New Drugs and Technologies

Cardiovascular Safety Evaluation in the Development of New Drugs for Diabetes Mellitus

Venu Menon, MD; A. Michael Lincoff, MD

The burden of type 2 diabetes mellitus across the United States continues to increase. Today, ≈25.8 million Americans are affected by type 2 diabetes mellitus, and its incidence in the Medicare age group exceeds 25%. The number of newly diagnosed subjects with type 2 diabetes mellitus aged >20 years approximated 1.9 million in the year 2010 alone, and the direct and indirect costs of managing this disease entity for the year 2007 neared 174 billion US dollars.1 The worldwide prevalence of diabetes mellitus has also increased from 153 million in 1980 to an estimated 347 million in 2008,2 with low- and middle-income countries accounting for 80% of the disease burden, a number that is expected to continue to rise exponentially over the next decade.

Although diabetes mellitus is the most common cause of blindness, renal failure, and nontraumatic amputation in the United States, the predominant mechanism of death in this population is cardiovascular. The current dramatic increase in the prevalence of type 2 diabetes mellitus is therefore a harbinger for increasing cardiovascular morbidity and mortality in the decades ahead. In the original observations by Haffner and colleagues, the 7-year hazard for cardiovascular death in middle-aged Finns with long-standing diabetes mellitus and without a previous myocardial infarction was similar to that observed in patients without diabetes mellitus who had experienced a previous myocardial infarction.3 In Multiple Risk Factor Interventional Trial (MRFIT), the risk of cardiovascular death was tripled in men with diabetes mellitus despite an adjustment for other traditional risk factors.4 With the use of a data set of 820,900 subjects randomly assigned across 97 clinical trials, the Emerging Risk Factors Collaborators estimated that a diagnosis of diabetes mellitus in a middle-aged man or woman 50 years of age resulted in a decrease in survival of 5.8 and 6.4 years, respectively, in comparison with subjects without diabetes mellitus, with cardiovascular death accounting for 58% of the observed survival difference.5

The increased rates of type 2 diabetes mellitus and the anticipated increase in cardiovascular morbidity worldwide is a clarion call for the development of new agents to treat diabetes mellitus that have both the potential to decrease microvascular and macrovascular complications, as well, from this entity. Unfortunately, in the century since the landmark discovery of insulin by Banting and Best,6 the development of novel pharmacotherapy in this area has primarily focused on compounds with the ability to lower blood glucose and achieve glucose homeostasis. Proof that an agent could lower blood sugar in a sustained and safe manner has been the only chosen benchmark to be met for commercial approval. This dependence on a surrogate marker to prove drug efficacy has proved inadequate, however. Although associated with cardiovascular benefit, intensive glycemic control in type 2 diabetes mellitus has not proven to reduce macrovascular complications and has even been associated with harm.7–10 Given the heightened cardiovascular risk associated with diabetes mellitus, ideal therapies would reduce cardiovascular complications and facilitate the achievement of euglycemia, as well. Moreover, agents with the ability to lower blood glucose successfully have actually been associated with deleterious cardiovascular outcomes that have impacted both regulatory approval and withdrawal from the market, as well.11–13

The approval and near-approval of promising glycemic control agents that have been associated with cardiovascular harm alarmed regulators, physicians, and patients alike. In response, the Food and Drug Administration (FDA) issued a guidance in 2008 that seeks to ensure that effective diabetic medications in development for type 2 diabetes mellitus will be beneficial or at least neutral with regard to cardiovascular outcomes.14 In this article, we will highlight the weaknesses in the previous diabetes drug development program that were addressed by the guidance and discuss the implications of this document on the current designs and conduct of clinical trials involving new agents in the treatment of type 2 diabetes mellitus.

Inadequacies of Previous Developmental Programs for Agents in Type 2 Diabetes Mellitus

The original regulatory objective of proving drug efficacy by effectively lowering blood glucose appears to have been overly simplistic. This glucocentric approach led to trials with inclusion criteria that focused on subjects most likely to show glucose reductions, while excluding those at high risk for cardiovascular and other complications. Although the durations of most trials of diabetic agents were long enough to prove efficacy with regard to glucose homeostasis, they were too short to ascertain the impact of the intervention on clinical

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safety and efficacy end points that might be relevant from the patient and regulatory perspective. In particular, the enrollment of patients at low risk for cardiac complications into short-duration trials proved to be of limited utility to estimate the long-term impact of new therapies on cardiovascular outcomes. These deficiencies became increasingly important as multiple studies challenged the validity of using biochemical surrogate end points, such as the reduction in fasting blood sugar or hemoglobin A1c or improvement in lipids, to predict effects on cardiovascular events. Moreover, when cardiovascular clinical end points were actually measured, end point definitions varied from study to another, and independent ascertainment of events across a drug development program were usually inconsistent. As a result, it was difficult for regulatory agencies to gauge cumulative clinical effect across a drug program and even more challenging to compare one therapeutic agent with another.

