Incidence of Pregnancy-Associated Venous Thromboembolism

TO THE EDITOR: We congratulate Heit and colleagues (1) on their study on the incidence of venous thromboembolism during pregnancy and the puerperium. However, we take issue with their statement that the venous thromboembolic incidence was 3.6% and 1.5% in the first and second weeks postpartum, respectively, similar to the 2% to 5% incidence of symptomatic venous thromboembolism after elective hip replacement in patients not receiving prophylaxis. This seems unlikely when only 105 maternal cases of venous thromboembolism were diagnosed during pregnancy or postpartum in 50,000 births.

This discrepancy relates to the method the authors have used to calculate the incidence. For some purposes, it makes sense to compare incidence rates per person-year at risk, as the authors have done. In this instance, in consideration of the possible benefit of thromboembolic prophylaxis, it is more relevant to know the chance of an individual having an event postpartum. It is misleading of the authors to compare the 2 types of measure. The incidence rate per 100,000 person-years in week 1 postpartum is 3573 per 100,000. However, this is not 3.6% of pregnant women who have an event in the first week postpartum. Because by this point women have only been at risk for 1 week out of 52 in a year, only 68 per 100,000 or 0.68 per 1000 will have had an event in that week. In the authors’ Table 1, the postpartum risk for venous thromboembolism in women older than age 35 years (the highest-risk group) is reported as approximately 900 per 100,000 person-years. Because the postpartum period defined by the authors is 3 months, the risk to a woman who has delivered is approximately 225 per 100,000 (13 of 52 of the risk period defined by the authors). The risk to a woman older than age 35 years is approximately 2 per 1000, which is about 0.68 per 1000 will have had an event in that week.

We report on a larger database, the National Hospital Discharge Survey (NHDS), which showed that pregnancy-related DVT occurred in 24,000 women throughout the United States from 1979 to 1999 (2). Pregnancy-associated DVT declined over the past 2 decades, whereas nonpregnancy-associated DVT among hospitalized women declined. Of importance, older age, black ethnicity, and delivery by cesarean section were associated with higher rates of pregnancy-associated DVT (2). During this period of study (1979–1999), the NHDS was based on data abstracted annually from 181,000 to 307,000 sampled patient abstracts from 400 to 480 nonfederal, short-stay, noninstitu-
tional hospitals in 50 states and the District of Columbia (2, 3). This represented approximately 8% of all such hospitals and 1% of all discharges (3). Strengths of the NHDS include the huge number of patients, the widely varying regions in which patients were hospitalized, the extended period over which data were collected, and the broad spectrum of patients evaluated. Weaknesses include an inability to determine the basis of the diagnosis of DVT and PE, whether antithrombotic prophylaxis or treatment was administered, or whether patients were hospitalized more than once in a given year.

On the basis of the data we reported (2), there is good reason for continued vigilance concerning pregnancy-associated DVT.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Dr. MacCallum and coworkers argue that we incorrectly reported our venous thromboembolism incidence rates for the first and second postpartum weeks as 3.6% and 1.5%, respectively, because of incorrect denominator calculations. The denominator calculations were based on the total number of live births in Olmsted County (n = 50 080) and “period at risk” definitions of 9 and 3 months for pregnancy and the postpartum period, respectively. A 1-week period of risk is 1/52 of a year (0.019), such that the woman-years at risk during the first postpartum week were 0.019 times the number of live births (0.019 × 50 080 = 951 woman-years). Thirty-four women had documented incident venous thromboembolism during this week, providing an incidence of 0.036 (34 of 951), or 3.6 per 100 woman-years (i.e., 3.6%). The incidence rate for the second postpartum week was calculated similarly. However, although the incidence rates are correct as reported, we incorrectly compared these rates with the proportion of patients developing venous thromboembolism after total hip replacement. According to data reported from the California Patient Discharge Data Set, among 56 720 patients undergoing elective total hip replacement between 1 January 1992 and 30 September 1996, 1358 developed symptomatic venous thromboembolism within 3 months (0.25 year) after surgery (1). Thus, there were 14 180 person-years at risk (56 720 × 0.25), and the venous thromboembolism incidence was 0.096 (1358 of 14 180), or 9.6 per 100 person-years. While this rate is similar to our incidence rates for the first and second postpartum weeks, at least some of the patients who had hip replacement probably received prophylaxis such that the incidence in the absence of prophylaxis could have been higher.

