The diagnostic and therapeutic management of pulmonary embolism

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CHAPTER 10

Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism

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ABSTRACT

Introduction

Treatment of acute venous thromboembolism (VTE) in cancer patients is challenging, owing to a high risk of recurrent VTE and bleeding complications. The anticoagulants of choice are low molecular weight heparins (LMWH), because of a proven higher efficacy than vitamin K antagonists (VKA) and a similar bleeding profile. The recently introduced new oral anticoagulants (NOAC) have the potential to be alternative options for these patients, as these drugs share practical advantages with LMWH, are administered orally, and had similar efficacy to VKA but a lower bleeding risk in phase 3 studies in the general VTE population.

Methods

A systematic literature search was performed to identify phase 3 trials investigating NOAC for the treatment of VTE. The efficacy outcome was recurrent VTE, and the safety outcome was major and clinically relevant non-major bleeding. Pooled incidence rates and risk ratios (RR) were calculated for cancer patients and non-cancer patients separately.

Results and discussion

Five studies were included, with 19 060 patients, of whom 973 (5.1%) had active cancer. The pooled incidence rates of recurrent VTE were 4.1% (95% confidence interval [CI] 2.6–6.0) in cancer patients treated with NOAC, and 6.1%(95% CI 4.1–8.5) in patients treated with VKA (RR 0.66,95% CI 0.38–1.2). The pooled incidence rates of major or non-major clinically relevant bleeding were 15%(95% CI 12–18) in cancer patients treated with NOAC, and 16% (95% CI 9.9–22) in patients treated with VKA (RR 0.94, 95% CI 0.70–1.3). These results form a solid basis for the initiation of a head-to-head comparison of NOAC with LMWH in cancer patients.

INTRODUCTION

Symptomatic acute venous thromboembolism (VTE) is a common complication in cancer patients, occurring in up to 15% of cancer patients during the course of their disease, and it is the second leading cause of death after the malignancy itself [1,2]. Anticoagulant treatment for acute VTE in cancer patients is complicated by both high risks of recurrent VTE and bleeding complications [3]. Hence, alternative treatment modalities are particularly interesting for this patient category.

In recent years, new oral anticoagulants (NOAC) have been developed, including direct factor IIa inhibitors (i.e. dabigatran) and direct FXa inhibitors (i.e. apixaban, edoxaban, and rivaroxaban), for which similar efficacy to that of vitamin K antagonists (VKA) and a superior safety profile have been reported for the treatment of patients with acute VTE [4–9]. A recent meta-analysis of phase 3 randomized controlled trials (RCT) comparing NOAC with VKA for the initial treatment of acute VTE demonstrated that the incidence of major bleeding (pooled risk ratio [RR] 0.60, 95% confidence interval [CI] 0.41–0.88) and of the combined endpoint of major bleeding and clinically relevant non-major bleeding (pooled RR 0.76, 95% CI 0.58–0.99) were significantly lower for patients treated with one of the NOACs, whereas the risk of recurrent VTE was similar (pooled RR 0.88, 95% CI 0.74 –1.1) [10].

The efficacy and safety of NOAC in patients with cancer-associated VTE have not been specifically addressed so far, although these drugs would constitute an interesting option for this specific patient group, for several reasons. First, the improved safety profile of NOAC may be of particular relevance, owing to the higher anticoagulation-associated bleeding risk observed in cancer patients [3]. This is made even more relevant by the fact that current guidelines recommend continuation of anticoagulant therapy for as long as the cancer is active and the bleeding risk remains acceptable. As a result, patients are exposed to a high risk of bleeding complications for periods ranging from 6 months to many years [11,12]. Second, low molecular weight heparins (LMWH) are the current preferred anticoagulants for cancer-associated VTE, because of their superior efficacy in preventing VTE recurrences, and a similar bleeding profile to that associated with VKA. However, these drugs confront patients with the burden of daily subcutaneous administration [13,14]. For some patients, this may be the reason for asking for VKA. Hence, if shown to be equally effective and safe or even safer, NOAC would have clear advantages over LMWH. Undoubtedly, clinicians will be faced with the choice of whether to use NOAC in cancer patients in the near future. In order to address the lack of any data on the efficacy and safety of NOAC for cancer-associated VTE, we performed a systematic review of the literature, and pooled relevant data in a meta-analysis.

