMC) in the whole process of regulatory submission and data dissemination and also type I error control for superiority and noninferiority tests across different study designs are discussed in this section.

One of the most important recommendations from the FDA pertains to the two-step sequential approach for ruling

out CV risk. Specifically, the FDA recommended that the sponsor should rule out a CV RR of >1.8 at the time of regulatory approval for drug marketing and rule out a CV RR of >1.3 in postmarketing trials to provide longer term definitive evidence of CV safety.⁶ While it is clear that these are two separate hypotheses, the sources of the data that could be used to test these hypotheses can vary: the data could come from 1) a combined set of studies (eg, Phase III studies in combination with an outcome study) or 2) two different studies (eg, Phase III studies ruling out a CV RR >1.8 and a separate CV outcome study ruling out a CV RR >1.3) (see Figure 2). A significant challenge is posed when a single CV study is used to rule out both an RR of >1.8 and an RR of >1.3 . If drug approval is sought after ruling out a CV RR of 1.8 or higher, these data will likely be released/made public by the regulatory approval process. This could very likely have a negative effect on the continuation of the single trial to rule out a longer term CV RR of 1.3 or higher. That is, patients will be aware that general efficacy, based on HbA_{1c} control, and early CV safety (ie, the initial finding of an RR <1.8) have been established and that the medication is now available to them, but they are being encouraged to remain on the blinded assigned study drug (active or placebo) until an RR of 1.3 or higher has been ruled out. This may appear to add pressure to the participant and thus pose an ethical dilemma for both physician and patient.

In the two-step approach, one or more trials to rule out a CV RR of 1.8 or higher would be used to establish regulatory approval. Potential patients in the second CV trial would be aware of the first trial results during the recruitment and consent process and would have the opportunity to enroll or not enroll in the second trial without pressure. It is likely that patients enrolled into the trial to rule out a CV RR of 1.3 or higher would not be the same as those enrolled in the trial(s) to rule out an RR of 1.8 or higher.

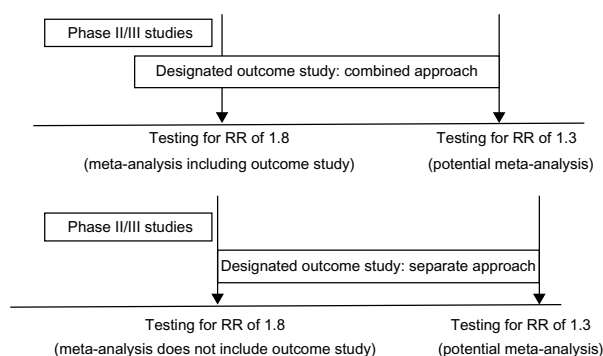


Figure 2 Graphic illustration of different trial plans and data analysis strategies.
Abbreviation: RR, relative risk.

This dilemma is still not resolved and continues to be a challenge for sponsors and investigators conducting T2DM trials. Perhaps the only immediate solution to this problem is to not submit early data for regulatory approval, although this delays the availability of new interventions for patients.

Another important aspect is to further clarify the role of the IDMC (also referred to as the data safety monitoring board) in various development programs/options. The traditional responsibility of the IDMC is to protect the safety of study participants and to assess the overall risk-to-benefit ratio. However, when the overall program is designed to use a combination of studies (eg, preapproval Phase III studies in combination with partial information from a single large outcome study started prior to approval) to evaluate CV safety, the IDMC may be asked to provide interim data analyses (prespecified) to facilitate the decision on various regulatory submissions, ie, provide data analysis results to show that a CV RR of >1.8 is ruled out while the large CV study is still ongoing to rule out an RR >1.3 . In this scenario, the responsibility is transferred to the IDMC, which will be a new challenge for the IDMC, sponsor, and regulatory agency alike.

Last but not least, an important consideration in outcome studies is around multiplicity control for primary endpoints and other secondary endpoints. The outcome study to rule out an RR of 1.3 usually requires 600–700 MACE, which will be translated into thousands of patients being followed up for several years. It will be a good opportunity to collect more information to explore some potential benefits which can only be evaluated by such large trials due to the low incidence, eg, composite microvascular endpoints or MACE superiority. However, strict multiplicity control for those secondary endpoints would make it impossible to claim marginal benefit, which may discourage the investigators to collect less information and to do selective analysis. Two studies, SAVOR-TIMI 53^{19,20} and EXAMINE,^{17,18} both using MACE as the primary endpoint and only including the MACE+ type of endpoint as a secondary endpoint, took sequential testing approaches similar to some published approaches (see Table 3).³² That is, after success of the noninferiority test for CV safety by ruling out an RR >1.3 , CV superiority and specified secondary endpoints were to be tested based on a predefined sequence. Note that in the SAVOR-TIMI 53 study, glycemic control-related endpoints are included under “other efficacy endpoints” and evaluated at a nominal type I error rate.^{19,20} No glycemic-related endpoint was included in the efficacy endpoints listed in the EXAMINE study.^{17,18} In the CAROLINA study, only the noninferiority and superi-