**Essential Features of the Current Guidance**

These limitations inherent in previous diabetic drug development programs led the FDA to issue guidance for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation. The central tenet of this guidance was that all effective agents in type 2 diabetes mellitus needed to prove cardiovascular neutrality or benefit before gaining full market approval. In principle, this guidance remains a recommendation and is not a statutory requirement, but its implications on future drug development in type 2 diabetes mellitus have been profound. The guidance accepts the reduction of hemoglobin A1c as an effective and meaningful primary end point for drugs seeking to treat hyperglycemia in diabetes mellitus, but emphasizes the importance of evaluating the impact of newer agents designed to treat type 2 diabetes mellitus on cardiovascular outcomes in a large well-powered data set. These proposed cardiovascular end points include a primary composite of relatively hard cardiovascular events, including cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, and hospitalization for unstable angina. When other cardiovascular events like hospitalization for heart failure or coronary revascularization are occasionally included in the composite end point, discussions with the FDA before trial conduct seek to ensure adequate core major adverse cardiovascular events like death, stroke, and nonfatal myocardial infarction.

The guidance emphasizes that the study protocol and the statistical methods, as well, must be standardized and outlined before the initiation of the drug development program with new agents for type 2 diabetes mellitus. It also encourages the enrollment of high-risk patients in clinical trials including elderly patients and patients with advanced diabetes mellitus and renal impairment. These subjects are at higher risk of cardiovascular events and will likely prove a better gauge of the drug’s performance postapproval in the real world. The guidance advocates the use of an independent blinded cardiovascular end points committee to ascertain and adjudicate clinical events across the entire phase 2/3 program of development for each drug. The definitions for these outcomes, including cardiovascular mortality, myocardial infarction, stroke, hospitalization for acute coronary syndrome, urgent revascularization, and heart failure, have also been standardized and are currently being validated.

There were concerns that the increased cost of drug development based on these requirements would discourage future innovation. To mitigate this risk, distinct pathways to obtain drug approval have been outlined for drugs for which the effectiveness in treatment of hyperglycemia has been demonstrated. These pathways include a 2-step option that provides drug developers the opportunity to potentially market a new agent during the ongoing conduct of adequately powered trials evaluating cardiovascular outcome.

An effective diabetic agent that completes an exhaustive cardiovascular outcome evaluation before the New Drug Application (NDA), defined by an upper boundary of the 2-sided 95% confidence interval for estimated increased cardiovascular risk is a hazard ratio (HR) <1.3, can be marketed on approval without further evaluation. This pathway clearly requires an extensive and prolonged phase 2/phase 3 program before the NDA, involving substantial expense and long-term follow-up for the sponsor before marketing. Alternatively, if the phase 2/3 development of the program of an effective agent reveals an upper boundary of the 2-sided 95% confidence interval for estimated increased cardiovascular risk versus placebo HR to be between 1.3 and 1.8, the drug may be approved for marketing with the mandate that an adequately powered postmarketing cardiovascular outcome trial be conducted that, in isolation or combined with premarking data, has the power to achieve the HR<1.3 upper safety boundary. This option enables the sponsor to market an agent with proven glycemic efficacy while investing in the expense of a large postmarketing trial to evaluate its impact on cardiovascular outcomes. A drug that does not meet the upper safety boundary of HR<1.8 in its phase 2/3 program cannot apply for an NDA, and a drug not making the upper safety boundary of HR<1.3 after a postmarketing cardiovascular outcome study may be withdrawn from the market.