METHODS

We systematically searched MEDLINE (via PubMed), EMBASE, the Cochrane Database of Systematic Reviews and the clinical trials registry from inception to May 2014 to identify randomized controlled trials comparing a NOAC with a VKA or a LMWH in patients with acute VTE, using a similar approach as in a recent meta-analysis [10]. From all identified studies, we included only those in whom outcomes for patients with active cancer were reported separately in the original publication, supplementary information, or related publications. In all included studies, the analysis specifically for cancer patients was a predefined subgroup analysis. If separate results for cancer patients were not available, we requested the pharmaceutical companies for additional information. The primary efficacy outcome of the current study was recurrent VTE, and the safety outcome was major bleeding or clinically relevant non-major bleeding while patients were receiving anticoagulant treatment. Two independent researchers performed the study selection and data abstraction. The quality of the studies was assessed with the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [15]. The only potential risk of bias identified was the open label design with blinded endpoint evaluation of the Einstein studies [10]. Incidence rates were pooled by the use of DerSimonian-Laird weights for the random effects model. RR with concomitant 95% CI were calculated with the Mantel–Haenszel random effects model, through REVIEW MANAGER (V. 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Assessment of heterogeneity was performed by calculation of the I^2 statistic.

RESULTS AND DISCUSSION

We identified six potentially relevant studies [4-9], all comparing NOAC with VKA. Separate outcomes for patients with active cancer were reported for all studies except for the Amplify study, in which apixaban was investigated [9]. We asked the manufacturer for additional information, but this was not provided (the search strategy and flow chart are provided in Data S1 and Data S2 available at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/). For the Re-Cover I and II studies, safety outcomes for cancer patients were only mentioned separately in an abstract presented at the Annual Meeting of the American Society of Hematology in 2013 [16]. Hence, we were able to include five studies, among which the results of the Re-Cover I and II studies are presented in combination.

The characteristics of the included RCT have been described in detail previously [4–10]. All studies compared a NOAC at a standard dosage with VKA treatment with a target International Normalized Ratio between 2.0 and 3.0. In total, the studies included 19 060

patients, of whom 973 (5.1%) had active cancer. Across the individual studies, the percentage of patients with an active malignancy ranged from 2.5% to 6.6%. Of the patients with active cancer, 514 (53%) were treated with a NOAC and 459 (47%) with a VKA.

The incidence rates of recurrent VTE in cancer patients treated with a NOAC varied from 1.8% to 5.8%, and those in cancer patients treated with a VKA varied from2.8% to 7.4% (**Table 1**). The pooled incidence rates were 4.1% (95% CI 2.6–6.0) for NOAC and 6.1% (95% CI 4.1–8.5) for VKA, with a non-significant pooled RR of 0.66 (95% CI 0.38–1.2) in favor of NOAC (**Figure 1**). For patients without active cancer, the recurrent VTE incidence rate varied from 2.0% to 3.0% in patients treated with NOAC, and from 1.8% to 3.5% in patients treated with VKA. The pooled incidence rates were 2.6% (95% CI 2.3–2.9) and 2.5% (95% CI 1.8–3.4) for NOAC and VKA, respectively, with a pooled RR of 0.98 (95% CI 0.83–1.2).

Table 1. The risk of recurrent venous thromboembolism and major bleeding in cancer patients and non-cancer patients separately.