Drs. Rajput and Rana suggest that cesarean section is a risk factor for venous thromboembolism. Our present study was not designed to address this question. However, in a previous population-based case–control study specifically addressing risk factors for pregnancy-associated venous thromboembolism (2), we could not identify cesarean section as a postpartum risk factor (univariate odds ratio, 1.17 [95% CI, 0.39 to 3.47]).

Dr. Stein and coworkers cite their study reporting an analysis of administrative data from NHDS and indicate that rates of pregnancy-associated DVT increased between 1979 and 1999 (3). Pregnancy-associated PE was too infrequent to analyze for trends. In contrast, we found a decrease in the overall incidence of pregnancy-associated venous thromboembolism, mostly due to a decrease in postpartum PE; the incidence of pregnancy-associated DVT declined slightly and nonsignificantly. These differences may be explained by different study designs. The time frame of our study was longer (1966–1995). Moreover, we only included women with a first lifetime event, while the NHDS database does not separate incident from recurrent events. Finally, almost 70% of women coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) as having pregnancy-associated DVT may be miscoded (4). Nevertheless, we certainly agree that there is a need for continued vigilance regarding pregnancy-associated venous thromboembolism.

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Potential Financial Conflicts of Interest: None disclosed.

References
4. White RH, Brickner LA, Scannell KA. ICD-9-CM codes poorly identified venous
TO THE EDITOR: The long-awaited randomized, controlled trial of plasma exchange by Clark and colleagues (1) has finally been published. As the largest trial on the subject, it was supposed to help define the role of plasma exchange in multiple myeloma. However, on closer evaluation of the data, I found more questions than answers.

First, what disease was actually treated with plasma exchange in this study? Autopsy data from Ivanyi (2) found light-chain deposition disease, amyloidosis, and cast nephropathy in 5%, 11%, and 32%, respectively, of the patients who died with myeloma (2). Others have shown acute tubular necrosis, tubulointerstitial nephritis, and plasma-cell infiltration as additional causes of acute renal failure in this population (3). Considering that most of Clark and colleagues’ patients did not have renal biopsy, how did the authors ensure that only cast nephropathy was being studied? It is equivalent to treating patients with monoclonal gammopathy without a bone marrow biopsy. Since plasma exchange is only intended to treat cast nephropathy, it is therefore not unexpected that this study found no benefit.

Next, why was death at 6 months included in the primary outcome? Since plasma exchange cannot decrease the tumor burden, increase the CD4 cell count, or improve cytogenetics (which are prognostic factors in this population [4]), it would seem unfair to expect it to improve short-term survival. This was reinforced by the fact that dialysis also did not appear to influence short-term survival in this study (1). Unfortunately, because death made up one third of the events in both groups, this weakened an already underpowered study to a point where no difference could be demonstrated.

Despite its randomized, controlled design, Clark and colleagues’ study led us no closer to the role of plasma exchange in cast nephropathy. It is important for nephrologists to understand the study’s limitations; our role in this disease is not to provide antimyeloma therapy but to reverse renal failure and preserve renal function. The main concern should not be limited to prolonging life but should include improving quality of life by getting patients off dialysis. Preservation of renal function also keeps therapeutic options open since many clinical trials exclude patients who are dialysis dependent. Nephrologists’ role in this disease is clear, even though the results of Clark and colleagues’ study are not.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: My coauthors and I concur that, on closer observation of our data, more questions are found than answers. We hope that most careful readers would experience this phenomenon when looking closely at data from other randomized, controlled trials. Dr. Leung raises the issue of an absence of renal biopsies and refers to an autopsy study published in 1990 (1), which indicated that 37% of patients with myeloma had light-chain or cast nephropathy and 11% had amyloidosis. Fewer than 20% of patients with myeloma have a clinical picture of acute renal failure and heavy proteinuria at diagnosis. As indicated in our Methods and Discussion sections, these are the entry criteria for patients who were enrolled in our study. Two pathologic studies (referenced in our paper) have shown that this clinical picture of progressive or acute renal failure has a 77% to 97% incidence of light-chain or myeloma cast nephropathy (2, 3). Dr. Leung asks why death was included as the primary outcome measure in our study, which was initiated in 1998. The decision to include death was based on the previously published findings of Zucchelli and associates (4). In this small randomized, controlled trial, which involved 29 patients, the plasma exchange group experienced a significant reduction in mortality attributable to the plasma exchange procedure (4). We agree with Dr. Leung that at this time plasma exchange cannot decrease the tumor burden, increase the CD4 cell count, or improve the cytogenetic factors that have been shown to be prognostic in this population.

