

uncertainty about ethical constraints can only lead to mischief.

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Assessing the Cardiovascular Safety of Diabetes Therapies

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The Endocrinologic and Metabolic Drugs Advisory Committee for the Food and Drug Administration (FDA), of which I am a member, convened in early July to consider whether data on long-term cardiovascular safety should be required for new and existing therapies for type 2 diabetes mellitus, whether trials should merely rule out harm or must show cardiovascular benefit, and at what point in the drug-approval process and by what methods cardiovascular data should be obtained.

Clinical treatment goals for patients with type 2 diabetes include alleviating acute symptoms of hyperglycemia and forestalling diabetes-related complications. Drugs that are approved by the FDA for treating diabetes are indicated for the improvement of glycemia, as measured by levels of the surrogate marker glycated hemoglobin. Improving glycemia reduces polyuria, polydipsia, polyphagia, blurred vision, general malaise, and longer-term microvascular complications, including retinopathy leading to blindness, nephropathy leading to

end-stage renal disease and dialysis, and painful peripheral neuropathy. However, although increases in glycemia are associated with a greater risk of cardiovascular disease (the leading cause of illness and death among patients with diabetes), it has been difficult to prove that reducing glycemia by any drug or treatment strategy has a direct cardiovascular benefit.

Type 2 diabetes is a chronic, progressive condition, so additional safe and effective agents would have considerable clinical importance. The approval of new therapies on the basis of their reducing glycated hemoglobin levels has led to the availability of multiple new classes of agents. For decades, only insulin and sulfonylureas and, for a short while, phenformin were available, but since 1995, eight new classes of drugs have been approved for diabetes management: metformin, α -glucosidase inhibitors, thiazolidinediones, glinides, glucagon-like peptide analogues, amylin analogues, dipeptidyl peptidase IV inhibitors, and bile acid sequestrants. Although metabolic con-

trol has been improved in an increasing proportion of patients and the prevalence of diabetes-related end-stage renal disease and loss of vision has been reduced, the cardiovascular and other long-term risks associated with many of these agents remain poorly characterized, rendering it difficult to make informed treatment choices.

Lately, concerns have been raised that some antidiabetes agents may impart greater cardiovascular risk than was previously appreciated. A recent meta-analysis of clinical trials of rosiglitazone (Avandia), a thiazolidinedione, pointed to an increased risk of myocardial ischemia (odds ratio, 1.43),¹ which fueled debate over whether long-term cardiovascular outcome trials should be part of the approval process for diabetes drugs. Some have also questioned the safety of older therapies — particularly sulfonylureas, which have been linked to increased cardiovascular risk by both early trials² and active surveillance of insurance databases.³ Meanwhile, the recent Action to Control Cardiovascu-

lar Risk in Diabetes (ACCORD) trial (ClinicalTrials.gov number, NCT00000620) found that a treatment strategy designed to lower blood glucose to near-normal levels was associated with increased mortality; of note, there were no apparent adverse cardiac effects of rosiglitazone.⁴ In contrast, no change in the rates of death or cardiovascular events was demonstrated in the Action in Diabetes and Vascular Disease: A Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial (NCT00145925).⁵ Thus, both macrovascular effects of anti-diabetes agents and the optimal glycemic goals, as well as other aspects of combined treatment strategies, remain incompletely understood.

Cardiovascular-outcome trials are not required at the time of approval of diabetes drugs (see box). Since conducting such a trial is expensive and can take years, some worry that requiring an outcome trial before marketing would delay the availability or inhibit the development of new agents. Yet delay in obtaining these data could put many patients at undue risk, and physicians and patients must choose drugs without knowledge of the risk–benefit balance.

Since, as the advisory committee agreed, it is sufficient for a diabetes drug to improve glycemia to be considered to have clinical merit, clinical trials could be designed to rule out an unacceptable increase in cardiovascular risk rather than be required to demonstrate cardiovascular benefit. Pharmacotherapy, after all, usually entails a balance between risk and benefit, and improved glycemia clearly has multiple met-

Phases of Drug Development.*	
Phase 1	Studies include the initial introduction into humans of an investigational drug or biologic agent. These studies are designed to determine metabolism, pharmacology, and potential side effects; are often conducted in healthy volunteers; and typically involve about 20 to 80 subjects.
Phase 2	Studies are controlled clinical trials designed to evaluate the effectiveness of a drug for a particular indication in patients with the disease under study and to discover common side effects or risks with short-term use. In type 2 diabetes, these trials are typically less than 6 months long and involve a few hundred subjects.
Phase 3	Studies are expanded controlled or uncontrolled trials performed to determine the relationship between benefit and risk after preliminary evidence has suggested that a drug or biologic agent is effective. In type 2 diabetes, phase 3 studies have involved placebo or active controls and have evaluated an agent's use either as monotherapy or in addition to other commonly used agents. These trials usually last at least 6 months and often have extension stages of 12 to 18 months to gather information on the safety of additional exposure. They typically include several hundred subjects, with data from phase 2 and 3 trials involving at least 2500 subjects.

* From the Code of Federal Regulations, Title 21, Volume 5, Revised April 1, 2007.

abolic and microvascular benefits. Moreover, absolute, relative, and population attributable risk are all important considerations.

