study with greater statistical power will be required to confirm these results.

We agree with the criticism of Alfonso et al. with respect to the surveillance strategy that was used in our study. In accordance with previous practice guidelines,[1] we recommended routine angiographic surveillance for patients receiving coronary stents but ischemia-oriented surveillance for patients undergoing bypass surgery. Therefore, in spite of rigorous adjudication of events, the revascularization rate that we report was undoubtedly inflated in the PCI group, as compared with the CABG group. It is interesting that the difference in revascularization rates was reduced between the two groups when only procedures that were performed on the basis of clinical judgment were considered. A further study applying the same surveillance protocol to both populations is required to avoid this bias.

We have previously reported on the potential benefit of intravascular ultrasonography in left main coronary stenting.[2] Practical information on its use during the stenting procedure has also been reported.[3] In brief, intravascular ultrasonography provided information on the extent of disease and vascular morphology before the procedure, which was helpful in determining the treatment strategy. During the stenting procedure, intravascular ultrasonography was used to confirm optimal stenting, including demonstration of sufficient luminal area and complete stent apposition. We believe that intravascular ultrasonographic guidance is responsible for our ability to obtain successful periprocedural and long-term outcomes in left main coronary-artery stenting.

Seung-Jung Park, M.D., Ph.D.
Young-Hak Kim, M.D., Ph.D.
Seung-Cheol Yun, Ph.D.

Asan Medical Center
Seoul, South Korea
sjpark@amc.seoul.kr

Since publication of their article, the authors report no further potential conflict of interest.

1. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina — summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation 2003;107:149-58.
2. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interv 2009;2:167-77.
3. Kang SJ, Mintz GS, Kim WJ, et al. Effect of intravascular ultrasound findings on long-term repeat revascularization in patients undergoing drug-eluting stent implantation for severe unprotected left main bifurcation narrowing. Am J Cardiol 2011;107:367-73.

Pioglitazone for Diabetes Prevention

TO THE EDITOR: DeFronzo and colleagues (March 24 issue) [1] reported that pioglitazone reduced the conversion from a condition of impaired glucose tolerance to type 2 diabetes. However, the results showed only that pioglitazone reduced patients' blood glucose levels during a glucose-tolerance test while they were taking the active drug. The cost of pioglitazone treatment was substantial weight gain and fluid retention. The potential disease-modifying effects of insulin-sensitizing agents have been investigated previously in studies involving metformin[2] and troglitazone.[3,4] Prevention of diabetes with these drugs can be attributed largely to their short-term pharmacologic effects, with progression to diabetes occurring in a large percentage of the study participants after the drug has been discontinued. In the study by DeFronzo et al., the critical question is whether pioglitazone might have a disease-modifying effect: as part of the primary analysis, the rate at which diabetes developed after the drug washout period should have been determined. The parallel rise in HbA_{1c} levels in both the placebo and the pioglitazone groups that followed the initial decline in these levels in the pioglitazone group suggests that this drug has only a short-term pharmacologic effect. If so, an end point that is more relevant than the effect of pioglitazone on glucose levels should be pursued.

Karen C. McCowen, M.D.
Vera T. Fajtova, M.D.

Harvard Vanguard Medical Associates
Boston, MA
karen_mccowen@vmed.org

No potential conflict of interest relevant to this letter was reported.

1. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104-15.
2. Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the Diabetes Prevention Program. Diabetes Care 2003;26:977-80.
3. Knowler WC, Hamman RF, Edelstein SL, et al. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. Diabetes 2005;54:1150-6.

4. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 2002;51:2796-803.

