Finally, the editorial comment (6) addresses our work on bioengineered septal occluder devices (7). These devices showed rapid complete neo-endothelialization. The scaffold can be heparin-coated in order to decrease further the thrombogenicity of the implant surface. The basic concept of this evolving device, however, is its biodegradability. Especially in children with an expected implant persistence of some 80 years, the degradation of the implant after ingrowth and concurrent replacement by autologous host tissue might be a concept not only to minimize foreign-body reactions (such as perforations) but also to avoid the potential for yet unknown long-term sequelae.

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Transcatheter Intracardiac Device Implantation for Atrial Level Defects and Thrombosis: A Call for Randomized, Controlled Data

In their review of transcatheter device implants for atrial septal defects (ASDs) and patent foramen ovale (PFO), Krumsdorf et al. (1) present an instructive example of how the cataloguing of non-standard indications for intervention, treatment techniques, and outcome assessment confounds the management of patients with congenital heart disease. Indeed, the lack of controlled data plagues the device arena and prevents us from making evidence-based treatment decisions in our patients with PFO and stroke. Unfortunately, the accompanying editorial by Moore and Levi (2) fails to call attention to the limitations of such nonrandomized, uncontrolled data. As a result we are concerned that erroneous conclusions will be drawn that can have a negative impact on patient recruitment in ongoing randomized, controlled clinical trials of device closure in patients with PFO.

The investigators present a large collection of patients but without a table of patient characteristics, making later analysis against their defined end point of device-related thrombosis all but impossible. The patient data that do exist lack a standardized preprocedural assessment of prothrombotic risks (including major serologic determinants of arterial and venous thrombosis such as antiphospholipid antibodies and homocysteine as well as external determinants such as cigarette and oral contraceptive use, thyroid or liver disease, blood dyscrasias, obesity or trauma, valvular heart disease, preprocedural palpitations, or atrial fibrillation). Those deficiencies, combined with non-standardized implant techniques, the use of postprocedural prothrombotic therapy (protamine), non-standard, periprocedural antiplatelet therapy, and variable device-specific follow-up protocols cloud the interpretation of the results.

The sensitivity and specificity of echocardiographically detected device-related thrombosis is not defined for any of the particular devices (each has different metallic composition and echocardiographic penetrance). In some cases, device characteristics may limit detection of the 3- to 5-mm thrombus that may be associated with neurologic events. Both intra- and interobserver variability in recognizing device-related thrombus are not discussed. Given the uncertainty about diagnostic accuracy, because very few occurrences were seen in the trial, correlation of outcome to causative factors becomes difficult at best.

Of particular concern is generalization from data obtained in a practice setting that the investigators themselves recognize is outside of current standards of care for device implants (namely, use of protamine at procedure termination in the first 813 patients): 19 of 20 thrombotic events occurred in this group. The applicability of such data for today’s patients, who receive implants without the use of postprocedure protamine, cannot be determined.

Moore and Levi (2) unfortunately generalize from the investigators’ unsupported conclusions to recommend care standards based upon differences in device design. In addition, the editorial comment does not place into context the additional recognized device-related complications such as cardiac erosion, death, valve interference, embolizations, fractures, and proarhythmia. We are deeply concerned by these editorial recommendations. Clinical care standards should be established only through the performance and analysis of randomized controlled clinical trials and not through anecdotal data as offered by Krumsdorf et al. (1).
We find the results of Krumsdorf et al. (1) to be of interest in its detail of the natural course of unusual device-related, large-burden thrombus in the now uncommon setting of protamine thrombus use. We consider other associative relationships, as well as the editorial recommendations of Moore and Levi (2), to be unsubstantiated. Clinicians should not base management decisions in patients with PFO and stroke on such anecdotal and highly selected data. We await the results of ongoing and future randomized clinical trials to address these concerns.

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Incidence and Clinical Course of Thrombus Formation on Atrial Septal Defect and Patent Foramen Ovale Closure Devices

Krumdsorf et al. (1) present impressive data concerning the risk of thrombus formation on closure devices for atrial septal defects (ASDs) and patent foramen ovale (PFO) in 1,000 consecutive patients.

The vast majority of these patients were treated in the Bethanien-Hospital where we worked together with Dr. Sievert from July 1995 until he left our institution in June 2003. Until October 27, 2000, we shared the scientific database for all patients who had received an atrial septal implant. Therefore, we would like to add some information on two of our patients who were apparently included in the series of Krumdsorf et al. (1).

One PFO patient with an Amplatzer (AGA Medical Corp., Golden Valley, Minnesota) occluder developed thrombus on the left atrial disk of the device, which was detected by transesophageal echocardiography (TEE) five weeks after implantation (implanted January 26, 2000; TEE date March 1, 2000). With heparinization and anticoagulation, the further course was uneventful.

Another PFO patient suffered two strokes 5.7 years after implantation of a Buttoned device (Custom Medical Devices, Amarillo, Texas). The TEE revealed a 10 × 7-mm thrombus on the left atrial disk of the occluder (implantation date March 4, 1996; TEE date November 16, 2001). The thrombus resolved after heparinization and anticoagulation, and the further clinical course was uneventful. The latter event was published as a case report (2).

We believe that these data might be clinically relevant, not only because thrombus formation may occur early after implantation of an Amplatzer device, but more importantly, even after more than five years following defect closure. Therefore, all investigators involved in the field of interventional ASD closure have the obligation to follow their (own) patients for an unlimited period of time.

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REPLY

We greatly appreciate the comments and suggestions by Drs. Landzberg and colleagues, Massimo and colleagues, Jux and Bertram, and Schräder regarding our recent paper (1).

First, we absolutely share the opinion of Landzberg and colleagues that randomized trials are superior to nonrandomized trials! Conversely, nonrandomized trials are better than no trials at all! And before a randomized trial can be initiated we have to have an idea about what we are looking for and what the incidence of a specific event like thrombus formation might be. Dr. Landzberg and his colleagues know very well how difficult it is to conduct a randomized trial in catheter closure of intracardiac defects. Although the first transcatheter atrial septal defect (ASD) closure was performed more than 25 years ago, until today no randomized trial has ever been started.