**Immediate Consequences of the Guidance**

As a result of the FDA guidance, a burden of proof of the cardiovascular safety of new therapeutic agents for diabetes mellitus now falls on the pharmaceutical industry. To achieve the safety boundaries set forth, large cardiovascular outcome trials accruing substantial numbers of end point events must be designed. The actual number of end points required to meet the upper HR boundary of 1.8 for premarking and 1.3 for postmarketing will depend on the actual true HR of the new drug relative to placebo (Tables 1 and 2). For example, in the neutral case of a drug that actually produces neither benefit nor harm with regard to cardiovascular outcomes (HR=1.0), a trial

<table>
<thead>
<tr>
<th>Upper HR Boundary</th>
<th>80%</th>
<th>85%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8</td>
<td>91</td>
<td>105</td>
<td>122</td>
</tr>
<tr>
<td>1.3</td>
<td>456</td>
<td>522</td>
<td>611</td>
</tr>
</tbody>
</table>

The values shown are the number of cardiovascular outcome events. HR indicates hazard ratio.
Table 2. Estimated Events Required in the Design and Conduct of Cardiovascular Outcome Trials Using the FDA Guidance as a Function of the Expected True HR of the Intervention

<table>
<thead>
<tr>
<th>True HR</th>
<th>Upper HR Boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>&lt;1.8</td>
</tr>
<tr>
<td>0.85</td>
<td>&lt;1.8</td>
</tr>
<tr>
<td>0.90</td>
<td>&lt;1.8</td>
</tr>
<tr>
<td>0.95</td>
<td>&lt;1.8</td>
</tr>
<tr>
<td>1.0</td>
<td>&lt;1.8</td>
</tr>
<tr>
<td>1.05</td>
<td>&lt;1.8</td>
</tr>
<tr>
<td>1.1</td>
<td>&lt;1.8</td>
</tr>
</tbody>
</table>

The values shown are the number of cardiovascular outcome events. HR indicates hazard ratio.

designed with 90% power would require 122 cardiovascular end point events to meet the premarking requirement of the upper bound of the 95% confidence interval for the HR<1.8 and 611 events to meet the postmarketing requirement of the upper bound <1.3. In contrast, if an investigational agent has a protective effect against cardiovascular complications with a true HR=0.85, only 75 end point events would need to accrue to demonstrate the upper bound <1.8 and 233 events for the upper bound <1.3. Conversely, an agent that produces even a slight excess of cardiovascular events (HR>1.0) would require substantially more end points to accrue before the required safety margins could be assured.

Given the uncertainty before a trial is actually conducted regarding the HR for cardiovascular events, phase 3 trials using the 2-step pathway are usually designed to accrue up to 150 outcome events in the premarking phase, with interim analyses prospectively planned to occur when specified numbers of adjudicated primary end points have been observed. For example, the upper bound of the 95% confidence interval may be calculated when 70, 90, 120, and 150 events have accrued. The statistical analysis plan adjusts for multiple looks at the data, and analyses are performed by a statistician and reported to a Data Safety Monitoring Board who are independent from the operational leadership of the trial. If the upper bound of the HR is demonstrated to be <1.8 during any of these interim analyses, the results may be used for regulatory filing of the NDA at that time; if ≥150 events accrue without excluding the HR bound of 1.8, stopping the study for futility at the premarking phase would be deemed appropriate (Figure 1).

To meet the postmarketing requirement to show the upper bound of the HR<1.3, substantially more events are required (Tables 1 and 2). This may be accomplished by conducting a separate postmarketing cardiovascular safety trial or by continuing the trial that provided the premarking results as additional events (typically up to a total of ≈650) accrue. At the completion of the postmarketing assessment, an upper boundary of the HR between 1.0 and 1.3 will meet the threshold of noninferiority to allow the medication to be marketed without further cardiovascular evaluation. Under a best-case scenario, the upper limit of the HR 95% confidence interval may actually be <1.0 in comparison with placebo, in which case superiority for the investigational agent with regard to protection against cardiovascular events may be claimed (Figure 1).

The duration and sample size of a trial designed to show cardiovascular safety will be defined by the expected cardiovascular end point event rate in the population studied. The higher the intrinsic risk of the population of patients with diabetes mellitus enrolled, the higher the expected event rate, resulting in a smaller sample size and shorter duration of follow-up. As a result, trials evaluating cardiovascular outcomes target patients with high-risk characteristics such as unstable ischemic syndromes, established cardiovascular disease, or multiple risk factors; sample sizes in current ongoing trials range from 4000 to 16000 subjects with follow-up periods ranging from 4.5 to 9 years. In some cases, these large trials will also provide the opportunity for promising new agents to show superiority to placebo, as the holy grail of a diabetic agent that effectively controls blood sugar while improving cardiovascular outcome remains to be met.

