CLINICAL RESEARCH STUDY

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Quantification of the External Validity of Randomized Controlled Trials Supporting Clinical Care Guidelines: The Case of Thromboprophylaxis

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ABSTRACT

BACKGROUND: Clinical guidelines are based on the results of several randomized controlled trials. However, due to the stringent exclusion criteria of these trials, their external validity may be low. We aimed to evaluate the external validity of the randomized controlled trials cited in the American College of Chest Physicians guidelines for the use of pharmacological thromboprophylaxis in hospitalized medical patients.
METHODS: We conducted a cross-sectional, chart-review study of a random sample of patients admitted between July 1, 2013 and June 30, 2014 to the Internal Medicine ward of a large Canadian teaching university hospital. We identified the proportion of our population presenting exclusion criteria used in the randomized controlled trials cited in support of clinical care guidelines on thromboprophylaxis in the medical setting.
RESULTS: Nine trials were identified for a total of 28,793 included patients following 23 distinct exclusion criteria. We included 429 patients. Median age was 65 years (interquartile ratio 51-77 years), and 236 (55%) were males. Of those not already anticoagulated at admission (n = 351), between 26% and 67% (weighted average, 51%) of our population presented at least one exclusion criterion, making them ineligible to be enrolled in randomized controlled trials. When restricting our population to patients with an indication for thromboprophylaxis based on a Padua risk score at admission ≥4, 21% to 76% (weighted average 55%) were ineligible to be enrolled in individual trials.
CONCLUSIONS: Our cross-sectional study illustrates that the external validity of randomized controlled trials cited in the guidelines was low in our population, and lower when applying the risk-stratification tool recommended by guidelines. This can bias the clinicians toward treating patients that were not represented in the supporting evidence.
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KEYWORDS: American College of Chest Physicians guidelines; Exclusion criteria; External validity; Medical hospitalized patients; Padua score; Pharmacological thromboprophylaxis; Risk scores

The 2012 American College of Chest Physicians (ACCP) guidelines recommended thromboprophylaxis for hospitalized medical patients at high risk for venous thromboembolism: "… *2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin, low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B)*…".[1] Use of the Padua score, a prediction score based on venous thromboembolism risk factors, is recommended by ACCP guidelines to stratify patients. High risk of bleeding is defined as a Padua score ≥4.[1,2] Assessment of bleeding risk and withholding of thromboprophylaxis in patients actively bleeding (or at high risk of bleeding) is also recommended.[1]

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The ACCP guidelines are based on the results of several randomized controlled trials. However, due to the stringent exclusion criteria of randomized controlled trials, the population included may not be representative of patients hospitalized on medical wards.[3] Furthermore, studies showing lack of clinical benefit[4] and increased risk of bleeding in certain patient populations, such as cancer patients[5] and the elderly,[6] have reopened the debate about the use of widespread thromboprophylaxis.

CLINICAL SIGNIFICANCE

- The American College of Chest Physician Clinical Care Guidelines for medical thromboprophylaxis are based on results of 9 randomized controlled trials.
- Prevalence of exclusion criteria from those trials in unselected medical inpatients ranges from 26% to 67%.
- Twenty-one percent of our population would have been excluded from all 9 trials, and only 25% included in all 9.
- External validity of trials for medical thromboprophylaxis is low for our population.

OBJECTIVE

The aim of this study was to evaluate the external validity of the randomized controlled trials cited in the ACCP guidelines for the use of pharmacological thromboprophylaxis in hospitalized medical patients. In other words, we sought to evaluate whether our patients were represented in the body of evidence from which clinical care guidelines were drawn.

METHODS

Following research ethics approval from the Centre de Recherche du Centre Hospitalier de l'Université de Montréal (a large teaching university hospital, Montreal, Canada), we conducted a targeted literature review and a cross-sectional study.

Targeted Literature Review

We identified all relevant randomized controlled trials from the ACCP guidelines and all meta-analyses comparing thromboprophylaxis with placebo in hospitalized medical patients. Because our focus is based on these patients, randomized controlled trials and meta-analyses of surgical patients, critically ill patients, or comparing different means of thromboprophylaxis were not included in our study. No attempt was made to identify the studies not included in guidelines.

Exclusion criteria were identified from every study. Similar criteria were merged. If additional precision was deemed necessary in order to define certain criteria, original study protocols were reviewed and authors were contacted. Trial sample sizes were also noted.

Cross-Sectional Study

Identification of hospitalized population: all patients admitted to our Internal Medicine teaching ward between July 1, 2013 and June 30, 2014 were identified. For each patient, only the first hospitalization during the study period was included. We used a computer-generated table of random numbers to select a random sample of patients in order to obtain a balanced number of them for each calendar month, to balance for seasonal and other variations in reasons for admission. We used a representative sample because we considered it sufficient to get an estimate of the prevalence of exclusion criteria from randomized controlled trials in our population. As this was an observational study, no formal sample size calculation was performed.

For each patient, the following data were extracted from electronic charts at admission: age, sex, active cancer, history of deep vein thrombosis, reduced mobility, thrombophilia, recent trauma or surgery, cardiac or respiratory failure, stroke, coronary artery disease, and other conditions necessary to calculate Padua risk score.[2] We also extracted use of thromboprophylaxis during hospital stay. Finally, for each patient, we noted the presence/absence of each exclusion criterion from previously identified studies. Following adoption of common definitions for each variable, data were extracted by SMB, AD, VN, JY, and XMS. Twenty files were reviewed collectively to ensure consistency prior to data extraction. Dissensions were resolved by discussion with ML and MD.

Outcomes

The primary outcome was the proportion of our population with exclusion criteria from the randomized controlled trials on which clinical care guidelines on thromboprophylaxis are based.

Statistical Analyses

Descriptive statistics were used to describe baseline characteristics of the hospitalized population.

For each patient, a binary variable was created for each of the studies' exclusion criteria. We calculated the proportion of our patients who would be excluded from each study. We then calculated a weighted average of exclusion from the total randomized controlled trial population (the sum of the 9 studies sample sizes), using study size as weights. This number gives the average prevalence of exclusion criteria from the overall trial population.

Then, the proportion of patients presenting each exclusion criterion was calculated. For each criterion, we also calculated the proportion of randomized controlled trials population to which that exclusion criterion applied, by dividing the number of patients included in trials with that