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LMWH in cancer patients with renal impairment – better than warfarin?

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KEYWORDS

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ABSTRACT

Venous thromboembolism (VTE) is one of the leading causes of death in cancer patients, which are known to have a 5- to 7-fold increased risk for VTE. The anticoagulant treatment of VTE in cancer patients is less effective with a three-fold increased risk of VTE recurrence compared to non-cancer patients, and it is less safe with more than double rates of major bleeding. Compared to vitamin-K antagonists (VKA), long-term secondary prevention with low molecular weight heparin (LMWH) has been shown to reduce the risk of recurrent VTE in cancer-associated thrombosis (CAT), and therefore, current international guidelines recommend the use of LMWH over VKA. With increasing age, cancer prevalence and VTE incidence increase while renal function decreases. Anti-cancer treatment may impair renal function additionally. Therefore, renal insufficiency is a frequent challenge in CAT patients, which is associated with a higher risk of both bleeding and recurrent VTE. Both VKA and LMWH may be associated with less efficacy and higher bleeding risk in renal insufficiency. Unfortunately, there is a lack of prospective data on renal insufficiency and CAT. A recent sub-analysis from a large randomized controlled trial shows that the bleeding risk in patients with severe renal insufficiency in CAT is not elevated with the use of LMWH compared to VKA while efficacy is maintained. In addition, LMWH treatment has several practical advantages over VKA, particularly in patients with CAT while they are receiving anti-cancer treatment.

Introduction

Cancer and venous thromboembolism (VTE) exhibit a two-way clinical association [1]: Cancer patients have a 5-7 fold increased risk of VTE compared to non-cancer patients [2-4], with incidence rates for VTE ranging from 0,5 to 20%, depending on cancer type, stage and time since diagnosis [5]; overall prevalance of VTE in cancer has been reported to range from 4 to 20% [6]. On the other side, about 20% of VTE-patients have an underlying malignancy [7] and up to 10% of patients with unprovoked VTE receive a diagnosis of cancer in the following year.

The risk of VTE increases with age (approximately 15–20% per decade) (Figure 1A) [8], and thus it is important to note that 70% of all patients treated for VTE are beyond the age of 60 years [9]. This is particularly important, because the prevalence of cancer is also strongly age-dependent (Figure 1 B) [10]. From these inter-relations it becomes evident that there is an overrepresentation of higher age in cancer associated thrombosis (CAT).

Treatment of cancer associated thrombosis

The standard maintenance treatment with vitamin K antagonists (VKA) is less effective in the treatment of established VTE in cancer patients and is associated with a one year VTE recurrence rate of over 20% versus 6.8% in patients without cancer (hazard ratio 3.2) [11], but VKA are also associated with a more than doubling of the rate of major bleeding [11]. Again, recurrence and bleeding rates are related to cancer severity. In accordance with these findings, a recent population-based case-cohort study found an up to 4-fold increase in VTE recurrence, depending on the stage of cancer [12]. In the RIETE registry [13] cancer patients had an odds ratio of 2.0 for fatal PE in the 3-months clinical outcome compared to non-cancer patients, and odds ratios of 2.7 for recurrent VTE and 2.9 for fatal bleeding, 2.6 for major bleeding and 6.2 for overall death, respectively.

In an attempt to reduce the high recurrence rate observed in cancer patients with VTE treated with VKA, several studies were performed to use long-term low molecular weight heparin (LMWH) instead of VKA as secondary prevention for a time period of 3 to 6 months [14-17]. These trials and meta-analyses [18] consistently show that LMWH compared to VKA reduce venous thromboembolic events, without increasing the risk of bleeding. Current international guidelines therefore recommend LMWH over VKA for the secondary prevention of VTE in patients with active cancer [19,20].

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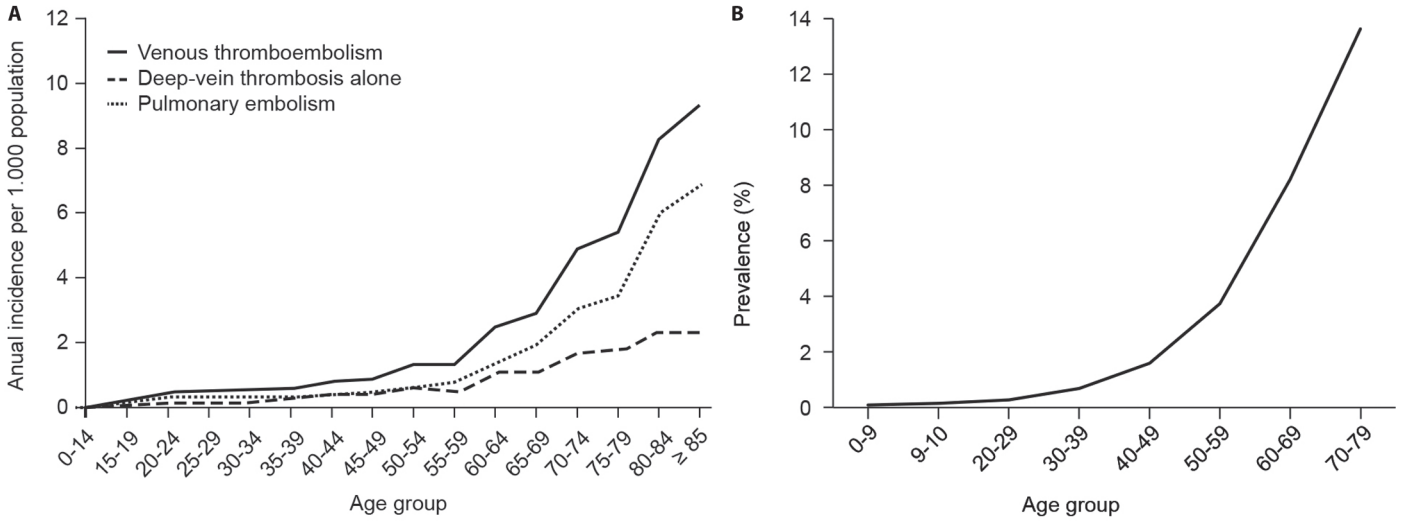