This 2-step process entails some unique considerations that have an impact on clinical trial conduct. If the operational team for the premarking phase becomes unblinded to the statistical analysis in order to submit the NDA, they must dissociate and firewall themselves from further study involvement as the investigation proceeds from the premarking phase to the completion of the large cardiovascular safety outcome trial. Study investigators should remain blinded to the results of these interim analyses. In practicality, the time window necessary to obtain premarking approval will also likely be long enough to enable the completion of enrollment into the larger outcome study.

**Early Impact of the Guidance on Drug Development**

The theoretical concern that the FDA guidance would impair diabetic drug development does not appear to have been realized. A number of clinical trials using this approval pathway have been completed or are underway. These trials are...
investigating a variety of agents including dipeptidyl peptidase 4 inhibitors, glucagon-like-peptide receptor 1 agonists, and sodium glucose cotransporter 2 inhibitors and are summarized in Table 3. The data sets derived from these large-scale investigations will vastly expand our understanding of the impact on cardiovascular outcome of new therapeutic interventions designed to achieve glycemic control.

The first 2 large cardiovascular outcome trials, The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) have recently been published.15,16 Both of these studies unequivocally established the safety of alogliptin and saxagliptin, respectively, with regard to ischemic cardiovascular outcomes. But, as summarized in Table 4, different approaches were used in these 2 trials to comply with the FDA guidance, and the examination of the differences between these examples illustrates key features of noninferiority versus superiority designs. Noninferiority trials generally intend to accrue events as quickly as possible; if there is no expectation of superiority of the study drug, there is no advantage to treating for long periods of time to enhance differences between the treatment arms. Thus, the most efficient trial design might be one with very high risk patients
and rapid accrual of events. In contrast, superiority trials must be designed to focus on patients in whom cardiovascular events are modifiable by antiatherosclerotic therapies and to allow sufficient treatment time for such therapies to exert their effects. Thus, lower-risk patients treated for longer periods of time and larger sample sizes are typical features of superiority designs. EXAMINE was intended principally as a noninferiority trial, and thus included patients with diabetes mellitus in whom cardiovascular risk profile was markedly elevated owing to recent acute coronary syndromes. High cardiovascular event rates would be expected to allow accrual of events over a short period of time to reach the noninferiority boundaries. An analysis of the results for noninferiority was prospectively planned at 550 events, with the option to progress to 650 events if noninferiority was not established at 550 events or if the conditional power for superiority based on this analysis was >20%. The trial terminated after analysis of 550 events when it met the criteria for noninferiority, although not the conditional probability to achieve superiority with further trial extension. These results were achieved with a trial sample size of 5400 subjects with a median follow-up of 18 months. In contrast, SAVOR\textsuperscript{15} was a large trial with 16,492 subjects followed over a median time period of 25 months with 1440 accrued events. The trial was designed primarily as superiority
trial; the inclusion criteria therefore included patients with diabetes mellitus and established vascular, coronary, or cerebrovascular disease, or the presence of multiple cardiovascular risk factors, with the intent that long-term exposure with saxagliptin would favorably modify the vascular substrate and reduce the risk of cardiovascular end points. The cardiovascular end point event rate in the patients enrolled in SAVOR was expected to be lower than that of patients with acute coronary syndrome included in EXAMINE, resulting in longer-term follow-up and potentially a greater likelihood of showing superiority if saxagliptin exerted an antiatherosclerotic effect. Similar to EXAMINE, SAVOR convincingly met the criteria for noninferiority with regard to cardiovascular outcomes, but was unfortunately unable to prove superiority over standard of care.

Early Benefits of the Guidance

A. Established cardiovascular safety. Although diabetes mellitus has been treated with pharmacotherapy for over a century, reliable information regarding the safety of these agents with regard to cardiovascular outcome has been lacking for most of that time because of the failure to perform robust clinical trials in this population. Within 4 years of the guidance, however, we now already have reliable evidence that 2 new agents, alogliptin and saxagliptin, neither increase nor diminish the risks of death, myocardial infarction, and stroke in patients with type 2 diabetes mellitus. The importance of drawing such conclusions from large-scale, adequately powered, end point–adjudicated trials cannot be overemphasized. Previous meta-analyses of cumulative data with dipeptidyl peptidase 4 inhibitors suggested that these agents resulted in significant improvement on cardiovascular outcomes.17 The null findings of the 2 definitive trials highlight the potential for spurious findings from underpowered studies and raise questions regarding all past assumptions made regarding the cardiovascular safety of other diabetic agents (Figure 2).18 Similar data are now being generated with a variety of agents in tens of thousands of subjects, and as a direct consequence, the cardiovascular risk profile of multiple classes of new therapeutics will be well-defined in the near future.

