Heparin based prophylaxis to prevent venous thromboembolic events and death in patients with cancer - a subgroup analysis of CERTIFY

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Abstract

**Background:** Patients with cancer have an increased risk of VTE. We compared VTE rates and bleeding complications in 1) cancer patients receiving LMWH or UFH and 2) patients with or without cancer.

**Methods:** Acutely-ill, non-surgical patients ≥70 years with (n = 274) or without cancer (n = 2,965) received certoparin 3,000 UaXa o.d. or UFH 5,000 IU t.i.d. for 8-20 days.

**Results:** 1) Thromboembolic events in cancer patients (proximal DVT, symptomatic non-fatal PE and VTE-related death) occurred at 4.50% with certoparin and 6.03% with UFH (OR 0.73; 95% CI 0.23-2.39). Major bleeding was comparable and minor bleedings (0.75 vs. 5.67%) were nominally less frequent. 7.5% of certoparin and 12.8% of UFH treated patients experienced serious adverse events. 2) Thromboembolic event rates were comparable in patients with or without cancer (5.29 vs. 4.13%) as were bleeding complications. All cause death was increased in cancer (OR 2.68; 95%CI 1.22-5.86). 10.2% of patients with and 5.81% of those without cancer experienced serious adverse events (OR 1.85; 95% CI 1.21-2.81).

**Conclusions:** Certoparin 3,000 UaXa o.d. and 5,000 IU UFH t.i.d. were equally effective and safe with respect to bleeding complications in patients with or without cancer receiving adequate anticoagulation.

**Trial Registration:** clinicaltrials.gov, NCT00451412

Background

Patients with cancer have a sixfold increased risk of venous thromboembolism (VTE) compared to those without [1,2], and active cancer accounts for about 20% of all new VTE events occurring in the community [3]. The prevention of VTE in patients with cancer is important, not only because cancer patients have a particularly high risk for VTE, but also because treatment of VTE may be less effective, associated with more bleeding complications and associated with a significant reduction in survival [4-9].

Given the known increased risk of VTE in hospitalized patients with cancer, current guidelines [10-13] recommend risk-stratified thromboprophylaxis for cancer patients at hospital admission with either unfractionated heparins (UFH), low molecular weight heparins (LMWH) or Fondaparinux. Both the European Society for Medical Oncology (ESMO) [14] and the Association of the Scientific Medical Societies (AWMF) in Germany [11] recommend prophylaxis for hospitalized patients with cancer. While ESMO equally recommends LMWH, UFH and Fondaparinux, the German guideline prefers LMWH over the other options based on extrapolations from three placebo controlled randomized trials with LMWH, in which between 5 and 15% of patients had cancer at baseline [11,15-18]. Beyond these data there are randomized controlled trials in cancer patients [19-22] which have demonstrated a prolongation of overall survival with the addition of LMWH, even in patients with advanced disease, but neither rates of VTE
nor bleeding complications differed between groups [23]. The German guidelines state that additional studies are needed to resolve this controversy and to clarify which anticoagulant regimes are most likely to be beneficial [10].

To further explore this issue we did a post-hoc analysis of the CERTIFY trial on patients with a diagnosis of co-morbid cancer. Patients had been randomized to receive either 3,000 U anti-Xa OD certoparin (Mono-embolex®, Novartis Pharma GmbH, Nürnberg, Germany) or 5,000 IU UFH t.i.d. for the prophylaxis of venous thromboembolism in acutely ill, non-surgical patients aged ≥70 years. We aimed to compare VTE risk and bleeding complications in 1) patients with cancer receiving either LMWH or UFH and 2) patients with or without cancer.

Methods
We performed a post-hoc subgroup analysis of CERTIFY trial on patients with a diagnosis of co-morbid cancer. Patients had been randomized to receive either 3,000 U anti-Xa OD certoparin (Mono-embolex®, Novartis Pharma GmbH, Nürnberg, Germany) or 5,000 IU UFH t.i.d. (Liquemin® N 5000, Hoffmann-LaRoche AG, Grenzach-Wyhlen, Germany) in a double-blind fashion [24,25]. The protocol was approved by the ethics committee of Berlin (Landesamt für Gesundheit und Soziales Berlin) and confirmed by local institutional review boards as required by local regulations. All patients provided written informed consent.