Fig. 1. A Age-dependent incidence of venous thromboembolism, deep vein thrombosis and pulmonary embolism. Modified from [8]. **B** Age-dependent prevalence of cancer in the United States. Modified from [10].

Renal function, age and cancer

Renal function continuously decreases with increasing age, and following the epidemiologic associations mentioned above, a high percentage of the patients with cancer and VTE is expected exhibit renal insufficiency [21]. In a large French observational study including nearly 5,000 patients with solid tumors, 16.6% were found to have a creatinine clearance (CrCl) below 60 mL per minute according to the Cockcroft-Gault formula, and 60.3% had a creatinine clearance below 90 mL per minute, respectively [22].

The Belgian Renal Insufficiency and Anticancer Medications (BIRMA) study [23] investigated the prevalence of renal insufficiency in cancer patients, and the profile and dosing of anticancer drugs prescribed. According to the abbreviated Modification of Diet in Renal Disease formula (aMDRD-GFR) out of 1,218 cancer patients, only 29.4% had a GFR above 90 mL per minute, 47.9% had a GFR of 89-60 mL per minute, 14.9% had 59-30 mL per minute and 0.9% had a GFR of 29-15 mL per minute and 0,3% below 15 mL per minute, respectively [23]. The impact of chemotherapy on renal function impairment was illustrated by the observation that 40.4% of the chemotherapy-naive patients had a normal renal function, i.e. a GFR above 90 mL per minute, compared with only 25.8% of the patients after chemotherapy. An example of the age-dependent deterioration of renal function with age in a large cohort of oncologic patients is depicted in Figure 2.

Renal function and anticoagulant drugs

Renal impairment alters binding to plasma proteins, volume of distribution and non-renal clearance of many drugs, leading to toxicity or ineffective therapy [24]. Although warfarin is a hepatically cleared drug, renal impairment may alter warfarin metabolism because of down-regulation of hepatic enzymes responsible for metabolism [24]. Thus, patients with renal impairment may require more frequent monitoring to ensure therapeutic anticoagulation with warfarin [25]. Chronic renal insufficiency, characterised by a progressive loss of renal function, is associated with decreased warfarin maintenance doses and decreased anticoagulation stability [34]. Warfarin dose adjustments are required almost twice as frequently in patients with CKD compared with patients with normal renal function (22% vs 12% of visits, respectively), and time in therapeutic INR range (TTR) is significantly lower in these patients (62% vs 74%, respectively) [26]. Patients with renal insufficiency are four times more likely to be over-anticoagulated (INR >4.0), with a higher risk in patients with severe (GFR <30 mL/min) compared with moderate (GFR 30–59 mL/min) renal insufficiency, increasing the possibility of haemorrhage [25,26]. The incidence of minor and major bleeding events is significantly increased in patients with severe renal insufficiency compared with patients with moderate renal insufficiency and those with normal renal function [25].

LMWHs are excreted renally [27]. Patients with renal impairment may experience bioaccumulation as a result of reduced renal clearance, the extent of which depends on the LMWH used and proportion of the drug cleared renally [28]. This may cause excessive anticoagulation, leading to an increased bleeding risk with standard LMWH doses [29]. A meta-analysis of 18 randomised studies showed that 5% of patients with severe renal impairment (CrCl <30 mL per minute) receiving anticoagulation for VTE experience major bleeding events compared with 2.4% of patients with CrCl ≥30 mL per minute [30].

Renal function and cancer associated thrombosis

Renal impairment has a profound impact on the management and complications of venous thromboembolism. Numerous clinical studies, as well as data from the prospective RIETE registry [31] indicate that VTE treatment in patients with renal impairment and also in patients at higher age and/or low body weight is associated with a higher bleeding risk. The treatment of renally impaired patients presenting with VTE is particularly complicated, because of the increase in fatal bleeding and fatal PE while they are receiving anticoagulant treatment [32,33].

Data from registries

Cancer patients with impaired renal function receiving treatment for VTE have an additional risk for VTE recurrence and bleeding: In the RIETE registry [13], 2,945 patients cancer and VTE were compared to 11,446 VTE-patients without cancer. Cancer patients with impaired renal function, defined as a serum creatinine above 1.2 mg/dL had an odds ratio of 2.6 for suffering a fatal PE and an odds ratio of 2.8 for suffering fatal bleeding. In the multivariate analysis, other significant risk factors for fatal PE were recent major bleeding (OR 2.8), Immobility of 4 or more days (OR1.9), prior symptomatic PE (OR13.9) and metastatic cancer (OR 2.9), respectively. Beside renal impairment, other risk factors for suffering a fatal bleeding event were body weight below 60 kg (OR 2.5), recent major bleeding (3.0, p=0.058), immobility of 4 or more days (OR 4.1) and metastatic