



Update on Safety Concerns in the Use of Antidiabetic Drug Therapies for Type 2 Diabetes

Practical strategies for maximizing the benefits from and minimizing the risks associated with tight glycemic control in patients with type 2 diabetes were the subject of one of three CE in the Mornings topics at the 45th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 (which are available at www.ashpadvantage.com/cemornings).

The program was presented by Stuart T. Haines, Pharm.D., FASHP, BCPS, BC-ADM. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Haines in a live webinar conducted on February 17, 2011. Highlights of this webinar pertaining to issues in the selection of antidiabetic drug therapy for patients with type 2 diabetes were described in an e-newsletter released in April. Webinar highlights pertaining to safety concerns regarding the use of antidiabetic drug therapies are addressed in this e-newsletter.

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Question: What role (if any) should thiazolidinediones play in the management of type 2 diabetes now that rosiglitazone has been linked with cardiovascular safety problems?

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a randomized study comparing the effects on cardiovascular events of intensive therapy (with a target A1C <6.0%) and standard therapy (with a target A1C of 7.0% -7.9%) in more than 10,000 patients with type 2 diabetes and cardiovascular risk factors.¹ The median A1C after 1 year was 6.4% with intensive therapy and 7.5% with standard therapy. The study was stopped early after a mean follow-up time of 3.5 years because of an increased risk for death from any cause (hazard ratio 1.22) and death from cardiovascular causes (hazard ratio 1.35) in the intensive-therapy group compared with the standard-therapy group. The incidence of the primary outcome, a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or death from cardiovascular causes, was lower with intensive therapy than standard therapy (hazard ratio 0.90), but the difference was not significant. The incidence of hypoglycemia was significantly higher in the intensive-therapy group (16.2%) than in the standard-therapy group (5.1%).



In a meta-analysis of five randomized controlled studies of the effect of intensive glucose-lowering therapy on cardiovascular outcomes, including the ACCORD study, there was an overall reduction in the risk of coronary heart disease events and a relatively similar reduction was observed in all five studies.² However, the effect of intensive therapy on all-cause mortality varied, with an increased risk in some studies (most notably the ACCORD study) and a reduced risk in other studies.

Many clinicians and researchers are grappling to understand why the risk of mortality in the ACCORD study was higher in the intensive therapy group. In the ACCORD study, treatment involved a thiazolidinedione (usually rosiglitazone) in most patients in the intensive-therapy group (92%) as well as a substantial portion of the patients in the standard-therapy group (58%), raising questions about whether the increased mortality in the intensive-therapy group might be attributed to use of rosiglitazone, not the intensity of the glycemic control per se. However, a post-hoc analysis of the ACCORD study data revealed that a high on-treatment A1C was associated with an increased risk for death from any cause.³ In the intensive-therapy group, the risk of death from any cause increased approximately linearly with A1C from 6% to 9%, and it appeared to be greater than that in the standard-therapy group only when the average A1C exceeded 7% (Figure). Thus, the increased all-cause mortality risk observed in the intensive-therapy group in the ACCORD study may be due to factors contributing to persistent high A1C levels, such as severe insulin resistance or poor medication use behaviors, rather than intensive therapy or rosiglitazone use.

Figure. Post-Hoc Analysis of ACCORD Study: High A1C Values in Intensive-Therapy Group Associated with Increased All-Cause Mortality

Higher A1C in Intensive Group Associated with Negative Outcomes

- The risk of mortality in ACCORD:
 - Higher average A1C was associated with greater risk of death.
 - The risk of death with the intensive strategy increased approximately linearly from 6-9% A1C
 - The risk of death was greater in the intensive treatment group than the standard strategy only when average A1C was >7%.
- Conclusions: Factors associated with persistently higher A1C levels, rather than a low A1C per se, are likely contributors to the increased mortality risk associated with the intensive glycemic treatment strategy in ACCORD.

Riddle MC et al. *Diabetes Care*. 2010; 33:983-90.