B. Insight into secondary cardiovascular outcomes. Although the primary adjudicated end point in most cardiovascular outcomes studies is the hard composite of cardiovascular death, myocardial infarction, and stroke, ongoing cardiovascular trials collect and will have available reports on important secondary cardiovascular outcomes including hospitalization for heart failure and admission for unstable angina. These events are more subjective, but reliable comparative estimates will likely be obtained owing to the blinded nature of the trial designs, prespecified event definitions, and the use of blinded central event committees to adjudicate events. Investigators will thus be able to characterize the cardiovascular risk profiles of these agents in a more complete fashion. In the recently published SAVOR trial, for example, exposure to saxagliptin was associated with an increased risk of hospitalization for heart failure (3.5 versus 2.8%; HR, 1.27; 95% confidence interval, 1.07–1.51; P=0.007). Such secondary findings can serve to generate relevant hypotheses regarding unexpected mechanisms of benefit or harm.

C. Recognition of side effects. The size, rigor, and completeness of completed and ongoing cardiovascular outcome trials also provides regulators and clinicians the opportunity to identify and quantify adverse events and off-target side-effect signals with new agents that may otherwise have depended largely on postmarketing surveillance. This enhanced scrutiny has the potential to protect the public from potential harmful exposures to infrequent but clinically serious adverse side effects. Preliminary public disclosure of the early termination of the ALECARDIO suggested that adverse effects outweighed any potential cardiovascular benefit with alogliptan, a dual proliferator–activated receptor (peroxisome proliferator-activated receptor agonist) with favorable metabolic and lipid effects. Similarly, development of Fasiglifam (TAK-875), a novel G-protein–coupled receptor 40 agonist was recently terminated after liver safety data from the development program, including a large phase 3 cardiovascular trial, suggested that the risks with the agent outweighed any potential benefit. Conversely, the SAVOR trial provided reassuring data that exposure to saxagliptin is not associated with increased risk of developing acute or chronic pancreatitis, a feared complication that had previously been associated by observational data with this class of agents.

D. Evaluation of high-risk subsets. Patients with high-risk features, such as the elderly, ethnic minorities, and those with renal dysfunction, tend to be underrepresented in randomized clinical trials. As a result, it becomes challenging to assess the balance between risk and benefit when approved drugs are used among these populations in clinical practice. The FDA guidance emphasizes the need to represent these high-risk subsets during the drug development program. As a result, these populations were well-represented in both the EXAMINE and SAVOR Trials (see Table 5). Both the SAVOR and EXAMINE trials permitted enrollment of patients with renal dysfunction, using adjusted dosages of the agents being evaluated. Although all subgroup analyses are intrinsically underpowered, the clinical experience gained with high-risk patients in these trials provide valuable insight into the effectiveness of these agents in actual clinical practice. The ability to perform these subgroup analyses may also yield new and potentially valuable exploratory hypotheses to be prospectively examined in future studies.

Adverse Consequences of the Guidance

Loss of Focus on Benefit

The main objective of the current regulatory guidance is to protect the patient population from potential exposure to anti-diabetic agents that may have detrimental cardiovascular outcomes. A major critique of this effort is that its fundamental design will make it difficult for researchers and drug manufacturers to identify agents that actually decrease these important
The costs of event-driven trials are essentially determined by the size, duration, and event rates in the population being evaluated. Thus, it is in the economic interest of the drug manufacturer to prove noninferiority by conducting trials in high-risk populations with high event rates, because this approach will provide the most rapid route to market approval and commercial gain. A major weakness with this strategy is that the deleterious vascular effects of diabetes mellitus may have progressed in high-risk populations so that the cardiovascular risk substrate is no longer modifiable. Thus, the desire to hasten approval of these agents commercially may disuade manufacturers from performing large trials in low-risk patients with impaired glucose tolerance and early diabetes mellitus, in whom there may actually be the greater potential to reverse and mitigate the deleterious macrovascular consequences of diabetes mellitus. A number of trials have also suggested that the true beneficial impact of intensive glycemic control lags behind the period of treatment and appears and is sustained years following the intervention.19–21 This legacy effect, if present, will be difficult to evaluate in the current regulatory milieu with short timelines to drug approval.

