TO THE EDITOR: The articles by Meier et al.\(^1\) and Carroll et al.\(^2\) and the corresponding editorial by Messé and Kent\(^3\) (March 21 issue) illustrate a major problem in clinical trials. When it is not obvious which of two therapies is better, sufficient numbers of events are essential to reach a conclusion. Performing a prospective, randomized trial is not enough. In the PC Trial (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale [PFO] Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism),\(^1\) primary-end-point events occurred in only 18 patients in the two groups, even though 414 patients and 29 international sites participated. Any difference may have been due to chance. The investigators in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment)\(^2\) trial enrolled 980 patients at 69 sites, yet there were only 25 primary-end-point events. The proper conclusion of these studies, even though they were well designed and carefully performed, is that too few events were observed to draw any conclusion.

When the Early Breast Cancer Trialists' Collaborative Group\(^4\) performed the first meta-analysis of the value of adjuvant tamoxifen — one of the most effective medications in our pharmacopoeia — for breast cancer, only 6 of 42 randomized trials had shown significant benefit. Only trials with many patients and many events are likely to overcome the play of chance.

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TO THE EDITOR: In the primary intention-to-treat analysis of the RESPECT trial, recurrent strokes occurred in 9 of 499 patients who underwent closure of a patent foramen ovale and in 16 of 481 patients in the medical-therapy group (P=0.08). In a secondary as-treated comparison (with patients classified according to treatment actually received), 5 patients in the closure group and 16 in the medical-therapy group had a stroke (P=0.007). Although the authors acknowledge that their primary results did not show a significant benefit of closure of a patient foramen ovale over medical therapy alone, they conclude that the secondary analysis showed “the superiority of closure.”

Patent Foramen Ovale and Cryptogenic Stroke

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However, the secondary analysis appears biased. Of the 25 patients who were removed from the intention-to-treat closure group by the investigators to form the as-treated group, 4 (16%) had a stroke. Because this 16% stroke rate substantially exceeds the 3% background stroke rate among patients in the medical-therapy group, these 25 patients were not representative of the overall study population. Their underlying predisposition to stroke was clearly higher, and removing them from the analysis probably created an as-treated group at below-average risk.

In a press release, a representative of the device company notes the “compelling clinical benefits of closure.” The data do not provide support for his comments.

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


TO THE EDITOR: In the RESPECT trial, interventional and medical therapy yielded similar outcomes in patients with previous cryptogenic stroke and a patent foramen ovale. However, a subgroup analysis revealed better outcomes with percutaneous closure than medical therapy in patients with an atrial septal aneurysm or a moderate or severe right-to-left shunt. These results compare well with those of previous studies that show these anatomic conditions to be associated with a higher risk of recurrence of cerebrovascular events.\(^1\)\(^2\)

The disparate findings between the general cohorts and subgroups suggest that patients were heterogeneous in terms of clinical risk; this resulted in an underpowered study, despite the larger number of patients enrolled relative to the PC Trial. Indeed, more generally, data are lacking from trials that enroll only patients with a high-risk patent foramen ovale. Nonetheless, risk assessment is only probabilistic in this condition. Therefore, while awaiting the results of conclusive trials, we recently published a position statement on the subject by eight national scientific societies.\(^3\) This statement proposed that multidisciplinary teams of cardiologists, neurologists, and neuroradiologists (with additional input from hematologists) assign treatments on the basis of individual risk estimates according to clinical and anatomic factors (Fig. 1).

**Figure 1. Recommendations for Treatment of Symptomatic or Asymptomatic Cryptogenic Stroke, Transient Ischemic Attack with Patent Foramen Ovale, or Both, According to Anatomical and Clinical Risk Factors.**

CT denotes computed tomography, MRI magnetic resonance imaging, and PFO patent foramen ovale. Data are from Pristipino et al.\(^3\)
cal equipoise, a useful trial design might be compared with anticoagulation and retain clinical equipoise. In this case, demonstration of the superiority of closure is unnecessary, since the decision of closure or anticoagulation, if the two methods were confirmed to be equally safe and efficacious. Thus, to show the noninferiority of closure as compared with anticoagulation and retain clinical equipoise, a useful trial design might be to include patients who have the combination of patent foramen ovale and an atrial septal aneurysm.