As a nephrologist and as a physician, I concur that it is important for nephrologists and other physicians to focus on improving quality of life for patients with acute renal failure at the onset of myeloma. My coauthors and I also believe that our role in this disease is clear: to carry out, wherever possible, interventions that are more likely to benefit and less likely to harm our patients based on the best available evidence to date. We strongly encourage all of our colleagues to actively participate in randomized, controlled trials to provide clearer treatment options.

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Potential Financial Conflicts of Interest: None disclosed.

References
TO THE EDITOR: We read with interest the report by Leff and colleagues on hospital at home (1). Their findings that hospital at home led to shorter length of stay, fewer medical complications, greater patient satisfaction, and reduced cost are important additions to the evidence supporting this service. They are also similar to our experience with the Jerusalem Home Hospital program, which, since its initiation in 1991, has treated more than 13,000 patients with intensive medical, subacute, and palliative care at home instead of in the hospital.

We previously reported that decreased hospital utilization was attributable to the establishment of our home hospital service (2, 3). Recent data confirmed these findings. When the chief administrator of our health maintenance organization (HMO) cut home hospital spending by 60% (a reduction from 400 to 150 patients treated simultaneously), it allowed our institution to monitor the impact of withdrawing this service on geriatric and medical hospitalization rates. An analysis of 45,000 HMO beneficiaries older than 65 years of age showed that per capita patient days and spending increased rapidly in the 12 months after the home hospital budget was cut, far exceeding forecasts based on previous trends. Hospital days in medical wards increased by 7.2% in contrast to a projected decline of 2.9%, and days in geriatric wards increased by 16.9% as opposed to a forecasted rise of 4.4%. On the basis of these data, the previous home hospital budget at our institution was restored.

The editorial by Shepperd (4) that accompanied the article by Leff and colleagues criticized home hospital programs on the basis of a recent Cochrane review (5). However, this review examined various home hospital models, some of which were not exclusively substituted for inpatient care; this dampened the effects of the intensive models. Shepperd also addressed the difficulties of comparing and generalizing findings from different health care systems. However, although the structure of health service provision is a fundamental element in understanding health care delivery, it is only the context in which treatments are provided. The success of home hospital programs transcends health care structure. Finally, the overwhelming majority of published literature comparing patient groups with or without home hospital treatment supports either reduced or no difference in per capita overall health expenditure among the home hospital patients. This is important because even in scenarios where savings were absent, home hospital did not incur greater costs than inpatient hospital care. Although medical and economic issues remain to be resolved, patients or health care professionals exposed to home hospital resoundingly confirm the benefits of the service. Home hospital is highly desirable and represents a uniquely humane face of modern medicine.

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Potential Financial Conflicts of Interest: None disclosed.

References

Strategies To Prevent Organ Disease by Cytomegalovirus in Solid Organ Transplant Recipients

TO THE EDITOR: The meta-analysis by Kalil and colleagues (1) examining universal prophylaxis and preemptive therapy for cytomegalovirus (CMV) organ disease addresses an important issue. However, the conclusions may be potentially misleading because of significant limitations of the included studies, variability in the duration of prophylaxis and the length of follow-up in the published studies, and the selection of trials for the meta-analysis. The studies by Conti (2) and Hibberd (3) and colleagues cannot truly be considered to examine preemptive therapy. Prophylactic use of an antiviral agent in patients receiving antilymphocytic antibodies was based on the likelihood of CMV infection during augmented immunosuppression rather than on the detection of CMV replication or viremia. Kalil and colleagues’ statement that the basis of indirect sequelae of CMV is intermittent viral replication may not apply to patients who receive therapeutic intervention before rather than at detection of viral replication, as in preemptive therapy.