Table 4. Trial Characteristics of the EXAMINE and SAVOR Trials Which Successfully Evaluated Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EXAMINE</th>
<th>SAVOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent evaluated</td>
<td>Alogliptin</td>
<td>Saxagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard of care</td>
<td>Standard of care</td>
</tr>
<tr>
<td>Design</td>
<td>Double-blind noninferiority</td>
<td>Double-blind superiority</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>5380</td>
<td>16492</td>
</tr>
<tr>
<td>Events to be accrued</td>
<td>550/650</td>
<td>1040</td>
</tr>
<tr>
<td>Inclusion clinical criteria</td>
<td>Recent acute coronary syndrome 15–90 days</td>
<td>Age &gt;40 y with</td>
</tr>
<tr>
<td></td>
<td>before randomization</td>
<td>1. Previous clinical CAD, PVD, or cerebrovascular disease or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Multiple cardiovascular risk factors</td>
</tr>
<tr>
<td>Inclusion glycemic criteria</td>
<td>Type 2 DM with HbA1c between 6.5%–11% and</td>
<td>Type 2 DM with HbA1c between 6% and 12%</td>
</tr>
<tr>
<td></td>
<td>7%–11% if on insulin</td>
<td></td>
</tr>
<tr>
<td>Primary end point</td>
<td>CV death, nonfatal MI, and nonfatal stroke</td>
<td>CV death, nonfatal MI, and nonfatal stroke</td>
</tr>
<tr>
<td>Median follow-up in years</td>
<td>18 months</td>
<td>25 months</td>
</tr>
</tbody>
</table>

Table 5. High-Risk Characteristics of Subjects Enrolled in the EXAMINE and SAVOR Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SAVOR</th>
<th>EXAMINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>65.1±8.5</td>
<td>61</td>
</tr>
<tr>
<td>Age &gt;65 y, %</td>
<td>N/A</td>
<td>36</td>
</tr>
<tr>
<td>Age &gt;75 y, %</td>
<td>14</td>
<td>N/A</td>
</tr>
<tr>
<td>Nonwhite, %</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>GFR &lt;60 mL, %</td>
<td>N/A</td>
<td>29</td>
</tr>
<tr>
<td>eGFR &lt;50 mL</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Median duration of diabetes mellitus in years</td>
<td>10.3</td>
<td>7.3</td>
</tr>
</tbody>
</table>

CI indicates coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; EXAMINE, Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care; HbA1c, hemoglobin A1c; MI, myocardial infarction; PVD, peripheral vascular disease; and SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus.
standard of care have unproven and possibly harmful cardiovascular profiles. Perhaps the most relevant example is the sulfonylurea group of agents that have been established as effective oral medications for type 2 diabetes mellitus for >5 decades. These insulin-providing agents bind to the β-cell sulfonylurea receptor of the pancreatic β-cell and block ATP channels, resulting in insulin release mediated via the activation of calcium-dependent proteins.22,23 In animal models, sulfonylureas have been shown to bind to receptors in the heart and negatively impact ischemic preconditioning responses.24–28 Adverse contractile responses to ischemia and on infarct size, have already been identified. Similar data on multiple agents have been noted.29 In clinical studies, the lack of effect of any treatment benefit possibility of modifying the effect of any treatment benefit cardiovascular outcomes with these agents. The overall use of sulfonylurea in the EXAMINE trial and SAVOR trials were 46% and 40%, respectively, with equal exposure in both the test and control arm. The use of these agents has the theoretical possibility of modifying the effect of any treatment benefit of the novel drug under evaluation.

**Conclusion**

The landscape for the development of new agents for the treatment of type 2 diabetes mellitus has undergone a radical change since the issuance of the FDA guidance in 2008. Two agents with a neutral effect on the end points of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke have already been identified. Similar data on multiple agents in this therapeutic space will be forthcoming. The future management of patients with diabetes mellitus will be guided by established data on cardiovascular outcome and not simply by the ability of the agent to control blood glucose levels. An agent that can be proven to help achieve euglycemia and mitigate cardiovascular risk remains the most important objective.

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**References**


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