

ration. Indeed, we believe that a major strength of our study was the effort taken to ensure the proper education of our health care providers. These efforts, as summarized in the Methods section of the article, included three stages. First, specialized educators from the manufacturer participated in centralized training sessions, as well as individualized training sessions conducted at each of the 14 sites. These sessions included instruction on the interpretation of values for fetal oxygen saturation. Second, all attending physicians were required to pass examinations, which included questions regarding such interpretation, before they could participate in the trial. Third, a mandated refresher course was conducted after the second year of the trial. It is our belief that such efforts ensured that participating physicians had a clear understanding of how to interpret levels of fetal oxygen saturation and that our conclusions remain valid.

Regarding the concern that the rate of cesar-

ean delivery should have been higher in the open group than it was, it is important to remember that values of fetal oxygen saturation are supposed to be interpreted in the context of a non-reassuring fetal heart rate. That is, one would not expect the group of women with a reassuring fetal heart rate to have had an increased rate of cesarean section.

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## Glycemic Durability of Monotherapy for Diabetes

**TO THE EDITOR:** Kahn et al. (Dec. 7 issue)<sup>1</sup> report on A Diabetes Outcome Progression Trial (ADOPT), which assessed the glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. It is difficult to maintain target levels of glycated hemoglobin with the use of traditional oral antidiabetic drugs, owing to declining  $\beta$ -cell function.<sup>2</sup>

In ADOPT, the annual increase in glycated hemoglobin levels over a 4-year period in patients with newly diagnosed diabetes was greatest with glyburide, intermediate with metformin, and least with rosiglitazone. Our longitudinal data (for 2005–2006) from a nationwide general-practitioner database in Germany (Disease Analyzer)<sup>3,4</sup> indicate similar findings. Among 12,304 patients with diabetes who were using oral antidiabetic drugs, the mean of the individual relative differences in glycated hemoglobin levels (those in 2006 divided by those in 2005) was 1.018 (95% confidence interval, 1.016 to 1.020). The mean relative difference in glycated hemoglobin levels was highest for glinides, followed by sulfonylureas, acarbose, metformin, and glitazones (Table 1). In multivariate logistic-regression analyses, the use of glitazones was associated with a significantly smaller increase in glycated hemoglobin levels than was the use of sulfonylureas, after adjustment for age, sex, the other oral antidiabetic drugs, health care use, and practice characteristics ( $P=0.007$ ); the same trend was observed for metformin ( $P=0.048$ ). Though all the oral antidiabetic drugs we studied are associated with progression of glycemia, our primary care data indicate the potential value of

**Table 1. Baseline Glycated Hemoglobin Levels and Annual Change among Patients with Diabetes Who Were Treated with Oral Agents in Primary Care Practices.\***

Oral Agents	No. of Patients	Glycated Hemoglobin Level		P Value <sup>†</sup>
		2005	Mean Relative Difference in 2006 (95% CI) <sup>‡</sup> percent	
Glitazones	1029	7.12±1.06	1.010 (1.002–1.017)	0.007
Metformin	8579	6.98±1.04	1.017 (1.015–1.019)	<0.001
Acarbose	873	6.93±1.07	1.017 (1.010–1.024)	<0.001
Sulfonylureas	5789	7.11±1.11	1.021 (1.017–1.024)	<0.001
Glinides	894	7.08±1.10	1.025 (1.017–1.032)	<0.001

\* Plus-minus values are means  $\pm$ SD. CI denotes confidence interval.

<sup>†</sup> P values, calculated with the use of paired t-tests, are for the difference between glycated hemoglobin levels in 2006 and those in 2005.

<sup>‡</sup> The relative difference in glycated hemoglobin levels was calculated for each patient as the levels in 2006 divided by the levels in 2005.

and need for new agents in the treatment of diabetes.<sup>2</sup>

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Mr. Kostev reports being an employee of IMS Health, a consulting company that received a grant from Eli Lilly, Germany, to carry out a database study of longitudinal changes in glycated hemoglobin values in patients with diabetes in primary care. Drs. Rathmann and Haastert report receiving consulting fees from IMS Health for this study.

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**TO THE EDITOR:** Table 1 in the article by Kahn et al., which details the baseline characteristics of the study population, does not mention the type of antihypertensive therapy subjects in the three groups were taking. As shown in previous studies, some types of antihypertensive treatment (i.e., angiotensin-converting-enzyme inhibitors,<sup>1</sup> angiotensin-receptor blockers, and calcium-channel blockers<sup>2,3</sup>) can improve glycemic control and can even result in normoglycemia in patients with impaired fasting glucose levels. On the other hand, thiazide diuretics<sup>4</sup> and beta-blockers<sup>5</sup> are known to worsen glycemic control.