Information for the initial assessment of potential cardiovascular risk could be improved through the development of an integrated trial design for all phase 2 and 3 preapproval trials, incorporating prespecified procedures that standardize the collection and analysis of data. The use of an independent adjudication committee for the blinded assessment of cardiovascular events would facilitate the identification of safety signals and help rule out a large excess of cardiovascular risk. Although meta-analyses of safety data from all phase 2 or 3 clinical trials of a given agent do not provide evidence of safety or risk similar to that afforded by a randomized, controlled trial, they could provide some evidence of risk during prod-

uct development. Setting an upper limit for the hazard ratio in an integrated set of data from multiple preapproval trials would provide an important first safety measure. Agents for which an unacceptable cardiovascular risk signal was detected would require further evaluation before approval. Industry might opt instead to slow or discontinue product development, as occurred with muraglitazar, a dual peroxisome proliferator–activated receptor agonist.

Pharmaceutical companies often plan to initiate large-scale, randomized clinical trials to measure health outcomes after drug approval, but once the marketing goal has been achieved, the urgency to complete the study is diminished. If these studies are not conducted in a timely manner or are inadequately powered to assess safety, patients can continue to be exposed to uncertain risk indefinitely. Under the FDA Amend-

ments Act of 2007 (FDAAA), there is increased authority for the FDA to regulate drugs after initial approval, including postmarketing clinical trials, manufacturers' labeling, and restrictions on distribution and use. The FDA could require manufacturers to submit a design for a cardiovascular-safety trial and ongoing progress reports to obtain and maintain a drug's approved status; failure to achieve milestones might lead to restrictions or withdrawal of approval. In any case, care providers should be reminded that limited safety information is available for the newest products.

Passive postmarketing-surveillance systems currently monitor for untoward drug effects. For example, MedWatch forms are supposed to be completed for adverse events that care providers believe might be drug-related. Despite a lack of uniformity in reporting, these systems can be useful for detecting rare events. However, with inherent underreporting, the lack of a comparator group, and the absence of randomization, passive surveillance is unlikely to reveal much about conditions commonly associated with the disease being treated, such as cardiovascular events in patients with diabetes. Active postmarketing surveillance, using large, linked patient registries from insurance or provider networks, is becoming more common. Although these investigations are also limited by their nonrandomized design and the incompleteness of information on potential confounders, they do provide a defined population

for evaluation. Yet only outcome trials provide randomization, with its absence of bias, systematic and reliable capture of events, timely adjudication, retention for targeted duration of follow-up, and achievement of the proper dose and duration of use for assessment of the risk-benefit ratio.

Many clinical studies focus on surrogate markers for early risk assessment, but since the relationships among the underlying disease, the intervention, the surrogate, and the end-organ outcome are not always direct, findings can be misleading. In patients with diabetes and cardiovascular disease, surrogates include weight, lipid levels, blood pressure, carotid-artery intima-media thickness, endothelial function, and circulating markers of oxidant stress, among others. Although using these measures means obtaining earlier indications of risk-benefit ratios, the validity of many surrogate markers is poorly established. These studies explore mechanistic hypotheses but cannot replace outcome-based trials.

The Endocrinologic and Metabolic Drugs Advisory Committee discussed a two-step process for evaluating the cardiovascular safety of new diabetes agents. It would consist of a randomized cardiovascular-event-driven trial, before approval, to rule out an unacceptable upper confidence limit for the hazard ratio. A longer, larger trial after approval could establish the safety margin more clearly. This approach might also demonstrate a new drug's cardiovascular superiority over a comparator, with no fur-

ther trial necessary. For the preliminary trial to be brief but include a sufficient number of events to permit evaluation, it would need to be performed in the highest-risk population, such as patients with diabetes who have already had a myocardial infarction, have required bypass or stenting procedures, or have an acute coronary syndrome. Such patients are highly vulnerable, however, and probably least able to tolerate adverse events. If a drug's presumed mechanism and preclinical data suggest a likelihood of substantial cardiovascular benefit for high-risk patients, this risk might be warranted; otherwise, it might be inappropriate to perform early investigations in this population.

The size and duration of any antidiabetes trial must depend on a drug's molecular mechanism and type, as well as on the number of adverse events that occurred during evaluations in vitro and in animals and humans. Finally, given the ethical importance of maintaining acceptable glycemic control for patients in long-term studies, one must carefully consider which comparators are being used. Is a drug that is used alone or in combination with other antidiabetes drugs being compared with placebo or with another drug or combination of drugs? In the absence of a single program for preapproval studies, pharmaceutical companies should work closely with the FDA to develop an individualized program.

Clearly, physicians face dilemmas regarding the use of new agents in patients with diabetes who are at high cardiovascular

risk. Agents for which there are data on long-term safety should be the preferred treatments while we await information and hard-outcome trials for new agents. We must also recognize that optimal therapy for diabetes includes not only glucose lowering but also management of lipid levels, blood pressure, and platelet aggregation, which together can dramatically reduce the rate of cardiovascular events.

Dr. Goldfine participated in the Endocrinologic and Metabolic Drugs Advisory

Committee meeting on July 1 and 2, 2008. All opinions expressed in this article are those of the author and do not necessarily reflect those of the other members of the advisory panel, the FDA, or the Joslin Diabetes Center.

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