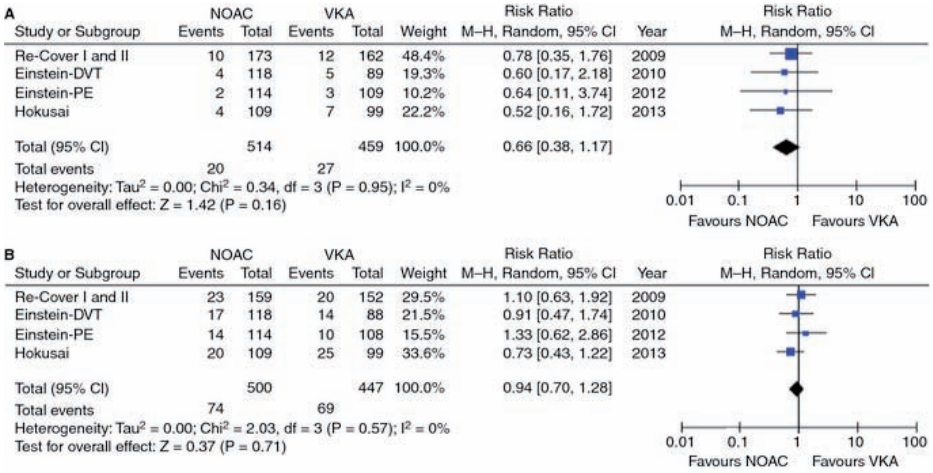
Study drug	Active cancer (%)	Recurrent VTE		Major bleeding and clinically relevant non-major bleeding	
		NOAC, no. (%)	VKA, no. (%)	NOAC, no. (%)	VKA, no. (%)
Dabigatran, Re-Cover I and II [16]	No (93.4)	58/2380 (2.4)	50/2392 (2.1)	86/2297 (3.7)	169/2310 (7.3)
	Yes (6.6)	10/173 (5.8)	12/162 (7.4)	23/159 (14.5)	20/152 (13.2)
Rivaroxaban, Einstein-DVT [6]	No (94.0)	32/1613 (2.0)	46/1629 (2.8)	122/1600 (7.6)	124/1623 (7.6)
	Yes (6.0)	4/118 (3.4)	5/89 (5.6)	17/118 (14.4)	14/88 (15.9)
Rivaroxaban, Einstein-PE [7]	No (95.4)	48/2305 (2.1)	41/2304 (1.8)	235/2298 (10.2)	264/2297 (11.5)
	Yes (4.6)	2/114 (1.8)	3/109 (2.8)	14/114 (12.3)	10/108 (9.3)
Edoxaban, Hokusai-VTE [8]	No (97.5)	126/4009 (3.1)	139/4023 (3.5)	329/3740 (8.1)	398/4023 (9.9)
	Yes (2.5)	4/109 (3.7)	7/99 (7.1)	20/109 (18.3)	25/99 (25.3)

Note: NOAC, new oral anticoagulant; VKA, vitamin K antagonist.

The incidence rate of the combined endpoint of major bleeding and clinically relevant non-major bleeding varied from 12% to 18% in cancer patients treated with NOAC, and from 9.9% to 25% in cancer patients treated with VKA. Pooled incidence rates were 15% (95% CI 12–18) and 16% (95% CI 9.9–22), respectively, and the corresponding RR was 0.94 (95% CI 0.70–1.3) (**Figure 1**). In non-cancer patients, the incidence rate of major bleeding and clinically relevant non-major bleeding varied from 3.7% to 10% in patients treated with NOAC, and from 7.3% to 11% in patients treated with VKA. Pooled incidence rates were 7.4% (95% CI 4.8–11) and 9.1% (95% CI 7.3–11), with an RR of 0.81% (95% CI 0.64–1.02) in favor of NOAC. The I^2 of all evaluated efficacy and safety outcomes was 0%, indicating low heterogeneity.

In summary, the most important results of this study are the RR of 0.66 (95% CI 0.38–1.2) for recurrent VTE and 0.94 (95% CI 0.70–1.3) for major bleeding and clinically relevant

Figure 1. Meta-analysis.
Risk ratios of recurrent venous thromboembolism (A) and major bleeding and clinically relevant non-major bleeding (B) in cancer patients with acute VTE.



