and aflibercept ($1,950), bevacizumab should be considered as first-line therapy in patients with a visual acuity of 20/40 or better.

For patients who present with a visual acuity of 20/50 or worse, improvement in vision was greatest with aflibercept and similar between bevacizumab and ranibizumab. Aflibercept should be considered as first-line therapy in these patients, with bevacizumab as the alternative given the lack of a significant difference in visual outcome between bevacizumab and ranibizumab and the large difference in cost between the two drugs. The equivalence of bevacizumab and ranibizumab and the large difference in cost between the two drugs. The equivalence of bevacizumab and ranibizumab in effects on visual acuity has now been shown in different disease states, including diabetic macular edema in the current trial and neovascular age-related macular degeneration in several multicenter clinical trials.5-9

There are powerful forces in addition to efficacy and safety that affect drug selection by physicians. These include the current requirement for a patient-specific prescription, which limits or delays access to compounded bevacizumab in some states; the rebates paid directly to physicians from pharmaceutical companies to reward use of a more expensive drug; and the policy of the Centers for Medicare and Medicaid Services to reimburse on the basis of a percentage of the cost of a drug, so that the agency provides higher payments to physicians when more expensive drugs are prescribed. We believe that all financial incentives and logistic barriers to providing the least expensive drug, among drugs equivalent in safety and efficacy, should be eliminated so that patients may benefit fully from the results of this Diabetic Retinopathy Clinical Research Network trial as well as those from other comparative trials.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Selecting Revascularization Strategies in Patients with Coronary Disease
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The treatment of patients with coronary artery disease includes risk-factor modification (e.g., treatment of hypertension, hyperlipidemia, and diabetes) and some combination of medical therapies and coronary revascularization.1 For patients for whom revascularization is deemed to be appropriate, a decision must be made between percutaneous coronary intervention (PCI) and coronary-artery bypass grafting (CABG). In direct comparisons, CABG has been shown to be associated with fewer repeat revascularizations than PCI. However, questions have been raised about incremental improvements in stent technologies that might narrow the outcome gap be-
tween the two approaches. These improvements have included, first, the progression from bare-metal stents to drug-eluting stents, and second, the further progression from so-called first-generation drug-eluting stents (with sirolimus or paclitaxel) to second-generation drug-eluting stents (with everolimus or zotarolimus).

Two articles now published in the *Journal* address the issue of whether the use of second-generation drug-eluting stents closes the outcome gap that favors CABG over PCI in patients with multivessel coronary artery disease.\(^2,3\) Bangalore and colleagues,\(^2\) using observational data from the New York State cardiac registries, compared outcomes in patients with multivessel coronary artery disease who underwent CABG with those who underwent PCI with everolimus-eluting stents, one of the second-generation drug-eluting stents. They found fewer strokes in the PCI group, as compared with the CABG group, but more myocardial infarctions and repeat-revascularization procedures. In patients who were considered to have had complete revascularization performed during PCI (i.e., had revascularization of all major vessels with clinically significant stenoses), they noted attenuation of the outcome differences between the PCI group and the CABG group. They conclude that the decision-making process by patients and their providers regarding revascularization should balance the short-term risks of stroke with the long-term consequences of myocardial infarction and repeat revascularization and place it in the context of individual values and preferences.

Bangalore and colleagues used a variety of sophisticated statistical techniques to adjust for confounders that are implicit in any nonrandomized comparison of treatment strategies. Although these data are useful, the limitations of observational studies remain. No technique has yet been developed that can replace randomization in comparisons of treatments that have modest differences in outcome.

Park and colleagues\(^3\) report the primary results from a randomized clinical trial involving patients with multivessel coronary artery disease in which CABG was compared with PCI with the use of everolimus-eluting stents. The trial was designed to enroll almost 1800 patients in a noninferiority comparison for the primary end point (a composite of death, myocardial infarction, or target-vessel revascularization) at 2 years. However, owing to slow enrollment, the trial was terminated after only 880 patients had undergone randomization. The outcomes data did not show noninferiority at 2 years, although at a longer follow-up of 4.6 years, there were significantly fewer spontaneous myocardial infarctions and repeat-revascularization procedures in the CABG group than in the PCI group.

So, how do these two complementary studies add to our knowledge base for treating patients with ischemic heart disease? Each of the studies suffers from the limitations of the method used for the study. First, observational data are always limited when used for these types of comparisons. This factor is important to consider because the mining of large data sets, including electronic health records in health systems, is becoming more pervasive as a means to inform practice. Second, clinical trials, as typically performed throughout the world, are hard to complete, especially given changing technologies and physicians’ preferences for one treatment over another, even when high-quality evidence is lacking. Enrollment in trials can be especially challenging when patients are asked to allow a decision about the choice between surgery and a nonsurgical alternative to be made on the basis of randomization.

To the extent that the data from these two studies can be relied on, there are clearly trade-offs between the two revascularization strategies that need to be discussed with patients as part of the shared decision-making process. The early hazard of CABG (the risk of stroke) may be unacceptable to some patients, whereas others might want to avoid the later hazards of PCI (the risk of needing a repeat PCI procedure or having a myocardial infarction). The decision should also take into account the results of coronary angiography, with particular focus on whether complete revascularization with PCI appears to be feasible — a factor that would make PCI more attractive than CABG.

Although these conclusions seem reasonable on the basis of the current data, we should do better than base clinical decisions on flawed observational studies and undersized randomized trials. It should be unacceptable to have evidence voids in areas so common and so costly (in clinical and financial terms) to the public health.\(^4\)
We need better ways to aggregate and analyze large amounts of clinical data to better inform practice at the point of care. We also need more streamlined methods of embedding randomization into clinical activities so that the research process is facilitated rather than impeded. The Swedish system of registry-based randomized trials is one such innovative approach; another is an initiative that uses networks of health-system electronic health record data that was launched recently by the Patient-Centered Outcomes Research Institute. In addition, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA; ClinicalTrials.gov number, NCT01471522), a large, international trial funded by the National Heart, Lung, and Blood Institute, is comparing a strategy of invasive management (cardiac catheterization and PCI or CABG on the basis of anatomy) with a strategy of conservative management (cardiac catheterization only if medical therapy fails) in patients with stable ischemic heart disease who have ischemia on functional testing. We should be making shared decisions on the basis of a continuously accumulating set of data that includes randomized comparisons when appropriate.

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