Confounding by Indication: Response
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DOI: 10.1177/0363546516638073

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>> Version of Record - Mar 31, 2016

What is This?
Dear Editor:

We read with great interest the recently published paper “The Prevalence of Symptomatic Deep Venous Thrombosis and Pulmonary Embolism After Anterior Cruciate Ligament Reconstruction,” by Gaskill et al in the November 2015 issue of The American Journal of Sports Medicine. The authors present the prevalence of venous thromboembolism (VTE) following anterior cruciate ligament (ACL) reconstruction. In addition, they report risk factors for VTE. Given the severity of the disease and the large number of interventions, identifying those at high risk is crucial to prevent VTE. This study supports the current evidence on the incidence and risk factors for VTE after ACL reconstruction. Nevertheless, we are concerned about one conclusion: that patients taking anticoagulant medication after ACL reconstruction have a strongly increased risk of developing VTE. An odds ratio of 98.32 (95% CI, 61.63-156.86) was reported for any postoperative anticoagulant versus no anticoagulant for VTE within postoperative 90 days.

In this study, only 147 patients (0.9%) received anticoagulant therapy following ACL reconstruction. While the American College of Chest Physicians advises against routine thromboprophylactic therapy for this indication, these patients must have had a reason for being given anticoagulation (ie, a higher risk of VTE). As the authors already discussed, there might be selection bias in their estimated association. However, the reported association is an example of confounding by indication (sometimes incorrectly called selection bias). The reason for receiving this therapy is a patient’s increased risk for VTE based on the presence of certain well-known risk factors, such as a history of VTE. This is associated with the probability of receiving anticoagulant therapy and also with the probability of developing VTE (Figure 1). Thus, patients receiving anticoagulant therapy have a higher probability of developing VTE, not because of the anticoagulant, but because of their increased intrinsic risk.

Furthermore, although it has not been shown that thromboprophylaxis reduces symptomatic VTE in these patients, an opposite effect of this treatment (ie, an increased risk) is in theory highly unlikely. Consequently, the authors should be careful in advising that patients receiving anticoagulants need to be actively screened for postoperative VTE. We agree that an individual’s VTE risk profile should be assessed. On this basis, doctors can consider whether to prescribe thromboprophylactic therapy after ACL reconstruction.

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The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

REFERENCES


Drs Nemeth and Cannegieter propose that one reported finding represents an example of confounding by indication—specifically, that those patients receiving anticoagulation following anterior cruciate ligament reconstruction (ACLR) have a strongly increased risk of developing venous thromboembolism (VTE). They propose that some other intrinsic patient characteristic is directly responsible for this association. We wholeheartedly agree. It was certainly not our intent to make this implication, and we attempt to illustrate this confounding to readers by noting that patients “prescribed anticoagulant medication postoperatively without documentation of VTE [were] for agreement with plural noun (“patients”) but to indicate difference from quoted material (ie, the brackets). Please confirm or advise] likely screened preoperatively as high-risk for VTE by their operating surgeon.” We appreciate the opportunity to clarify our rationale for the inclusion of these data, as well as our suggestion that more diligent monitoring may be prudent in this patient cohort.

To be included in this subset of the analysis, patients were screened as “high risk” for VTE and postoperatively prescribed an anticoagulant in an attempt to minimize this perceived risk following surgery. As Drs Nemeth and Cannegieter eloquently illustrate in their included figure, it is these “intrinsic” risk factors identified preoperatively that are likely to directly portend a greater VTE risk to the patient—not the prescribed anticoagulant itself. The administration of anticoagulants is therefore associated with this “screened risk” and the probability of developing VTE, thereby making it a confounding variable.

Nonetheless, the simple fact that a variable is a statistical confounder does not necessarily vitiate its value clinically. As Drs Nemeth and Cannegieter accurately suggest, the use of anticoagulants should theoretically decrease the risk of deep vein thrombosis. In this circumstance, the association described remains considerable (odds ratio, 98.32; 95% CI, 61.63-156.86) despite the use of postoperative therapeutic anticoagulation. While we are not able to objectively measure the reduction in risk imparted by the use of anticoagulants in this population, the risk remains significantly higher than that of patients who did not receive them.

To this end, it is a valuable indicator from a clinical perspective for two primary reasons. First, the association indicates that in a screened high-risk group, the use of therapeutic anticoagulants did not obviate VTE risk. For clinicians, this realization is critical to avoid the misconception that anticoagulants uniformly prevent VTE in this cohort of patients. In fact, the risk of this identified group (anticoagulant use) is significant enough that despite anticoagulant use, the prevalence of VTE remains considerably higher than that of the comparative cohort receiving no anticoagulation therapy. This awareness, in our opinion, is critical to optimal postoperative patient care.

Second, the variable can be used clinically as a simple screening tool to assess risk in the postoperative setting. Specifically, it is helpful to realize that it may be beneficial to monitor this cohort of patients (regardless of the directly related risk factor) more closely in the perioperative setting for VTE given that they remain at higher risk despite anticoagulation therapy. It is this identified risk, not the specific administration of anticoagulants, that may warrant more diligent monitoring or active screening in the perioperative setting.

We would also raise a point of contention regarding Drs Nemeth and Cannegieter’s citation of American College of Chest Physicians (ACCP) guidelines noted in their letter. The ACCP absolutely does not advise “against routine thromboprophylactic therapy for this indication [ACLR],” as Drs Nemeth and Cannegieter suggest. The applicable guidelines (2.5 and 4.0) suggest no prophylaxis for patients undergoing “knee arthroscopy without a history of prior VTE” but do suggest dual prophylaxis for patients undergoing “major orthopaedic surgery.” While ACLR is performed with arthroscopic assistance, we believe that this is certainly a greater operation than basic “knee arthroscopy.” As our surgical techniques improve, the distinction between “knee arthroscopy” and a “major orthopaedic surgery” becomes blurred and currently remains a purely subjective one. No definitive guidance within the ACCP guidelines or from the American Academy of Orthopaedic Surgeons exists in this circumstance. It is important that readers do not misconstrue this point.

In closing, we summarize by agreeing with Drs Nemeth and Cannegieter that anticoagulants are not directly related to VTE occurrence, that the finding does represent confounding (perhaps more accurately described as confounding by indication), and that the implication that these variables are directly related was certainly not our intent. We do believe, however, that it is critical for clinicians to recognize that patients requiring therapeutic postoperative anticoagulation remain strongly associated with symptomatic VTE as compared with a nonanticoagulated cohort. More precisely, the act of anticoagulation does not eradicate VTE risk in this patient cohort; in fact, it remains quite high. It is our opinion that this understanding certainly warrants more diligent clinical monitoring to minimize the risk of this rare but potentially catastrophic complication.

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The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

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