Note: CI, confidence interval; d.f., degrees of freedom; M–H, Mantel–Haenszel; NOAC, New oral anticoagulant; VKA, vitamin K antagonist.

non-major bleeding, indicating that both the efficacy and safety of NOAC in cancer patients were at least comparable to those of VKA. These results require comment, and some of them should be interpreted with caution. First, none of the included studies gave a detailed definition of 'active cancer'. Only in the abstract of the Re-Cover studies was a definition given: 'a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment; any treatment for cancer within 5 years before enrolment; or recurrent or metastatic cancer'; the more generally used standard definition is 'a diagnosis of cancer within 6 months prior to enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer' [13,14]. This specific definition and the use of certain exclusion criteria in the trials (e.g. 'a limited life-expectancy' and 'a high bleeding risk') suggest that the cancer patients in the studies were relatively healthy, and do not compare well with those in previous trials, which were specifically designed for patients with acute VTE and active cancer [17]. This is further emphasized by the observed VTE recurrence risk of 6.1% in cancer patients treated with VKA in the NOAC studies, which is considerably lower than the 16% and 17% reported in two previous studies specifically performed in a population with active cancer [13,14].

Second, NOAC were compared only with VKA in the available studies, whereas LMWH constitute the current treatment of choice for cancer-associated acute VTE [11,12]. Hence, NOAC should preferably be compared with LMWH to investigate their efficacy and safety in patients with cancer-associated VTE. In a Cochrane meta-analysis, it was

demonstrated that LMWH have a similar safety profile to VKA (RR for major bleeding of 1.05, 95% CI 0.53–2.1), with higher efficacy in preventing recurrent VTE (RR 0.47, 95% CI 0.32–0.71) [17]. Interestingly, and supportive for future trials, the RR for NOAC as compared with VKA in our meta-analysis show the same trend. A lack of power (973 patients in our meta-analysis vs. 1325 patients in the Cochrane meta-analysis) might be the cause of statistical significance not being reached for the efficacy outcome.

Third, whereas previous studies have demonstrated non-inferior safety of LMWH as compared with VKA with regard to the risk of major bleeding, only the numbers for the combined endpoint of major and clinically relevant non-major bleeding were available for NOAC. Major bleeds in cancer patients were not separately reported. Also, the number of VTE recurrences in the studies was too low for comparison of the severity of these events, i.e. risk of fatal pulmonary embolism or risk of recurrent deep vein thrombosis versus recurrent acute pulmonary embolism.

Fourth, NOAC share many of the advantages of LMWH over VKA, such as the lack of the need for monitoring of anticoagulant effect and the shorter half-life, which facilitates temporary interruptions for invasive procedures or when thrombocytopenia occurs [18]. On the other hand, the oral administration might raise concerns in cancer patients about gastrointestinal tract absorption during episodes of vomiting or mucositis. A potential additional disadvantage of NOAC is the existence of drug interactions with several chemotherapeutic agents and drugs used for supportive care through the CYP3A4 enzyme and/or P-glycoprotein transporter, although the clinical implications of these interactions are not yet known. However, drug interactions also exist for VKA and several chemotherapeutic agents. Capecitabine, for instance, may enhance the anticoagulant effect of VKA, and thereby increase the risk of major bleeds [19].

A final concern is the current unavailability of specific antidotes for NOAC, which may be problematic in cases of severe life-threatening major bleeding or emergent invasive procedures. It is acknowledged that antidotes are under development, and phase 3 trials with antidotes are currently being planned [20,21].

In conclusion, we have demonstrated that both the efficacy and safety of NOAC in the treatment of cancer-associated acute symptomatic VTE are at least comparable to those of VKA. This suggests that, for cancer patients without major bleeding risks, the use of NOAC is not contraindicated. However, the current NOAC trials in VTE management were clearly not designed to provide definite conclusions on the efficacy and safety of NOAC in cancer patients, relative to LMWH. Because of the lack of a direct comparison with LMWH with selective inclusion of cancer patients only, NOAC cannot yet be recommended as the first-line treatment for VTE in cancer patients. Nonetheless, our results strongly support the initiation of a head-to-head comparison of NOAC with LMWH in the near future.

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