Exclusion criteria for CERTIFY were immobilization longer than three days prior to randomization; immobilization due to cast or fracture; expected major surgical or invasive procedure within three weeks following randomization; patients with severe sepsis or need for ventilatory support (permitted were continuous positive airway pressure, oxygen mask etc.); LMWH or UFH longer than 48 hours in the five days prior to randomization; indication for anticoagulation or thrombolysis; life expectancy less than six months or illness with very high acute mortality (>30%); acute symptomatic DVT/PE; acute or history of heparin induced thrombocytopenia type II (HIT-II); acute or history of non-hemorrhagic stroke (<3 months); hemorrhagic stroke or intracranial bleeding (<12 months); acute or ongoing intracranial disease; high risk of gastrointestinal bleeding; spinal or epidural anesthesia, lumbar punction within the last twelve hours; uncontrolled hypertension; severe liver or renal disease; acute endocarditis; known active retinopathy, intravitreal or other intraocular bleeding.

Endpoints
The primary efficacy measure for the present analysis, as for the overall CERTIFY study, was the combined incidence of proximal DVT, symptomatic non-fatal PE and VTE related death occurring during the core study (covering the treatment period of 8-20 days after which compression ultrasound sonography was performed). All endpoints were adjudicated by a blinded expert committee. Secondary efficacy measures included each of the components of the primary efficacy measure, the incidence of distal DVT (alone and in combination with proximal DVT), the incidence of symptomatic DVT, the incidence of a combination of proximal DVT, non-fatal PE and death from all causes including PE, the incidence of death from all causes; incidence of documented symptomatic VTE.

Bleeding complications
Major bleeding was defined as fatal bleeding, clinically overt bleeding associated with a fall of the hemoglobin concentration greater than 2 g/l compared to the baseline hemoglobin concentration, clinically overt bleeding that required transfusion of two or more units of packed red cells or whole blood, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, retroperitoneal, and pericardial). All non-major bleeding complications were classified as minor bleeding.

Statistical analysis
All patients that received at least one dose of study drug were included in the safety analysis (safety population). All patients from the safety population were also included in the intention to treat (ITT) population. The number of patients from the ITT population evaluable for each of the end points is indicated in the respective figures. Point estimates and respective 95% confidence intervals (CIs) were calculated. For details of the statistical analysis of the overall trial see Riess et al. [24]. P-values were determined from 2-sample t-tests for continuous- or from asymptotic odds ratio tests (logistic regression) for binary variables [26]. P-values were determined from univariate logistic regression or from the interaction term of a logistic regression model with factors treatment, subgroup and treatment times subgroup as appropriate.

Results
VTE and bleeding complications in cancer patients receiving certoparin or UFH
Cancer patients receiving certoparin (n = 133) and UFH (n = 141) respectively did not differ substantially in any of the documented patient characteristics (Table 1).

Thromboembolic event rates in patients receiving certoparin (4.50%) or UFH (6.03%) were not significantly
different (OR 0.73; 95%CI 0.23-2.39) (Table 2). Event rates for single thromboembolic endpoints were largely comparable between both treatment groups, with total death showing the lowest OR (0.33; 95%CI 0.06-1.64). Although bleeding complications were not statistically different between treatment groups (Table 3), there was a nominal increase in minor bleeding complications in the UFH group.

Adverse as well as severe adverse events were comparable in certoparin vs. the UFH treated patients (59.4 vs. 67.4% for AEs and 7.5 vs. 12.8% for SAEs).