Although the post-hoc analysis might appear to exonerated rosiglitazone as a cause for the observed increase in mortality in the ACCORD study, results from the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination for Type 2 Diabetes (RECORD) study demonstrate a mixed safety picture.⁴ In this open-label, non-inferiority study of 4447 patients with type 2 diabetes who had been receiving metformin or a sulfonylurea as monotherapy, the addition of rosiglitazone (i.e., use of rosiglitazone plus either metformin or a sulfonylurea) was compared with the use of a combination of metformin and a sulfonylurea (the control group). After a mean follow-up time of 5.5 years, the criterion for non-inferiority was met for cardiovascular hospitalization or cardiovascular death (the primary endpoint). This data provides some reassurance that rosiglitazone does not significantly increase the risk of cardiovascular death. However, a significantly larger number of patients in the rosiglitazone group than in the control group experienced heart failure resulting in hospital admission or death (hazard ratio 2.10). An increased risk of upper and distal lower limb fracture primarily in women also was observed with rosiglitazone use in this trial.

Most experts have fewer concerns with pioglitazone than rosiglitazone because the cardiovascular data have been generally favorable. In a randomized, placebo-controlled study of 5238 patients with type 2 diabetes and cardiovascular disease who were receiving diabetes medications, the addition of pioglitazone titrated from 15 mg to 45 mg once daily resulted in a significant 16% reduction in a composite measure of all-cause mortality, non-fatal MI, and stroke after an average follow-up time of 34.5 months.⁵ None-the-less, while this results is considered a positive finding, the benefits of pioglitazone were partly offset by an increased risk of hospitalization due to heart failure when compared to placebo (6% vs. 4%, respectively).⁵ Studies comparing the impact of glimepiride with pioglitazone 15-45 mg once daily on carotid artery intima media thickness in patients with type 2 diabetes without coronary artery disease (CAD) and atheroma volume in patients with type 2 diabetes and CAD revealed regression of atherosclerosis with pioglitazone and progression of atherosclerosis with glimepiride.^{6,7}

The use of thiazolidinediones in patients with type 2 diabetes generally should be avoided because of the lingering safety concerns and the relatively high cost, although the drugs may play a role in managing blood glucose in patients with an inadequate response to other glucose-lowering therapies. The risks of heart failure and fractures from the thiazolidinediones are not inconsequential. If use of a thiazolidinedione is needed, pioglitazone is preferred over rosiglitazone, and a conservative daily dosage (30 mg or less) should be used.

Information about the cardiovascular risks from rosiglitazone has been added to the labeling and patient medication guide for products containing this drug.⁸ The Food and Drug Administration (FDA) has restricted the use of rosiglitazone-containing products to patients already receiving these products or whose blood glucose concentrations cannot be controlled with other antidiabetic medications and who after consulting with their healthcare professional do not wish to use pioglitazone-containing medication.⁸



Question: Should the use of insulin glargine be avoided in patients with a history of cancer because of its mitogenic effects? What is the association (if any) between other insulins or oral antidiabetes medications and cancer?

Type 2 diabetes has been linked with an increased risk of various cancers (e.g., colorectal, breast, liver, pancreatic).^{9,10} Hyperglycemia (i.e., poor glycemic control) does not appear to cause cancer. However, insulin is a growth factor, which provides a plausible biological basis for cancer promotion. Hyperinsulinemia, insulin resistance, and elevated insulin growth factor-1 may promote tumor growth.⁹

A meta-analysis of large, landmark, randomized, controlled trials of intensive glucose-lowering therapy in patients with type 2 diabetes, including the ACCORD and RECORD studies, found no impact on the risk for cancer from the use of intensive therapy instead of standard therapy.¹¹ A reduced risk for cancer was found in some other studies comparing various antidiabetic therapies. A 57% reduction in cancer mortality was associated with the use of metformin compared with non-use of the drug after a median follow-up time of 9.6 years in a study of 1353 patients with type 2 diabetes.¹² The reduction was dose-related. An 8% to 20% reduction in the risk for breast and prostate cancer was observed from the use of thiazolidinediones instead of other oral antidiabetic agents in three large nested case-control studies.¹³

