CHEST

Direct Oral Anticoagulants in Patients With VTE and Cancer

A Systematic Review and Meta-analysis

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BACKGROUND: Direct oral anticoagulants (DOAs) have been shown to be as effective and at least as safe as conventional anticoagulation for the prevention of recurrences in patients with VTE. Whether this is the case in patients with cancer-associated VTE remains undefined.

METHODS: We performed a meta-analysis of randomized controlled trials with the aim of assessing the efficacy and safety of DOAs in patients with VTE and cancer. MEDLINE, EMBASE, and CENTRAL were searched up to December 2013 with no language restriction. The primary outcome of the analysis was recurrent VTE. Data on major bleeding (MB) and clinically relevant nonmajor bleeding were analyzed. Data were pooled and compared by ORs and 95% CIs.

RESULTS: Overall, 10 studies comparing DOAs with conventional anticoagulation for treatment of VTE including patients with cancer were included in the review. Six studies were included in the meta-analysis (two with dabigatran, two with rivaroxaban, one with edoxaban, and one with apixaban), accounting for a total of 1,132 patients. VTE recurred in 23 of 595 (3.9%) and in 32 of 537 (6.0%) patients with cancer treated with DOAs and conventional treatment, respectively (OR, 0.63; 95% CI, 0.37-1.10; I^2, 0%). MB occurred in 3.2% and 4.2% of patients receiving DOAs and conventional treatment, respectively (OR, 0.77; 95% CI, 0.41-1.44; I^2, 0%).

CONCLUSIONS: DOAs seem to be as effective and safe as conventional treatment for the prevention of VTE in patients with cancer. Further clinical trials in patients with cancer-associated VTE should be performed to confirm these results. CHEST 2015; 147(2):475-483

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ABBREVIATIONS: CLOT = Comparison of Low-Molecular-Weight Heparin vs Oral Anticoagulant Therapy for Long-Term Anticoagulation in Cancer Patients With Venous Thromboembolism; DOA = direct oral anticoagulant; LMWH = low-molecular-weight heparin; RCT = randomized clinical trial; TTR = time in therapeutic range

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Patients with malignancy have a fourfold to sevenfold greater risk of VTE when compared with patients without cancer.[1,2] The risk for recurrent VTE while on anticoagulant treatment is particularly high in patients with cancer, as it is the cause of bleeding complications.[3-5] Low-molecular-weight heparins (LMWHs) have been shown to be more effective than and as safe as conventional anticoagulation with initial LMWH followed by vitamin K antagonists.[6-9] Thus, LMWHs are currently recommended over anticoagulation with vitamin K antagonists for the treatment of VTE in patients with cancer.[10]

A risk for recurrence as high as 15% per year once anticoagulation treatment is withdrawn[10] candidate patients with cancer-associated VTE to indefinite anticoagulation treatment. Thus, extended anticoagulant therapy beyond 3 months (and until cancer is cured) is recommended in these patients; extended treatment is suggested even in case of high bleeding risk.[10] Consistent recommendations have been released by the different guidelines.[11-14]

Practical issues regarding the long-term use of LMWH include the cost of the drug, the feasibility of long-term parenteral therapy, quality of life, and also the lack of evidence of their efficacy and safety when given indefinitely.

New direct anti-Xa and anti-IIa oral anticoagulants with no recommended need for laboratory monitoring or dose adjustment have been shown in trials to be as effective as and probably safer than conventional anticoagulation for the treatment of VTE.[15-21] Their predictable response, oral administration, and fixed-dose regimens make direct oral anticoagulants (DOAs) attractive for the treatment of VTE in patients with cancer. However, only a minor proportion of patients with cancer (about 5%) was included in each of these trials. Thus, whether the results of phase 3 trials also apply to the general population of patients with cancer remains undefined. We performed a systematic review and a meta-analysis to assess the efficacy and safety of DOAs in patients with VTE and cancer.

Materials and Methods

Data Sources and Searches

A protocol for this review was prospectively developed detailing the specific objectives; criteria for study selection; approach to assess study quality, outcomes, and statistical methods. We performed an unrestricted search in MEDLINE, EMBASE, and CENTRAL through December 17, 2013. The search strategy is reported in e-Table 1. No language restrictions were applied. Reference lists of retrieved articles and review articles were manually searched for other relevant studies. The term ximelagatran was excluded from the search because this drug was withdrawn from clinical use.

Study Selection

Two reviewers (M. C. V. and F. G.) performed study selection independently, with disagreements resolved through discussion and the opinion of a third reviewer (C. B.). Studies were considered potentially eligible for this systematic review if they met the following predetermined criteria: (1) they were phase 3 randomized clinical trials (RCTs) or phase 2 RCTs; (2) DOAs were compared with therapeutic doses of vitamin K antagonists in patients with VTE; (3) patients defined as having "active cancer" were included; and (4) VTE recurrences and bleeding events were objectively assessed in both groups. Phase 2 RCTs were eligible for inclusion if at least one of the evaluated dosages was subsequently used in phase 3 trials. Studies could be included in the meta-analysis if the following data were available: number of patients with and without study outcomes (VTE recurrences and bleedings) among patients with cancer receiving DOAs and among those receiving conventional treatment (heparin followed by vitamin K antagonists). For duplicate publications, the most complete was considered. To assess agreement between reviewers for study selection, we used the κ statistic, which measures agreement beyond chance.[22]

Data Extraction and Quality Assessment

Data were extracted and presented according to the Providing Innovative Service Models and Assessment (PRISMA) criteria.[23] For each study, the following data were extracted independently by two authors (M. C. V. and F. G.): general data (study design, year of publication), population characteristics (number, mean age, sex), and treatment (therapeutic indication, type of drug, dose, duration). Information on the following outcomes was collected for the two treatment groups where available: number of VTE recurrences, mortality, and major and clinically relevant nonmajor bleedings. Outcomes were reported as defined in the individual studies.

Study quality was assessed by two reviewers (M. C. V. and F. G.) using the Cochrane Collaboration's tool to assess risk of bias in randomized trials, which covers the following bias domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias.[24] High quality was defined when at least six of the seven criteria within these bias domains were satisfied. We resolved disagreements about study data extraction and quality assessment by consensus or by discussion with a third reviewer (C. B.).

Statistical Analysis

We determined pooled ORs and 95% CIs for VTE recurrences in patients with cancer who received heparin followed by vitamin K antagonists or treatment with a DOA. Furthermore, the pooled ORs of VTE recurrence and major or clinically relevant nonmajor bleeding (clinically relevant bleeding) in the two treatment arms were calculated.

Data were pooled by using the Mantel-Haenszel method[25]; we reported results according to a fixed-effects model in the absence of significant heterogeneity and to a random-effects model in the presence of significant heterogeneity.[26] We used the random effects model because it accounts for variations between studies in addition to sampling error within studies. The appropriateness of pooling data across studies was assessed using the Cochran χ^2 test and the I^2 test for heterogeneity, which measure the inconsistency across the study results and describe the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error.[26,27] Statistically significant heterogeneity was considered to be present when $P < .10$ and $I^2 > 50\%$. Funnel plots were used to assess for publication bias.[25]

We planned to perform separate analyses of study period (6 months and 12 months), studies including study drug (new anti-Xa and