THE ORTHOPAEDIC FORUM

Selection Bias, Orthopaedic Style

Knowing What We Don't Know About Aspirin

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Within the first 4 months of the 2019 calendar year, 3 articles appeared in highly respected peer-reviewed publications that seemingly crowned aspirin as the king of venous thromboembolism (VTE) prophylaxis following total hip arthroplasty (THA) and total knee arthroplasty (TKA)[1-4]. Not surprisingly, such a proclamation could not be more welcomed and better received among the orthopaedic community. After all, aspirin is familiar to nearly all medical practitioners as well as the lay public, it is inexpensive and conveniently used without the need for any monitoring, and conventional wisdom holds that it is fraught with the fewest number of bleeding complications in surgical patients compared with more potent anticoagulants that are used for the same purpose. The problem, however, is that because of the joy that is associated with such an uplifting message, we fail to analyze the scientific basis, and hence the credibility, of the message, perhaps to our detriment and that of our patients. In fact, the currently available data do not conclusively show that aspirin is the best VTE prophylaxis after THA and TKA.

The American College of Chest Physicians (ACCP), a perennial authority on VTE prophylaxis, issued their first set of clinical practice guidelines in 1986, and have continued to issue guidelines through 2012[5]. Guideline writers relied predominantly on evidence from prospective randomized trials after THA and TKA, often based on a finding of deep venous thrombosis (DVT) on screening venography as a presumed precursor to pulmonary embolism (PE), and endorsed potent anticoagulants over aspirin, with relatively low concern for bleeding associated with anticoagulant use. During the 1990s, the introduction of fractionated heparins for VTE prophylaxis after total joint replacement heralded the way for a plethora of clinical trials, and surgeons witnessed a dramatic increase in perioperative bleeding complications. In response, the orthopaedic community quietly drifted to aspirin for prophylaxis, largely on the strength of its perceived low bleeding risk, but without strong efficacy data. Orthopaedic surgeons placed greater value on the prevention of clinical PE rather than asymptomatic DVT, with a competing desire to mitigate the risk of bleeding that may result in wound hematoma, reoperation, secondary infection, and removal of the joint prosthesis[6]. During this time, some centers published large observational studies that used routine aspirin prophylaxis in patients with total hip and knee replacement with favorable results, except for 15% to 20% of patients who were considered "high risk" and selectively received warfarin prophylaxis[7-9].

In 2008, after 7 successive renditions of the guidelines shunning aspirin, the ACCP offered a specific recommendation against the use of aspirin for VTE prophylaxis following THA and TKA[10]. That same year, the American Academy of Orthopaedic Surgeons (AAOS) responded with its first set of clinical guidelines, endorsing the use of aspirin for patients at "typical" risk for VTE after hip and knee replacement, and introducing an algorithm for risk stratification of patients[11]. Hence began the fabled VTE prophylaxis "guideline wars."[12] The AAOS did

Disclosure: The PEPPER Trial is supported by the Patient-Centered Outcomes Research Institute (PCORI). On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article*, one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work (http://links.lww.com/JBJS/F670).

not endorse aspirin for patients perceived to be at "elevated" risk of VTE; it was recommended that these patients receive more potent anticoagulants. For patients at "elevated" risk of bleeding, potent anticoagulants were omitted in favor of aspirin, warfarin, or mechanical compression devices. In the face of an "elevated" risk of both VTE and bleeding, less potent anticoagulation was recommended. The AAOS has consistently endorsed less-intensive anticoagulation with aspirin or low-intensity warfarin, largely based on observational reports; with randomized clinical trials that are underpowered to demonstrate significant differences, both agents have been associated with comparable rates of fatal PE and less bleeding than more potent anticoagulants.