Our major concern is the sample size in the subgroup analyses. For example, the donor-positive/recipient-negative group, in which Kalil and colleagues documented no statistically significant benefit of preemptive therapy for CMV disease, included only 33 patients with 3 disease events (the authors’ Figure 2). Rather than state that preemptive therapy is not as optimal as universal prophylaxis for specified subgroups, we believe it would have been better to note that there were insufficient patients in the preemptive therapy group to draw a rational conclusion. The conclusions regarding the impact of preemptive therapy on secondary end points (for example, opportunistic infections and mortality) are also of concern (1). Although these outcomes have not been systematically assessed in CMV antiviral trials in general, the number of preemptive therapy studies, in particular with regard to secondary outcomes, is so small as to preclude meaningful assessment of the impact of preemptive therapy on indirect sequelae of CMV infection. For example, if trials based on the use of preemptive therapy at viral detection are considered, then the analysis of the effect of this approach on mortality in Kalil and colleagues’ meta-analysis (the authors’ Figure 4) would have included only 2 studies involving a total of only 72 patients (4, 5).

Regardless, examination of the graphical data show that 95% CIs of all comparisons have a considerable degree of overlap. If the null hypothesis is that preemptive therapy and universal prophylaxis are equivalent, then the data presented do little to refute it. However, we agree with the authors that only a carefully conducted random-
ized trial can discern the efficacy of these 2 approaches with regard to direct and indirect outcomes associated with CMV.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We appreciate Dr. Singh’s and Ms. Wagener’s comments but must address several points of disagreement. First, we do not agree that our conclusions may be misleading. As discussed in our paper, trial design limitations, duration of follow-up, and prophylaxis were thoroughly evaluated by sensitivity analyses, and the conclusions of our meta-analysis remained unchanged.

Second, Dr. Singh and Ms. Wagener do not feel that the studies by Hibberd (1) and Conti (2) and colleagues can truly be considered preemptive therapy. Of interest, both of these studies have the words “preemptive ganciclovir therapy” in their titles. After considering the objectives and quality of these 2 trials, we decided that they should be included in our analysis. Nonetheless, because the patients in these studies were more intensely immunosuppressed and because of the potential differences in the design of the preemptive therapy (which Dr. Singh and Ms. Wagener pointed out), we also performed a sensitivity analysis, which was not included in our manuscript. The overall results for CMV organ disease in the preemptive analysis remained similar and statistically significant (odds ratio, 0.24 [95% CI, 0.07 to 0.85]); P = 0.014 [Mantel–Haenszel test]; P = 0.188 [Breslow–Day test]).

Third, as in any well-designed, large clinical trial or meta-analysis, the sample size for the subgroup analyses is always a potential concern; no single trial or meta-analysis is likely to be adequately powered for all subgroup analyses. The studies are powered for the group, not for the subgroups. Therefore, we agree with Dr. Singh’s and Ms. Wagener’s concerns about the subgroup power.

Fourth, we never stated that “preemptive therapy is not as optimal as universal prophylaxis for specified subgroups,” and we did not draw conclusions on the basis of subgroup results only. What we actually said in our Discussion section is found in the final paragraph: “Our results suggest that universal prophylaxis may be the preferred method of treatment because of its reduction in post-transplantation CMV organ disease and its reduction in bacterial and fungal opportunistic infections, allograft rejection, and death. However, a prospective trial . . . needs to be done to confirm our findings.” This statement is based on the results from the primary and secondary outcome analyses.

Fifth, Dr. Singh and Ms. Wagener state, “if trials based on the use of preemptive therapy at viral detection are considered, then the analysis of the effect of this approach on mortality in Kalil and colleagues’ meta-analysis . . . would have included only 2 studies involving a total of only 72 patients.” This is incorrect. The 2 studies in question (3, 4) included 140 patients.

In conclusion, while we agree that both universal prophylaxis and preemptive approaches are very effective in preventing CMV organ disease, the debate about the differences in the magnitude of the effect and the costs can only be brought to a close by a randomized trial.

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Potential Financial Conflicts of Interest: None disclosed.

References

Controlling the Troll

TO THE EDITOR: We read Dr. Dummer’s editorial (1) about our study (2) with interest. However, we would like to make some clarifications.