Thus, the type of antihypertensive therapy subjects received in the trial conducted by Kahn et al. might have been a factor affecting the primary outcome and should have been documented as a baseline characteristic. Randomization according to this factor at the beginning of the study could have added sophistication to the study design and credibility to the results. Similarly, documentation of the use of aspirin therapy as prophylaxis

against coronary artery disease in the three groups might have shed more light on the differences seen in the rates of cardiovascular events.

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**TO THE EDITOR:** The conclusion by Kahn et al. that rosiglitazone slows the loss of  $\beta$ -cell function seems unwarranted. The three treatment groups started with similar baseline values for  $\beta$ -cell function, determined with the use of homeostasis model assessment (HOMA 2), and at the end of the study there was no significant difference in the values between the rosiglitazone group and the glyburide group and only a small difference between the rosiglitazone group and the metformin group. The rate of decline in  $\beta$ -cell function was greatest in the glyburide group because of an initial increase in  $\beta$ -cell function according to HOMA 2; it does not represent the true state of  $\beta$ -cell function. The stopping of all drugs or switching of all patients to a similar regimen for 3 months might have made clearer assessment possible.

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Dr. Garg reports receiving speaking fees from Merck and Novartis.

**TO THE EDITOR:** ADOPT focused on the effect of diabetes medications on an end point of questionable importance to patients (the need for a second medication). In fact, ADOPT results leave patients in the dark as to whether they are better

off in important ways (the quality of life and risks of illness and death) with any of these agents, particularly given the burden of their adverse effects as reported for this trial.

ADOPT is not a special case: only 20% of randomized studies of diabetes have reported important patient outcomes.<sup>1</sup> We believe the time has come for a broad consensus on a standard set of important outcomes for patients in diabetes trials, like the Outcome Measures in Rheumatology (OMERACT) initiative,<sup>2</sup> in order to improve the relevance of such evidence for clinical decision making.

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**THE AUTHORS REPLY:** Gandhi and Montori discuss the need for clinical trials to examine outcomes such as morbidity and mortality. We agree, but this was not the aim of our study. Our study was designed to determine whether the loss of glucose control in patients with type 2 diabetes could be slowed, and we were able to answer this important question definitively. Since improved glucose control clearly reduces microvascular complications,<sup>1</sup> slowing the progression of hyperglycemia would be expected to reduce morbidity and increase the quality of patients' lives.

Parashar and Varma correctly mention that antihypertensive agents have dissimilar effects on glucose metabolism. Table 2 of our article shows the percentages of subjects with concomitant use of various antihypertensive agents at some time during the study. There was no significant difference in the use of these medications among the three groups; thus, differential use cannot explain the differences in glycemia that we observed. Similarly, concomitant use of aspirin ranged from 31.6% of patients in the glyburide group to 33.0% in the metformin group and therefore also cannot explain the differences in outcomes.

The importance of the rate of loss of  $\beta$ -cell function in determining the progression of type 2 diabetes is well documented.<sup>2</sup> Garg is correct that  $\beta$ -cell function according to HOMA 2 was simi-

lar in the rosiglitazone group and the glyburide group at baseline and after 4 years of treatment. However, since the two medications have different mechanisms of action and establishment of their maximal biologic effectiveness takes months, we prespecified that our analysis would commence at 6 months. From then on, the rate of change differed markedly between the two groups, which partly explains the greater durability of the lowering of glucose levels with rosiglitazone. Since insulin sensitivity is a critical determinant of  $\beta$ -cell secretory demand,<sup>3</sup> the similar  $\beta$ -cell function according to HOMA 2 among patients receiving rosiglitazone and those receiving glyburide, with better insulin sensitivity among patients receiving rosiglitazone, indicates that at the end of the study, the  $\beta$  cells of the patients receiving rosiglitazone were performing qualitatively better. With regard to the use of glucose-lowering medications before the study commenced, since no patients were taking these medications at the time of randomization, there was no need to discontinue their use or to use the same agent initially before switching to one of the three study treatments.

The primary care data reported by Rathmann et al. confirm our finding that glucose-lowering agents have differential effects in slowing the rate of progression of glycemia, providing support for our conclusion that the choice of initial monotherapy has to be guided by clinical efficacy along with a consideration of adverse events and costs. The challenge now is to develop new agents and approaches that can slow progression even more effectively.

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