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


TO THE EDITOR: The results of the RESPECT trial and the PC Trial showed no significant differences in outcomes between closure of the patent foramen ovale and medical therapy. The interventional community must be held responsible for the delayed enrollment, which began 10 years ago in the RESPECT trial and 13 years ago in the PC Trial. Concurrently, Swiss interventionalists, including Meier et al., reported a rate of closure of a patent foramen ovale that was 10 times as high as the total enrollment in the PC Trial; this highlights the enormous potential for device overuse even before evidence is available. 1

Although paradoxical embolism is rarely diagnosed during life, it is assumed to be a major cause of cryptogenic stroke in young patients. Yet, a patent foramen ovale is detected on transesophageal echocardiography in only about half these patients. Moreover, rates of stroke recurrence are low, and in the first randomized trial of closure of a patent foramen ovale, the causes of stroke recurrence were not related to a patent foramen ovale in 87% of the patients. Unfortunately, the PC Trial and RESPECT investigators did not report the cause of stroke recurrence; this precludes any clarification of who, if anyone, is likely to benefit from closure of a patent foramen ovale. 2

TO THE EDITOR: The two recent trials of percutaneous closure of patent foramen ovale by Meier et al. and Carroll et al. leave unanswered questions. Mas et al. 1 provide useful guidance for future trial designs because they show that the combination of patent foramen ovale with an atrial septal aneurysm poses an elevated risk of stroke even when the patient receives aspirin. This high-risk combination clearly warrants consideration of either closure or anticoagulation, since antiplatelet therapy is ineffective. Aspirin alone appears to be effective for an isolated patent foramen ovale.

Many patients and clinicians who are faced with the choice of closure or anticoagulation would choose closure simply because of the unwanted risks and lifestyle modifications associated with anticoagulation, if the two methods were confirmed to be equally safe and efficacious. In this case, demonstration of the superiority of closure is unnecessary, since the decision by the patient and clinician would be served just as well by demonstration of noninferiority.

Thus, to show the noninferiority of closure as compared with anticoagulation and retain clinical equipoise, a useful trial design might be to
DRS. MEIER AND JÜNI REPLY: Wood and Switchenko appropriately point out that both the PC Trial and the RESPECT trial were underpowered and that definite conclusions cannot be drawn. At the outset of the PC Trial, an annual event rate of at least 3% was assumed for patients in the medical-therapy group. As pointed out by Meyer-Cestone and Küchler, we estimate that only 5 to 10% of patients considered for closure of a patent foramen ovale were enrolled in the trial, and we assume that patients deemed to be at higher risk were directly referred for closure of a patent foramen ovale rather than being randomly assigned. Many investigators did not believe in equipoise of closure of a patent foramen ovale and medical therapy in these patients. This is likely to have resulted in low recruitment rates and considerably lower than expected event rates. Although chance is a plausible explanation for the observed results, the PC Trial and the RESPECT trial, taken together, suggest that a real benefit of closure of a patent foramen ovale with the PFO Occluder is an appreciably more likely explanation for observed results than chance alone.

We concur with Pristipino et al. that the characteristics of a patent foramen ovale affect the propensity of a patent foramen ovale to mediate paradoxical embolism. However, the PC Trial and the RESPECT trial did not show a consistent outcome in subgroup analyses according to the severity of the shunt or the presence of an atrial septal aneurysm. Hence, we are uncertain about their recommendation that a low-risk patent foramen ovale should be treated by default with medical therapy after a first clinical event. The patient might have to be given a choice. The ongoing randomized trials of patent foramen ovale (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence [CLOSE, ClinicalTrials.gov number, NCT00562289], Device Closure versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale [DEFENSE-PFO, NCT01550588], and Gore Helex Septal Occluder/ Gore Septal Occluder for Patent Foramen Ovale [PFO] Closure in Stroke Patients [REDUCE, NCT00738894]) are unlikely to have the power to specifically address the effect of closure of patent foramen ovale as compared with medical therapy in subgroups.

The appeal by Pristipino et al. and Newman to focus on patients with high-risk patent foramen ovales in future trials is well taken. However, if data from ongoing studies provide support for closure of the patent foramen ovale with an effective device, there may be controversy about whether random assignment of patients with a patent foramen ovale and stroke or systemic embolism to closure or medical therapy remains ethical, particularly since medical therapy involves lifelong oral anticoagulation. It is appropriate, in our view, to inform patients at high risk about the level of invasiveness of closure of a patent foramen ovale (i.e., venous puncture only, same-day discharge, and no postinterventional restrictions) and the likelihood of superior protection against stroke. In turn, the patient may opt for closure, which would negatively affect rates of trial recruitment.

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DR. CARROLL AND COLLEAGUES REPLY: Wood and Switchenko express concern about the low event rates seen in the RESPECT trial. A low risk of recurrence may be the true natural history of stroke related to patent foramen ovale. Follow-up from our study is ongoing. We agree that data are lacking from a meta-analysis of randomized trials, and we are collaborating in a pooled, patient-level analysis.

Brett raises the issue of bias in analyses involving different cohorts. We acknowledge that bias can occur even with prespecified analyses such as those in the RESPECT trial, but we submit that the totality of evidence must be presented and discussed.