Table 3 Study design and testing strategy for selected CV outcome studies

Study	Study design	E1	E2	Glycemic endpoint included?	Testing strategy
EXAMINE ^{17,18}	Noninferiority with RR margin of 1.3	MACE	MACE+	No	E1 for noninferiority → E2 for superiority → E1 for superiority
SAVOR-TIMI 53 ^{19,20}	Superiority with 17% RR reduction	MACE	MACE+	Yes: in the “other efficacy endpoints” category, eg: <ul style="list-style-type: none"> • Rescue (need for increase in dose or addition of new antidiabetic medication); • Insulin (initiation of insulin therapy in patients not receiving insulin therapy at baseline) 	E1 for noninferiority → E1 for superiority → E2 for superiority Glycemic endpoint not subject to multiple comparison
CAROLINA ²³	Noninferiority with RR margin of 1.3	MACE plus hospitalization due to unstable angina	NA	Yes: in the “secondary outcome” category, eg: <ul style="list-style-type: none"> • Treatment sustainability; • HbA_{1c} 	Only to primary endpoint E1 for noninferiority → E1 for superiority All other analyses are exploratory, with no correction for multiple hypotheses

Abbreviations: CV, cardiovascular; E1, primary CV endpoint; E2, secondary CV endpoint; MACE, major adverse cardiac events; MACE+, additional CV-related events; NA, not applicable; RR, relative risk.

ority of the primary endpoint (MACE plus hospitalization due to unstable angina) are included in the testing sequence (also see Table 3).²³ Glycemic endpoints are included in the “secondary objectives” and, per study design, “all other secondary analyses will be exploratory with no correction for multiple hypotheses.” Published results from this study are not available yet.

Based on the trial information outlined above, it seems reasonable to separate the test of glycemic control endpoints from CV endpoints to allow for evaluation of the glycemic-related endpoints without multiple comparison adjustments with respect to the CV endpoints.

For other endpoints (eg, microvascular events, renal parameters), the picture is not that clear. As pointed out earlier, the CV outcome study in T2DM patients is not only a study to evaluate CV safety, but also a great opportunity to evaluate microvascular benefit and other health outcome benefits, in addition to evaluating long-term glycemic control. However, important clinical endpoints, such as microvascular benefit, were not included in the list of secondary endpoints in the examples above. This may have been due to the fact that the studies were not long enough and were not powered to evaluate microvascular events. Nevertheless, if researchers also are interested in the effect of medication on microvascular benefits (as well as CV benefit/superiority) and would like to make formal inferences for these endpoints, a testing strategy to have proper multiplicity control will be needed in addition to adequate sample size. The testing procedures outlined in the above examples – 1) CV noninferiority → CV superiority → secondary endpoints (eg, microvascular) or 2) CV noninferiority → secondary endpoints (eg, microvascular) → CV superiority – are all mathematically valid,

but do not make logical sense. One might ask why testing CV superiority should be contingent on the success of microvascular endpoints or vice versa. In a broader sense, the question really is about whether a superiority test that followed the success of a noninferiority test should be subject to multiplicity control with other secondary endpoints when the superiority test is not the primary objective from a clinical point of view. Under a traditional approach, once noninferiority is achieved, CV superiority and other secondary endpoints would be tested, either sequentially using gatekeeping procedures or by other means of type I error adjustment, such as the methods of Hochberg and Hommel, as reported by Hung and Wang.³² The former procedure has weaknesses as discussed, and the latter procedure has its own drawbacks, since some endpoints may be tested at a reduced alpha level, depending on the significance of other endpoints.

Discussion

In this paper, we have explored the different options to assess CV outcome. We considered several factors that impact the CV outcome studies in diabetes. These include risk factors such as lipids and blood pressure, as well as treatment. These need to be assessed when exploring the CV data from different development programs, which can vary by population and different background of previous CV events. In addition, statistical testing procedures also have an impact on the design of study.