We agree with Dr. Dummer’s recommendation that because of potential confounding factors related to differing outcomes in the preemptive and prophylactic trials, “it would be unwise to directly compare the results achieved with the 2 strategies.” Our study made no such formal, direct comparisons. In the Discussion section, we clearly stated that comparison of these 2 approaches needs to be based on a “prospective trial directly comparing universal prophylaxis with a preemptive approach.”

Dr. Dummer stated that “the rates of CMV [cytomegalovirus] infection following liver transplantation. Transplantation. 2001;72:881-5. [PMID: 11571454]
Letters

IN RESPONSE: Kalil and colleagues’ meta-analysis of CMV management trials (1) is an important contribution to the literature that should be widely cited. The goal of my editorial was not to rephrase or critique their article, which can stand on its own merits. Rather, I hoped to communicate some historical perspective on the topic and discuss the current controversy between prophylactic and preemptive approaches to the management of CMV infection.

One concern I had was that some readers might see CMV prophylaxis as the better overall strategy, because the meta-analysis found more benefits for this management strategy than for preemptive therapy. I wanted to issue a caveat against drawing this sort of conclusion. In order to strengthen that caveat, I extracted and analyzed data from Kalil and colleagues’ article that, in fact, showed that their preemptive and prophylactic populations were quantitatively and qualitatively different. I believe that this was a valid and legitimate exercise and that it supported my claim that no reliable conclusion could be drawn from the data favoring either approach to CMV management.

I stand by my statement that all of the large (>100 patients) placebo-controlled trials cited in the study were studies of prophylaxis. The trial by Hibberd and colleagues (2) was randomized and contained more than 100 patients, but it was not placebo-controlled or blinded. It is important to recognize that more resources have been invested in the study of CMV prophylaxis than in preemptive therapy of CMV, and this may have produced a playing field that is not completely flat.

Finally, this letter gives me an opportunity to redress my neglect of acyclovir, whose prophylactic use was shown by the meta-analysis to reduce CMV disease. Acyclovir is clearly less potent than ganciclovir (3) and is never used for preemptive therapy or therapy of established CMV disease, but as Kalil and colleagues have shown, it has proven benefits in the prophylactic setting. Further studies of acyclovir analogues seem warranted. A particularly intriguing regimen to study in high-risk patients would be the combination of valacyclovir prophylaxis and valganciclovir preemptive therapy.

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Potential Financial Conflicts of Interest: Consultancies: Roche Labs; Honoraria: Roche Labs.

References

Clinical Observations

Primary Patent Foramen Ovale Closure To Relieve Severe Migraine

TO THE EDITOR: Background: Migraine headaches are highly prevalent in the general population and account for significant morbidity, lost productivity, health care visits, and dollars spent. The prevalence of migraine headaches is higher in patients with patent foramen ovale (PFO), which causes paradoxical embolism and cryptogenic stroke, than in the general population (1). Previous studies

Primary Patent Foramen Ovale Closure To Relieve Severe Migraine

TO THE EDITOR: Background: Migraine headaches are highly prevalent in the general population and account for significant morbidity, lost productivity, health care visits, and dollars spent. The prevalence of migraine headaches is higher in patients with patent foramen ovale (PFO), which causes paradoxical embolism and cryptogenic stroke, than in the general population (1). Previous studies
have suggested that closure of the PFO may reduce or resolve migraine symptoms (2, 3). Currently, percutaneous transcatheter closure of PFO is reserved for patients with recurrent migraine headaches who have a history of stroke (3, 4).

**Objective:** To assess possible indications for and results of transcatheter PFO closure in patients with severe, disabling migraine headaches and no history of stroke.