TO THE EDITOR: This prospective study by DeFronzo and colleagues is likely to spur an increased use of pioglitazone in wider segments of the population. An older and larger prospective trial involving pioglitazone[1] was remarkable for an increase in bladder cancer in the subjects randomly assigned to this drug. In that trial, hematuria or a history of bladder cancer was not exclusionary for participation as it was in the DeFronzo study (see the Supplementary Appendix, available with the full text of their article at NEJM.org). Bladder cancer was significantly increased in studies of rodents given pioglitazone in doses comparable to doses in humans, as based on body-surface area.[2] It is plausible that pioglitazone triggers the growth of bladder tumors by increasing the local expression of vascular endothelial growth factor.[3] The Food and Drug Administration is evaluating a large, observational study of patients with type 2 diabetes to determine whether there is a connection between pioglitazone therapy and bladder cancer.[4] A 5-year interim analysis has shown a significant increase in bladder cancer after 2 years of exposure to this drug. Therefore, physicians should avoid prescribing pioglitazone to patients with a history of bladder cancer or unexplained hematuria.

Mark R. Goldstein, M.D.
9410 Fountain Medical Ct.
Bonita Springs, FL
markrgoldstein@comcast.net

Luca Mascitelli, M.D.
Comando Brigata Alpina Julia
Udine, Italy

No potential conflict of interest relevant to this letter was reported.

1. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROACTIVE Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-89.
2. Actos. Lincolnshire, IL: Takeda Pharmaceuticals America, 2004 (package insert).
3. Fauconnet S, Lascombe I, Chabannes E, et al. Differential regulation of vascular endothelial growth factor expression by peroxisome proliferator-activated receptors in bladder cancer cells. J Biol Chem 2002;277:23534-43.
4. FDA drug safety communication: ongoing safety review of Actos (pioglitazone) and potential increased risk of bladder cancer after two years exposure. September 17, 2010. (http://www.fda.gov/Drugs/Drugsafety/ucm226214.htm.)

THE AUTHORS REPLY: McCowen and Fajtova question whether pioglitazone modifies the disease course in patients with impaired glucose tolerance and whether adverse clinical outcomes will be reduced. Although the incidence of diabetes 1 year after pioglitazone discontinuation in the ACT NOW study is currently being analyzed, we personally believe that thiazolidinediones do modify the disease course and would refer these authors to an excellent review by Buchanan.[1] In contrast to studies that simply mask diabetes onset by lowering glucose — a situation in which the cumulative incidence of diabetes in the intervention group catches up with the control group shortly after the end of the trial — thiazolidinediones result in continued separation long after the intervention has been discontinued. However, it is not likely that any antidiabetic agent can reverse the basic genetic defect. Thus, if a specific antidiabetic agent is discontinued, it would not be surprising for blood glucose levels to rise at some point after the medication is stopped. If an antidiabetic agent is continued and HbA_{1c} remains within the normal range, it is reasonable to infer that microvascular complications (e.g., blindness, kidney failure, and neuropathy leading to amputation) might be prevented. Furthermore, on the basis of data from our study and others, pioglitazone appears to confer benefits with respect to atherosclerosis and cardiovascular events.[2] Since weight gain and fluid retention are related to dose response, such side effects can be addressed by reducing the dose and adding diuretics that act on the distal renal tubule. Paradoxically, the greater the weight gain, the greater is the decline in HbA_{1c} levels and the greater are the improvements in insulin sensitivity and beta-cell function.[3] Thus, if side effects can be managed successfully, this subgroup of patients with impaired glucose tolerance may actually derive the greatest benefit.

We believe that it is essential to select subjects at high risk, as was done in the ACT NOW study, and that lifestyle changes should precede the use of medications. However, lifestyle intervention is often unsuccessful — about 40 to 50% of patients at risk progress to diabetes despite successful interventions of this type.[4] Of note, the American Diabetes Association recommends metformin for treating persons with prediabetes.[5] Results from the Diabetes Prevention Program have shown that treatment with generic metformin is cost-effective in persons who have

impaired glucose tolerance; in 2012, pioglitazone will likely be available as a generic drug.

We agree with Goldstein and Mascitelli that anyone with a history of bladder cancer or unexplained hematuria should not receive pioglitazone, although a definitive link between bladder cancer and pioglitazone has not been established.