There are certain limitations of the paper. First of all, the paper discussed several aspects of CV outcome study design and interpretation; there are many factors which would have an impact on CV outcome study which are beyond the scope of what has been outlined or are not known to the

researchers. Second, the paper considered several aspects of the trial design in terms of proper statistical planning; the clinical outcome and data from clinical study would also mostly depend on the biological plausibility/rationale and may not be fully explained statistically. Third, the first and second considerations outlined earlier, focused on the evaluation of CV efficacy and safety in a clinical trial setting. This has bias, as, in the trial setting, subjects are included within certain criteria and are often excluded when there are several comorbidities. Furthermore, the behavior of participants and their physicians in the trial results in greater adherence to guidelines for control of lipids and blood pressure resulting in better control and less CV events than would be seen in the real-world setting. The evaluation of CV efficacy and safety in the “real-world” clinical practice setting might be considered more important and should be considered further. Last but not least, the paper outlined some challenges of statistical evaluation of secondary endpoints and more work/guidance is needed on resolving the multiple comparison issues.

Conclusion

The FDA guidelines outline the scope of evidence/data that would be considered appropriate to determine CV safety during the development of a T2DM medication. There are many different pathways to obtaining the data and proper evidence, and accordingly multiple ways to analyze the data. For example, there are at least 2^3 (or 16) different development pathways upfront in the planning stage, considering only the following (previously discussed) four factors:

- patient population selection (ACS population versus general high-risk patients);
- overall development program planning (independent outcome study versus simultaneous Phase III/outcome study);
- outcome study planning (noninferiority alone versus superiority also); and
- safety/clinical endpoint selection (MACE versus MACE+).

Each of the pathways has its pros and cons. Depending on the medicine in development (agent) and potential biological effects (biomarkers), and the stage of development (before or after approval), one should choose one pathway over the other after careful consideration.

These options give certain challenges for statistics, including the changing role of the IDMC. When outcome studies are conducted simultaneously with other Phase III studies, the IDMC would be involved, eg, asked to provide

data analysis and input to the sponsor for the submission decision or to satisfy regulatory agency requests. This is different from the traditional IDMC role, and the implication of the release of data halfway through the study needs further evaluation. Finally, the statistical analysis and type I error control/multiple comparisons in various design options also need to be carefully evaluated. Multiple comparison adjustment has special importance as it would be a key factor to influence the study outcome and design, especially if the study includes a secondary endpoint other than glycemic control. All this information is critical to patients, clinicians, and health care providers. To address those objectives and make formal statistical inferences from the data, one would need a testing strategy to have proper multiplicity control.

Acknowledgments

Dr Jill Donaldson (GlaxoSmithKline) provided editorial support for the manuscript. This manuscript was prepared according to the International Society for Medical Publication Professionals’ “Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines”. Funding for this work was provided by GlaxoSmithKline. Editorial assistance (copy editing, formatting, and preparation of submission package) was provided by PharmaWrite LLC of Princeton, NJ, USA and was funded by GlaxoSmithKline.

Disclosure

Fred Yang is a former employee of GlaxoSmithKline. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Patient population/risk factor comparison for outcome studies

	PROactive ¹	ADVANCE ^{2,3}	ADOPT ⁴	VADT ^{5,6}	ACCORD ⁷	RECORD ⁸	BARI 2D ^{9,10}	EXAMINE ^{11,12}	SAVOR-TIMI 53 ^{13,14}
Male	66.1%	58%	57.7%	97%	62%	52%	70.4%	69.7%	67%
Age group	35–75 years	>55 years	30–75 years	>40 years	40–79 years	40–75 years	>25 years	29–91 years	>40 years
Mean age	61.8 years	66 years	57 years	60.5 years	62.2 years	58.5 years	62.4 years	60.9 years	65 years
Duration DM	9.5 years	8 years	<3 years	11.5 years	10 years	7 years	10.4 years	7.3 years	10.3 years
Prior CVD	100%	32%	0%	40%	35%	21%	100%	100%	78%
Statin use	40.8%	28%	NA	NA	59.3%	NA	74.9%	20.9%	NA

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; NA, not applicable.

Table S2 Endpoint selection for CV safety evaluation

Traditional CV safety/ efficacy endpoint: MACE	Potential safety endpoint (2008 FDA guidelines ¹⁵): MACE+
MI	MI
CV death	CV death
Stroke	Stroke
"Plus others**"	Hospitalization due to unstable angina eg, hospitalizations for HF, TIA, revascularizations

Note: *Additional CV events to be considered.

Abbreviations: CV, cardiovascular; FDA, US Food and Drug Administration; HF, heart failure; MACE, major adverse cardiac events; MACE+, additional CV-related events; MI, myocardial infarction; TIA, transient ischemic attack.

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