For the ensuing decade, guidance from the ACCP and the AAOS remained at odds, resulting in confusion for both patients and practitioners over optimal management[12]. However, with the backing of the AAOS guidelines, orthopaedic surgeons increasingly used aspirin prophylaxis for all but those patients who were identified as being at "high" risk. Such a "high-risk" group would include, but not be limited to, patients with a personal history of an unprovoked DVT or PE, a provoked DVT or PE after joint replacement despite chemoprophylaxis, or a documented history of thrombophilia, such as the presence of factor V Leiden. From the surgeon's perspective, as well as the patient's[13], increased bleeding is at least as worrisome as an increased PE risk; indeed, in practice, fatal PEs occurred substantially less often than did major bleeding events. Finally, in 2012, the guideline debate ended with reconciliation between the 9th ACCP[5] and 2nd AAOS[14] editions, which were based on an increased value attached to bleeding complications. Both groups also conceded that, using clinical PE as the important end point, there were insufficient data to endorse any specific prophylaxis regimen as "best practice." Perfect harmony was achieved in 2014 when the American College of Surgeons Surgical Care Improvement Project (SCIP) added aspirin to its list of acceptable VTE prophylaxis agents[15]. All groups now decline to endorse any preferred regimen, other than to recommend doing something for VTE prophylaxis after hip and knee replacement.

Accordingly, observational reports must be considered in light of the prevailing clinical practice guidelines informing VTE prophylaxis. The 3 clinical studies that were published in 2019 all share a common theme demonstrating comparable clinical VTE outcomes with aspirin prophylaxis and with more potent anticoagulants. However, each of those reports also relies on retrospective observational data that were accumulated from 2000 to 2017, during a period when orthopaedic surgeons favored aspirin prophylaxis except for those patients perceived to be at highest risk, who selectively received warfarin or another potent anticoagulant. Indeed, the Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI) data were collected entirely after the ACCP and AAOS guideline reconciliation and, with only 31% of patients receiving solely aspirin prophylaxis and more than two-thirds receiving a potent anticoagulant, the data were highly selective with respect to aspirin use[1,2]. The 2 reports from Philadelphia acknowledge a switch from routine warfarin to routine aspirin prophylaxis except for the highest-risk patients, who still selectively received warfarin[3,4]. Thus, in all 3 of the reports, patients were specifically selected to receive something other than aspirin prophylaxis if they were felt to be at higher risk than other arthroplasty patients. This selection bias in current clinical practice strongly favors observational data demonstrating the effectiveness of aspirin prophylaxis, and negatively biases effectiveness outcomes for more potent anticoagulants. Indeed, to our knowledge, the last time a prospective randomized clinical trial was conducted with single-drug VTE prophylaxis using either aspirin or warfarin, the trial was stopped before completion because of an unacceptably high rate of clinical VTE observed in the aspirin group[16]. A more recent prospective clinical trial with aspirin used combination therapy with randomization to aspirin occurring postoperatively, only after all patients had received 5 days of rivaroxaban during the period of greatest VTE risk[17].

The analysis of observational data sets, no matter how many times or by which sophisticated methodology might be elected, may remain flawed by the prevailing selection bias implicit in the underlying observational data. In each of the 3 studies mentioned above, the investigators used sophisticated methods to attempt to adjust the selection bias of lower-risk patients receiving aspirin. However, the statistical methods that were used cannot adjust for unmeasured confounding variables or residual confounding. Therefore, no matter how welcome a favorable endorsement of aspirin for VTE prophylaxis after total joint replacement might be, we lack critical data from prospective randomized clinical trials that randomly assign patients with similar risk profiles to aspirin versus potent anticoagulants for the sake of a credible and level comparison.

We await the results of the Pulmonary Embolism Prevention after Hip and Knee Replacement trial (also known as The PEPPER Trial; NCT02810704), a large comparative effectiveness trial funded by the Patient-Centered Outcomes Research Institute (PCORI), to shed some light on this perplexing issue. In The PEPPER Trial, 20,000 patients undergoing either primary or revision THA or TKA will receive 4 weeks of VTE prophylaxis and be randomized to either rivaroxaban (20 mg daily) starting 24 hours after surgery, aspirin (81 mg twice daily) starting immediately before surgery, or warfarin adjusted to an international normalized ratio (INR) target of 2.0 starting immediately prior to surgery. With >9,000 patients randomized from 28 centers in North America, The PEPPER Trial is nearly halfway to completion. In the meantime, any conclusions based on observational data must consider the implicit selection bias in current practice that purposefully limits aspirin prophylaxis to only the lowest-risk patients following THA and TKA. ■

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