(We regret that Dr. DeFronzo did not disclose having received a grant from Bristol-Myers Squibb, lecture fees from NovoNordisk, and royalties from John Wiley and that he inadvertently checked "consultancy" instead of "board membership" for Boehringer Ingelheim and Isis when our March 24 article was published. An updated disclosure form has been posted with the article at NEJM.org.)

Ralph A. DeFronzo, M.D.
University of Texas Health Science Center
San Antonio, TX
albarado@uthscsa.edu

Peter D. Reaven, M.D.
Phoenix Veterans Affairs Health Care System
Phoenix, AZ

Dr. DeFronzo reports receiving grants from Takeda, Amylin–Eli Lilly, and Bristol-Myers Squibb and being a member of the speakers bureaus for Takeda, Amylin–Eli Lilly, and Novo-Nordisk. He is on the Advisory Board for Amylin, Boehringer Ingelheim, ISIS, and Takeda.

Since publication of his article, Dr. DeFronzo reports that he has no further disclosures other than those noted above.

1. Buchanan TA. (How) can we prevent type 2 diabetes? Diabetes 2007;56:1502-7.
2. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROACTIVE Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-89.
3. Miyazaki Y, De Filippis E, Bajaj M, et al. Predictors of improved glycemic control with rosiglitazone therapy in type 2 diabetic patients: a practical approach for the primary care physician. Br J Diabetes Vasc Dis 2005;5:28-35.
4. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
5. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753-9.

Pulse Oximetry

TO THE EDITOR: In their review of pulse oximetry, Ortega et al. (April 21 issue)[1] suggest that the value for arterial oxygen saturation (SaO_2) displayed by a pulse oximeter (as SpO_2) is determined directly by dividing the "concentration of oxyhemoglobin by the concentration of both oxyhemoglobin and deoxyhemoglobin." However, this is not completely accurate.

Pulse oximeters cannot determine the concentrations of oxyhemoglobin or deoxyhemoglobin; they provide an estimate of SaO_2 rather than a direct measurement. For each of the two wavelengths of light used in pulse oximeters, a ratio of the relative absorbance of oxyhemoglobin and deoxyhemoglobin is calculated.[2] This ratio is empirically related to SaO_2, as measured in experimental studies in human volunteers.[3]

Since it is unethical to induce a degree of oxygen saturation below 70% in volunteers,[4] pulse oximeter readings of approximately 70% represent the lowest limit of accurate output. As Ortega et al. recommend, readings lower than approximately 80% should be regarded as inaccurate since they represent extrapolation of the empirical data. Thus, pulse oximeters do not measure SaO_2 but provide estimates.

Alexander Avidan, M.D.
Phillip D. Levin, M.D.
Hadassah Hebrew University Medical Center
Jerusalem, Israel
alex@avidan.co.il

No potential conflict of interest relevant to this letter was reported.

1. Ortega R, Hansen CJ, Elterman K, Woo A. Videos in clinical medicine: pulse oximetry. N Engl J Med 2011;364(16):e33. (Available at NEJM.org.)
2. Pologe JA. Pulse oximetry: technical aspects of machine design. Int Anesthesiol Clin 1987;25:137-53.
3. Barker SJ, Tremper KK. Pulse oximetry: applications and limitations. Int Anesthesiol Clin 1987;25:155-75.
4. Hanning CD, Alexander-Williams JM. Pulse oximetry: a practical review. BMJ 1995;311:367-70.

TO THE EDITOR: The video on pulse oximetry and a recent Case Records article (March 10 issue)[1] outline the principles of pulse oximetry — specifically, the distinct light-absorption properties of oxygenated and deoxygenated hemoglobin (at two wavelengths, 660 nm and 940 nm) used to estimate blood oxygenation. These articles highlight clinically relevant limitations of pulse oximetry, such as the presence of hemoglobin variants. We would emphasize that measurements of carbon dioxide (CO_2) and acid–base balance are