**Methods and Findings:** Our cohort consisted of 10 patients (8 women and 2 men; mean age, 35 years [SD, 6.7]) who had severe, disabling migraine headaches despite antiheadache therapy, PFO diagnosed by echocardiography as part of a headache evaluation, and no history of cryptogenic stroke. The patients were referred to our multidisciplinary center, where a team of neurologists, internists, and interventional and noninterventional cardiologists specialize in the evaluation of cryptogenic stroke and PFO-related syndromes (platypnea–orthodeoxia, paradoxical coronary and peripheral embolism, scuba divers’ embolism). We used 5 clinical features to justify transcatheter PFO closure: recurrent migraine headaches affecting the patients’ active work and social life for more than 40% of each week despite antiheadache therapy (8 patients); severe neurologic aura, defined as blurred vision, hemianopsia, cortical blindness (2 patients), or hemis lateral loss of force and paresthesias (4 patients); evidence of atrial septal aneurysm found on transesophageal echocardiography (7 patients); shower or curtain pattern of shunt on contrast-enhanced transcranial Doppler ultrasonography (5 patients); and abnormalities of the coagulative cascade proteins (antithrombin III deficiency and factor V Leiden) or antiphospholipid or anticardiolipin antibodies (6 patients). We identified 5 patients who had all 5 features as the leading candidates for transcatheter closure of PFO (Table).

After we advised the patients of the occluder device’s off-label use for migraine symptoms and they gave their informed consent, the patients underwent PFO transcatheter closure with mechanical intracardiac echocardiography guidance. Amplatzer PFO occluder devices (AGA Medical Corp., Golden Valley, Minnesota) were used; a 25-mm device was used in 2 patients, and a 35-mm device was used in 2 others. A 35/35 Amplatzer Cribriform occluder device was implanted in 1 patient. The procedure was successful in all 5 patients; no perioperative or in-hospital complications were reported, and no abnormalities were found on transthoracic echocardiography before discharge. All patients received aspirin therapy for 6 months. Follow-up evaluation consisted of transesophageal echocardiography (1 month after occlusion in all patients and repeated in 6 and 12 months if a residual shunt was detected), transthoracic echocardiography (6 and 12 months after occlusion), and transcranial Doppler ultrasonography (at 1 and 12 months). Although transcranial ultrasonography is less specific than transesophageal echocardiography for detection of PFO, the study reduces the number of false-positive echocardiography readings that arise from other causes of shunts. After a mean follow-up of 6.7 months (SD, 5.8), all patients were free from migraine symptoms. Complete PFO closure was documented by transesophageal and transcranial Doppler ultrasonography in 4 out of 5 patients, and a small residual shunt was detected in 1 patient 3 months after the procedure.

**Discussion:** Primary transcatheter closure of the PFO resulted in complete resolution of migraine headaches in our small series of patients with clotting abnormalities and no history of paradoxical embolism or cryptogenic stroke. Obviously, this case series cannot establish any role for this off-label therapy in the panorama of emergent indications for PFO closure. However, our experience suggests some specific clinical features that can be used as a basis for enrollment protocols of future large studies.

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<th>Table. Clinical Features of Patients Who Underwent Percutaneous Transcatheter Closure of Patent Foramen Ovale</th>
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* As determined by transcranial Doppler ultrasonography.

**Potential Financial Conflicts of Interest:** None disclosed.

**References**
Correction: Trends in the Incidence of Venous Thromboembolism during Pregnancy or Postpartum: A 30-Year Population-Based Study
In the Discussion section of an article on venous thromboembolism during pregnancy or postpartum (1), the incidence rates for the first and second postpartum weeks were incorrectly compared with the proportion of patients developing venous thromboembolism after total hip replacement in another study (2). According to data reported from the California Patient Discharge Data Set, among 56,720 patients undergoing elective total hip replacement between 1 January 1992 and 30 September 1996, 1,358 developed symptomatic venous thromboembolism within 3 months (0.25 year) after surgery (3). Thus, there were 14,180 person-years at risk (56,720 × 0.25), and the venous thromboembolism incidence was 0.096 (1,358 of 14,180), or 9.6 per 100 person-years. While this rate is similar to the incidence rates reported by Heit and colleagues for the first and second postpartum weeks (3.6% and 1.5%, respectively), at least some of the patients who had hip replacement probably received prophylaxis such that the incidence in the absence of prophylaxis could have been higher.

Correction: Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy
In an article on acute pain management for patients receiving maintenance methadone or buprenorphine therapy (1), the third bold-faced heading in Table 2 should have read as follows: “If the patient is receiving methadone maintenance therapy and requires opioid analgesics.” The text “2 options are available” is incorrect and should not have appeared.

Reference