| Table 1 Baseline demographic characteristics for patients with or without cancer (safety population) |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| | Pts with cancer at admission | Pts with cancer at admission | Pts without cancer at admission | Pts without cancer at admission |
| | Certoparin | UFH | Total | Certoparin | UFH | Total | p-value vs. pts with cancer |
| | (n = 133) | (n = 141) | (n = 274) | (n = 2965) |
| Female (%) | 37.6 | 40.4 | 39.1 | 61.0 | < 0.0001^ |
| Mean age (± SD) (y) | 79.7 ± 6.4 | 78.3 ± 5.8 | 79.0 ± 6.1 | 78.8 ± 6.3 | 0.6922^ |
| Mean bodyweight (± SD) (kg) | 73.4 ± 14.6 | 71.2 ± 13.7 | 72.3 ± 14.2 | 72.1 ± 15.9 | 0.8076^ |
| Body Mass Index (± SD) (kg/m²) | 25.9 ± 4.5 | 25.4 ± 4.6 | 25.6 ± 4.6 | 26.6 ± 5.4 | 0.0041^ |
| Reason for hospitalization (%) | | | | |
| Infections and infestations | 23.3 | 28.4 | 25.9 | 27.7 | 0.5210^ |
| Cardiac disorders | 14.3 | 8.5 | 11.3 | 23.2 | < 0.0001^ |
| Respiratory disease | 6.8 | 106 | 88 | 180 | < 0.0001^ |
| Neurologic disease | 6.8 | 64 | 66 | 66 | 0.9791^ |
| Gastrointestinal disease | 9.0 | 9.2 | 9.1 | 6.3 | 0.0753^ |
| Vascular disease | 3.0 | 64 | 47 | 5.9 | 0.4454^ |
| Renal status | | | | |
| GFR ≤ 30 ml/min/1.73 m² | 4.6 | 2.9 | 3.7 | 6.1 | 0.1106* |
| 30 < GFR ≤ 60 ml/min/1.73 m² | 52.7 | 50.0 | 51.3 | 52.2 |
| GFR > 60 ml/min/1.73 m² | 42.7 | 47.1 | 45.0 | 41.6 |
| Antiplatelet use | | | | |
| Yes | 51.1 | 48.9 | 50.0 | 52.2 | 0.4905^ |
| No | 48.9 | 51.1 | 50.0 | 47.8 |
| Hospitalization (mean ± SD) (days) | 13.0 ± 8.5 | 12.6 ± 5.2 | 12.8 ± 7.0 | 12.3 ± 6.0 | 0.2500^ |
| Immobilization (mean ± SD) (days) | 10.7 ± 6.3 | 10.7 ± 4.5 | 10.7 ± 5.5 | 9.8 ± 4.2 | 0.0038^ |
| Mean exposure (± SD) (days) | 9.2 ± 3.9 | 9.1 ± 4.0 | 9.2 ± 3.9 | 9.1 ± 3.3 | 0.6264^ |

Legend: Pts, patients; SD, standard deviation; UFH, unfractionated heparin; ^ Chi-Square Test; * Chi-Square Test comparing only GFR ≤ 30 ml/min/1.73 m²; ~ t-Test.

VTE and bleeding complications in patients with or without cancer

Out of a total of 3,239 patients randomized and treated in CERTIFY, 274 had cancer and 2,965 patients no signs of cancer at hospital admission. All were anticoagulated with either certoparin or UFH. Patients with cancer were less frequently female (39.1 vs. 61.0%; p < 0.0001), had a lower body mass index and longer immobilization. With respect to co-morbidity, patients with cancer had less cardiac (11.3 vs. 23.2%; p < 0.0001) or respiratory disorders (8.8 vs. 18.0%; p < 0.0001) (Table 1).

| Table 2 Event rates in patients with cancer treated with certoparin or UFH |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Pts with cancer at admission | Certoparin | UFH | OR (95%CI) | p-value* |
| n/avail. | % | n/avail. | % | |
| Thromboembolic events | | | | |
| Combined endpoint | 5/111 | 4.50 | 7/116 | 6.03 | 0.73 (0.23-2.39) | 0.6078 |
| Proximal DVT | 5/111 | 4.50 | 5/114 | 4.39 | 1.03 (0.29-3.65) | 0.9656 |
| Symptomatic non-fatal PE | 0/129 | 0 | 1/128 | 0.78 | - | - |
| VTE related death | 0/131 | 0 | 1/132 | 0.76 | - | - |
| Distal DVT | 10/101 | 9.90 | 7/106 | 6.60 | 1.55 (0.57-4.25) | 0.3908 |
| Proximal or distal DVT | 12/101 | 11.88 | 9/106 | 8.49 | 1.45 (0.58-3.61) | 0.4213 |
| Symptomatic DVT | 1/128 | 0.78 | 1/125 | 0.80 | 0.98 (0.06-15.78) | 0.9866 |
| Death from any cause | 2/131 | 1.53 | 6/132 | 4.55 | 0.33 (0.06-1.64) | 0.1743 |

Legend: Pts, patients; UFH, unfractionated heparin; DVT, deep venous thrombosis; PE, pulmonary embolism; OR, odds ratio; CI, confidence interval; * two-sided p-value for null-hypothesis: difference = 0 or odds ratio = 1.
overview of cancer types see table 4. A total of 5.5% of patients were receiving chemotherapy. Thromboembolic event rates (proximal DVT, symptomatic non-fatal PE and VTE related death) were not significantly different in patients with cancer versus those without (5.29 vs. 4.13%; p = 0.4097) (Table 5). While differences in single thromboembolic endpoints were only minor, the rate of patients dying from any cause was increased in patients with cancer (3.04 vs. 1.16%; p = 0.0136). The rate of major and minor bleeding complications was comparable between both patient groups (Table 6).