In a population-based cohort study of more than 10,000 patients with type 2 diabetes, a higher rate of cancer mortality was associated with the use of insulin (hazard ratio 1.9) or a sulfonylurea (hazard ratio 1.3) when compared to metformin.¹⁴ Following the publication of several observational studies that suggested an increased risk of cancer from use of insulin glargine, the FDA began a thorough safety review.^{15,16} The agency has not concluded that insulin glargine increases the risk of cancer because the evidence is inconclusive, although its safety review is ongoing. Whether the risk for cancer from the use of other insulin products differs from that associated with insulin glargine is unknown.¹⁷

Safety concerns regarding the use of other antidiabetic agents and the risk of cancer have also been raised. In rodent studies, large doses of liraglutide, a glucagon-like peptide-1 (GLP-1) analog approved by FDA in January 2010, were associated with thyroid C-cell hyperplasia and tumors, which can lead to medullary thyroid cancer in these animals.¹⁸ Although medullary thyroid cancer has not been reported in humans receiving liraglutide, this malignancy is uncommon, so an increase in incidence would be difficult to detect. Levels of calcitonin, a biomarker for medullary thyroid cancer, increased slightly in clinical trial participants receiving liraglutide but levels remained within normal limits.¹⁸

Thyroid carcinomas were not associated with the GLP-1 analog exenatide in rodent studies.¹⁹ Exenatide suppressed *in vitro* breast cancer cell growth, but the implications of these findings are unknown.²⁰

The data linking various antidiabetic treatments with cancer are conflicting and reflect the influence of many confounding variables. Large randomized, controlled trials failed to show an increase in cancer-related mortality or morbidity from antidiabetic treatment. The available evidence should be discussed with patients who have type 2 diabetes and a history of cancer, but the evidence should be placed into proper perspective. Patients should be encouraged to adhere to their diabetes treatment regimen because any increase in cancer risk is probably small compared with the risk of morbidity and mortality from diabetes-related complications.



“ The potential risk of cancer associated with antidiabetic treatments should be weighed against the substantial risk of morbidity and mortality from diabetes-related complications. ”

—Stuart T. Haines, Pharm.D., FASHP, BCPS, BC-ADM

Practice Changes

Attendees at the CE in the Mornings program on type 2 diabetes at the ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 were asked to identify changes to practice that they might implement based on the knowledge acquired by participating in the program and what barriers might interfere with these plans. Half of the 585 respondents planned to evaluate the benefits and risks of intensive glycemic control in patients with type 2 diabetes and consider patient-specific factors, including age, duration of diabetes, and the presence of cardiovascular disease, when establishing a goal A1C value. Other changes that attendees at the program might make in the future include:

- Consider current evidence-based guidelines when determining glycemic goals (A1C, fasting and postprandial blood glucose) for patients with type 2 diabetes (40%)
- Become more active in identifying and counseling patients with type 2 diabetes or at risk of developing type 2 diabetes (23%)
- Implement a practical strategy for monitoring patients with type 2 diabetes (13%)

Many attendees do not practice in a clinical setting, but found the program informative, with applicability to family members who have diabetes. Some attendees who practice in a clinical setting gained clarity about the risk of lactic acidosis from use of metformin in patients with renal impairment, an issue also addressed in the March 2011 Ask the Expert: Issues in Selecting Antidiabetic Drug Therapy for Patients with Type 2 Diabetes e-newsletter.

Various barriers to implementing the plans were identified by attendees at the CE in the Mornings program:

- Management inertia and lack of support from and acceptance by other pharmacy staff and physicians
- Physician lack of knowledge of evidence-based guidelines and awareness of new antidiabetic drugs
- Inconsistency among physicians in treatment strategies
- Lack of access to laboratory data (A1C, fasting and postprandial blood glucose)
- Time constraints and competing responsibilities
- Patient nonadherence

Information provided in the CE in the Mornings program on type 2 diabetes and subsequent webinar and e-newsletters should help overcome these barriers and improve patient care and outcomes.



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