Institutes of Health, the President's Council of Advisors on Science and Technology, the World Economic Forum, the Gates Foundation, the Wellcome Trust, and the Food and Drug Administration are but a few of the institutions encouraging greater interaction between academics and industry, to provide tangible value for patients. A cogent example has been a vaccine against Ebola virus disease. All the candidate vaccines currently in trials have grown out of collaborations among academics, industry, funders, nongovernmental organizations, and patients. But Ebola is only the most recent crisis; we have yet to deal with the infectious threats of human immunodeficiency virus (HIV), malaria, and tuberculosis and the noninfectious threats of cancer, heart disease, chronic lung disease, obesity, and diabetes. Simply put, in no area of medicine are our diagnostics and therapeutics so good that we can call a halt to improvement, and true improvement can come only through collaboration.

How can the divide be bridged? And why do medical journal editors remain concerned about authors with pharma and biotech associations? The reasons are complex. This week we begin a series of three articles by Lisa Rosenbaum[5] examining the current state of affairs. We hope that you will find the series engaging and provocative and that it will perhaps reshape the way you think about interactions between physician-scientists and industry. Beginning at 5:00 p.m. (ET) on May 20, we will invite you to put yourself in the role of a journal editor and to comment at NEJM.org on the suitability of three hypothetical potential authors of review articles. The questions will be challenging; we will report on the feedback from the community sometime in the summer. We look forward to the insight your comments may provide.

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

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Balancing the Risks and Benefits of Dual Platelet Inhibition

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Cardiovascular and cerebrovascular events commonly arise from atherosclerotic plaque rupture that produces platelet activation, thrombus formation, and reduction of blood flow to the brain or heart. The inhibition of platelets with aspirin is effective in the secondary prevention of acute coronary events.[1] The addition of clopidogrel (i.e., dual antiplatelet therapy), a platelet $P2Y_{12}$-receptor antagonist, produces even greater secondary prevention of coronary events in high-risk patients for up to 1 year.[2] Second-generation $P2Y_{12}$ inhibitors (i.e., prasugrel and ticagrelor) produce further reductions in the risk of ischemic events over the same time frame, albeit with more bleeding complications.[3,4]

Dual antiplatelet therapy is recommended for 1 year after an acute coronary syndrome, but the effect of longer-term therapy is not clear. Concern exists regarding the balance between reducing the risk of cardiovascular events and the risk of bleeding complications, because bleeding complications are linked to adverse outcomes in patients with an acute coronary syndrome.[5] Bonaca et al., in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial,[6] provide insight into this balance in high-risk patients with a previous myocardial infarction. In their study, the results of which are now reported in the *Journal*, they randomly assigned 21,162 patients to placebo or ticagrelor. Because long-term $P2Y_{12}$ inhibition increases bleeding risk, the investigators compared two doses of ticagrelor (60 mg and 90 mg) to maximize information

derived from the trial concerning drug efficacy versus adverse events. As compared with placebo, either dose of ticagrelor was associated with a 15% decrease in the rate of the primary end point of death from cardiovascular causes, myocardial infarction, or stroke. However, ticagrelor treatment also increased clinically significant bleeding complications by a factor of 2.3 to 2.7 and transfusions by a factor of 3.1 to 3.8. There was similar efficacy in the reduction of the rate of the primary end point with either ticagrelor dose, suggesting that the lower dose should be preferred in this patient population because it may limit clinically significant bleeding events.

These data prompt speculation as to whether dual platelet inhibition with high-potency agents is approaching the point of diminishing returns. Bonaca et al. found that, as compared with placebo, ticagrelor was associated with an absolute benefit of 1.19 percentage points (with the 90-mg dose) and 1.27 percentage points (with the 60-mg dose) in the primary end point, as well as with absolute increases of 1.54 and 1.24 percentage points, respectively, for clinically significant bleeding and 1.71 and 1.37 percentage points for transfusion. On the basis of the 60-mg ticagrelor dose, treating 10,000 patients for 1 year would prevent approximately 42 primary end-point events and produce approximately 31 TIMI major bleeding events — close to an even proposition. Granted, one could argue that major bleeding events do not have the same effect on patients as ischemic cardiovascular events. Nevertheless, we should note that the patient population studied by Bonaca et al. was at particularly high risk for ischemic events (e.g., diabetes, renal disease, multivessel disease, and recurrent myocardial infarction) and had had no recent bleeding episodes or indication for anticoagulation. Thus, not all patients who have a myocardial infarction will fit these same criteria and, as a consequence, may not be appropriate candidates for long-term treatment with ticagrelor. Patients without high-risk features for ischemia, or with higher bleeding risks, will probably not realize as much net benefit as those included in the study by Bonaca et al.