Pristipino et al. suggest that heterogeneity of the treatment effect of closure of patent foramen ovale is likely and that risk stratification with the use of clinical and anatomic factors may...
guide clinical practice when definitive evidence is lacking. We agree, and we analyzed modifiers of the treatment effect with the use of a forest plot. A trial limited to patients with “high-risk patent foramen ovale” is problematic because it is not definitively known what features attributable to patent foramen ovale pose a high risk of recurrence. We caution that the algorithm proposed in their figure is not based on randomized clinical trials but rather predominantly on clinical judgment, observational trials, and opinion as well as assumptions regarding pathophysiologic features.

In our opinion, Newman’s proposed noninferiority trial is not tenable, since anticoagulation has not been shown to be superior to antiplatelet therapy for a patent foramen ovale, with or without an atrial septal aneurysm.

Meyer-Cestone and Küchler bemoan the slow enrollment into the RESPECT trial and suggest that practice decisions are ahead of the data, especially when closure of the patent foramen ovale is the “ genie out of the bottle.” Incidental patent foramen ovale and recurrent strokes that are not related to patent foramen ovale complicate interpretation of trials. We agree that the cause of stroke recurrence should be ascertained, with the caveat that assigning causation is not straightforward. We recently presented data from RESPECT on mechanisms of recurrent stroke.

Finally, in their editorial, Messé and Kent note that clinical trials must guard against referral bias in adjudicating end points. The RESPECT trial used a validated questionnaire at every follow-up visit to identify symptoms of potential stroke or transient ischemic attack. Any positive answer, no matter how trivial, triggered an automatic review of end points by an adjudication committee whose members were unaware of the treatment assignments. There were 232 referred events in the closure group and 244 referred events in the medical-therapy group. The high number of referrals (476 candidates with 25 confirmed events) and the balance of referrals across treatment groups confirm that referral bias was unlikely in the RESPECT trial.

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THE EDITORIALISTS REPLY: We agree with the statement by Wood and Switchenko that it would be ill-advised to accept as conclusive or definitive the results of a small number of studies that each had few end points. As we noted in our editorial, one or two additional events in either group of these studies would lead to dramatically different conclusions.

Regarding the comments by Newman: the data on the effect of an atrial septal aneurysm are mixed at best. Although the cited article by Mas et al. showed a significant increase in recurrent stroke in patients with both a patent foramen ovale and an atrial septal aneurysm, subsequent large, prospective, observational cohorts did not confirm this finding. Even if a higher risk of recurrence was established in this subgroup, a noninferiority trial comparing anticoagulation with closure would not be useful to guide therapy, given that neither intervention has proven efficacy relative to an antiplatelet medication.

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Circulating Tumor DNA to Monitor Metastatic Breast Cancer

TO THE EDITOR: Dawson et al. (March 28 issue)\(^1\) suggest that the detection of circulating tumor DNA in 58% of patients with metastatic breast cancer can be used as an effective indicator of tumor load during treatment with standard systemic therapies. The study does not address the clinical utility of circulating tumor DNA. Moreover, the authors claim that circulating tumor DNA represents a more effective monitoring tool than the enumeration of circulating tumor cells. This statement is incorrect, considering that the enumeration of circulating tumor cells proved the ability to predict prognosis and monitor treatment efficacy in all patients with metastatic breast cancer, regardless of disease subtype.\(^2\) Furthermore, new detection methods describe the molecular heterogeneity and measure dynamic phenotypic changes in circulating tumor cells during metastasis.\(^3,4\) We propose that circulating tumor DNA provides a complementary method in the assessment of patients with detectable mutations and should be more appropriately used to select and monitor molecularly targeted therapies. Combined diagnostic methods will provide a more effective approach than each method alone to the implementation of precision medicine and improved clinical outcomes.

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TO THE EDITOR: Dawson et al. propose circulating tumor DNA as a new biomarker for metastatic breast cancer. In our opinion, the timing of the analysis is crucial for the correct interpretation of such data obtained from samples acquired during chemotherapy.

Apoptosis leads to the augmented release of cell-free DNA,\(^1\) so chemotherapy is expected to temporarily increase the levels of circulating tumor DNA. Thus, the assumption that such increases reflect tumor load may be incorrect, depending on the time point chosen.

We suggest a dual role for analysis with circulating tumor DNA. First, the difference between basal levels before and peak levels after the administration of chemotherapy may serve as an indicator of tumor responsiveness. Second, levels of circulating tumor DNA measured several days after the last chemotherapy cycle may serve as a surrogate marker for total tumor mass.

Analysis of the kinetics of circulating tumor DNA during the use of various chemotherapeutic drugs and regimens may pave the way for the clinical translation of analysis with circulating tumor DNA.

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THE AUTHORS REPLY: We support the idea that combined methods involving circulating tumor cells and circulating tumor DNA could be used to analyze tumor status and changes. By the criterion of sensitivity for detection of disease burden, our data clearly show an advantage to the