CLINICAL RESEARCH STUDY

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Lack of Evidence to Support Thromboprophylaxis in Hospitalized Medical Patients with Cancer

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ABSTRACT

BACKGROUND: The administration of anticoagulant thromboprophylaxis for all patients with cancer who are hospitalized for acute medical illness is considered standard practice and strongly recommended in clinical guidelines. These recommendations are extrapolated from randomized controlled prophylaxis trials not specifically conducted in cancer cohorts. Because hospitalized patients with cancer constitute a unique population with increased risk of venous thromboembolic events and major hemorrhage, validation of the efficacy and safety of primary thromboprophylaxis in this population is critical. We sought to summarize the rates of venous thromboembolic events and major bleeding episodes among hospitalized patients with cancer who were receiving anticoagulant therapy compared with placebo.

METHODS: A systematic literature search strategy was conducted using MEDLINE, EMBASE, and the Cochrane Register of Controlled Trials. Two reviewers independently extracted data onto standardized forms. The primary end points were all venous thromboembolic events. Secondary end points included major bleeding episodes and symptomatic venous thromboembolic events. Pooled analysis with relative risk using a random effect model was used as the primary measurement.

RESULTS: A total of 242 citations were identified by the literature search. Of these, 3 placebo-controlled randomized trials included venous thromboembolic events as a primary outcome and were analyzed according to cancer subgroups. The pooled relative risk of venous thromboembolic events was 0.91 (95% confidence interval, 0.21-4.0; I^2: 68%) among hospitalized patients with cancer who were receiving thromboprophylaxis compared with placebo. None of the trials reported the rates of symptomatic venous thromboembolic events or major bleeding episodes according to cancer status.

CONCLUSIONS: The risks and benefits of primary thromboprophylaxis with anticoagulant therapy in hospitalized patients with cancer are not known. This is especially relevant because numerous Medicare-type pay-for-performance incentives mandate prophylaxis specifically in patients with cancer.

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KEYWORDS: Cancer; Hospitalized patients; Major bleeding episodes; Thromboprophylaxis; Venous thromboembolism

Hospitalized patients with cancer are at increased risk of venous thromboembolism.[1] Current clinical practice guidelines from the American Society of Clinical Oncology, National Comprehensive Cancer Network, American College of Chest Physicians, and European Society of Medical Oncology all recommend the use of usual prophylactic doses of low molecular weight heparins for patients with cancer requiring hospitalization for acute medical illness in the absence of bleeding or other contraindications to anticoagulation.[2-5] These high-level recommendations are based

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on extrapolation from large placebo-controlled trials assessing the efficacy and safety of thromboprophylaxis in medically ill hospitalized patients.[6-8] However, the risk–benefit ratio of thromboprophylaxis in patients with cancer who are hospitalized with a medical illness has never been formally assessed. We conducted a systematic review and pooled analysis to evaluate the rates of venous thromboembolic events among medically ill hospitalized patients with cancer who were receiving low molecular weight heparin or placebo to formally assess the benefit of prophylaxis in this high-risk population.

CLINICAL SIGNIFICANCE

- No benefit was found for the use of primary thromboprophylaxis with anticoagulants to prevent venous thromboembolism in all patients with cancer who were hospitalized for medical illnesses.
- The safety of primary thromboprophylaxis in hospitalized medically ill patients with cancer is unknown because the rates of major bleeding episodes have never been reported.

MATERIALS AND METHODS

A systematic literature search strategy was conducted using MED LINE, EMBASE, the Cochrane Register of Controlled Trials, and all Evidence-Based Medicine Reviews to identify all randomized controlled trials comparing a low molecular weight heparin with placebo in hospitalized medically ill patients (Figure E1, online). References of included studies and narrative reviews were reviewed for additional potential studies. The protocol and systematic search strategy of the review are documented online (International Prospective Register of Systematic Reviews [PROSPERO] registry - CRD42012002845). The search was restricted to humans. There were no restrictions on language or publication year.

With the use of a structured question format to aid the literature search strategy, all abstracts were reviewed. Potentially relevant articles were reviewed in full length to ensure that they satisfied 3 criteria: (1) prospective enrollment of consecutive hospitalized medically ill patients; (2) patients were randomized to parenteral pharmacological thromboprophylaxis or placebo; (3) one or more of the primary or secondary outcomes were reported according to the cancer status.

The primary end point was venous thromboembolic events. Venous thromboembolic events were defined as a composite outcome of:

- deep vein thrombosis by protocol scheduled screening studies;
- symptomatic deep vein thrombosis (distal or proximal) or pulmonary embolism;
- fatal pulmonary embolism; or
- sudden death without another plausible cause.

Secondary end points included major bleeding episodes and symptomatic venous thromboembolic events (lower limb deep vein thrombosis and pulmonary embolism).

Two reviewers (MC and PM) independently assessed the eligibility of articles identified in the initial search strategy for inclusion in the review; discussed those deemed potentially eligible; independently extracted data (baseline characteristics, definition of outcomes, numbers of events) using a standardized data abstraction form; and assessed studies' methodological quality using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials.[9] Corresponding authors of articles were contacted if the primary or secondary outcomes could not be extracted from the original article.

Relative risk using a random effect model was used as the primary measurement with 95% confidence intervals. The I^2 statistic was used to estimate total variation among the pooled estimates across studies. An I^2 greater than 50% was considered as high level.[10] Analyses were performed using StatsDirect software version 2.7.3 (StatsDirect Ltd, Cheshire, UK).

RESULTS

A total of 242 citations were identified by the literature search, and 7 articles were deemed potentially eligible (Figure E2, online). Of these, 3 placebo-controlled randomized trials included venous thromboembolic events as a primary outcome and were analyzed according to cancer subgroups.[6-8] The baseline characteristics of the included studies are depicted in **Table 1**. None of the studies reported a definition for cancer status. These 3 major trials included 307 cancer patients out of 5134 total study subjects (6%) and compared thromboprophylaxis (enoxaparin 40 mg, dalteparin 5000 IU, or fondaparinux 2.5 mg daily) with placebo.[11-13] The pooled relative risk of venous thromboembolic events was 0.91 (95% confidence interval, 0.21-4.0; I^2: 68%) among hospitalized patients with cancer who were receiving thromboprophylaxis compared with placebo (**Figure 1**). None of the trials reported the rates of major bleeding episodes according to the cancer status. An additional 4 placebo-controlled randomized trials reported symptomatic venous thromboembolic events as a secondary end point.[14-17] However, none of the trials reported the rates of symptomatic venous thromboembolic events or major bleeding episodes according to cancer status, and cancer-specific venous thromboembolic events rates for analysis were not made available by the primary authors or primary funding sources.

The study quality of the included randomized controlled trials was adequate. All randomized controlled trials reported adequate sequence generation, allocation concealment, blinding, and outcome reporting. Only 1 of the trials[7,18] had a study protocol available, but all expected outcomes were reported for all other studies.