The results of the recently reported Dual Antiplatelet Therapy (DAPT) trial by Mauri et al.[7] suggest that the results of Bonaca et al. apply to the thienopyridine $P2Y_{12}$ antagonists clopidogrel and prasugrel as well. In that study, the effect of continued dual antiplatelet therapy (thienopyridine plus aspirin) was tested beyond 12 months after the implantation of a drug-eluting stent. The outcome of the study by Mauri et al. was qualitatively similar to that of the study by Bonaca et al. Long-term dual antiplatelet therapy produced a significant reduction, as compared with placebo, in the risk of ischemic cardiovascular events (hazard ratio, 0.71), at the expense of an increase of 1.56 times in the rate of moderate or severe bleeding,[7] somewhat less than that observed by Bonaca et al. This distinction is probably a consequence of differences between the two patient populations. The patients studied by Mauri et al. had received 12 months of dual platelet inhibition without clinically significant bleeding or discontinuation of dual antiplatelet therapy. Thus, the patients in the study by Mauri et al. would be expected to have a lower risk of bleeding than the patients in the study by Bonaca et al., who may not have had previous $P2Y_{12}$ inhibition. Moreover, as compared with the patients in the study by Mauri et al., the patients in the study by Bonaca et al. had a higher burden of risk factors for subsequent cardiovascular events — features that also predict increased bleeding rates with platelet inhibition.[8]

An important calculus for any treatment strategy is the long-term potential for harm. The study by Mauri et al. was characterized by excess mortality with the administration of clopidogrel or prasugrel, largely due to bleeding and cancer,[7] a finding that was not seen with long-term use of clopidogrel in a previous trial.[9] In the study by Bonaca et al., ticagrelor did not significantly affect overall mortality, and the numerical excess of deaths from noncardiovascular causes appeared to be related to cancer, a feature not seen in the Study of Platelet Inhibition and Patient Outcomes (PLATO).[4] Collectively, these data do not support a unified concern with respect to excess mortality with dual antiplatelet therapy, but they do remind us of the fragile balance between efficacy and adverse events.

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The Elephant in the Delivery Room

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In 2000, the *Journal* published the first in a series of articles documenting rates of survival and neurodevelopmental impairment among children born at extremely low gestational ages (from 22 to 25 weeks of gestation) in the British Isles.[1] Survival rates were low, and approximately half the children who survived had impairments at follow-up in the third year after birth. This article received responses that ranged from "You are obviously no good at looking after babies born at low gestations" to "Why even provide care for such babies?" A series of articles followed that compared these results with additional, competing data sets and explored ethical aspects of decisions made in the delivery room.[2] The decision about whether to provide active treatment at birth is a critical predictor of subsequent outcomes, and if a policy to not provide any active treatment is pursued, survival is highly unlikely. What have been missing until now are studies that determine the ways in which the decision to provide or not to provide active treatment influences rates of survival and impairment across centers.

In this issue of the *Journal,* Rysavy and colleagues[3] help to close this knowledge gap. Using data from 24 hospitals included in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN), the investigators explored the extent to which the likelihood of a hospital providing active treatment at birth explained variation in outcomes among almost 5000 infants born before 27 weeks of gestation.

Among infants born at the lowest gestational ages, the variation across hospitals in rates of active treatment was substantial. For infants born at 22 weeks of gestation, four hospitals never provided active intervention, whereas five hospitals always provided active intervention, and among infants born at 23 weeks of gestation, rates of active intervention ranged from 25 to 100%; nearly all hospitals provided active treatment for infants born at higher gestational ages. Clearly, there is little consensus about the appropriate policy for treating infants born at low gestational ages, and yet hospital practices regarding the initiation of active intervention have a dramatic influence on rates of survival and survival without impairment. Hospital rates of active treatment accounted for 78% of the between-hospital variation in survival and 75% of the variation in survival without severe impairment at 18 to 22 months of age among children born at 22 or 23 weeks of gestation. Among the most preterm infants, the survival rate among infants who received active treatment was higher than the rate in the overall cohort of infants (23% vs. 5% among infants born at 22 weeks of gestation, and 33% vs. 24% among infants born at 23 weeks of gestation); the rate of survival without severe impairment was also