With respect to patient safety, the number of those experiencing any severity of adverse events was comparable (63.5 vs. 61.2%; OR 1.05 (0.85-1.31)), while serious adverse events and especially death were significantly more common in those with cancer (Table 7). Differences between SAE death rates and those of the efficacy analysis are because of a different denominator (intention to treat vs. safety population).

Discussion
The present subgroup analysis of the CERTIFY trial resulted in the following findings: 1) Thromboembolic events were reduced from 6.03 to 4.50% with the use of certoparin in comparison with UFH, although this did not reach statistical significance. Further there was a nominal but not statistically significant increase in minor bleeding complications as well as all cause death in the UFH group. 2) The rates of venous thromboembolism in cancer patients are comparable with adequate anticoagulation (LMWH or UFH) with no difference in bleeding complications. Serious adverse events and especially all cause death were however significantly more common in those with cancer.

VTE and bleeding complications in cancer patients receiving certoparin or UFH
Both certoparin and UFH were statistically equally efficacious to prevent thromboembolic events in the present analysis (6.03% with UFH, 4.50% with certoparin; p = 0.6078). This is overall in good agreement with the results of the total CERTIFY trial population in which event rates were 4.52% with UFH and 3.94% with certoparin [24], indicating non-inferiority of certoparin vs. UFH.

The only comparable analysis was a subanalysis of the MEDENOX study, in which enoxaparin (20 or 40 mg)

Table 3 Bleeding complications in patients with cancer treated with certoparin or UFH

| Pts with cancer at admission | Certoparin | UFH | OR (95%CI) | p-value* |
|-----------------------------|------------|-----|------------|----------|
| n/avail. | % | n/avail. | % |       |
| Patients with cancer at admission | | | | |
| with major bleeding | 1/133 | 0.75 | 1/141 | 0.71 | 1.06 (0.07-17.13) | 0.9669 |
| with minor bleeding | 1/133 | 0.75 | 8/141 | 5.67 | 0.13 (0.02-1.02) | 0.0523 |

Legend: Pts, patients; SD, UFH, unfractionated heparin; OR, odds ratio; CI, confidence interval, * two-sided p-value for null-hypothesis: difference = 0 or odds ratio = 1.

Table 4 Cancer types in patients with cancer

| | Certoparin (n = 133) | UFH (n = 141) | Total (n = 274) |
|---|---|---|---|
| | n | % | n | % | n | % |
| Metastases | 21 | 15.8 | 18 | 12.8 | 40 | 17.9 |
| Blood | 17 | 12.8 | 24 | 17.0 | 41 | 15.0 |
| Lung/bronchus | 11 | 8.3 | 26 | 18.4 | 37 | 13.5 |
| Prostate | 23 | 17.3 | 12 | 8.5 | 35 | 12.8 |
| Colon/rectum | 14 | 10.5 | 12 | 8.5 | 26 | 9.5 |
| Breast | 16 | 12.0 | 6 | 4.3 | 22 | 8.0 |
| Pancreas | 14 | 10.5 | 8 | 5.7 | 22 | 8.0 |
| Skin | 10 | 7.5 | 8 | 5.7 | 18 | 6.6 |
| Gastroesophageal | 7 | 5.3 | 6 | 4.3 | 13 | 4.7 |
| Urogenital | 4 | 3.0 | 9 | 6.4 | 13 | 4.7 |
| Liver | 4 | 3.0 | 8 | 5.7 | 12 | 4.4 |
| Kidney | 6 | 4.5 | 6 | 4.3 | 12 | 4.4 |
| Gynecological | 3 | 2.3 | 7 | 5.0 | 10 | 3.6 |
| CNS | 4 | 3.0 | 5 | 3.5 | 9 | 3.3 |
| Others | 4 | 3.0 | 3 | 2.1 | 7 | 2.6 |
| Unclassified | 9 | 6.8 | 8 | 5.7 | 17 | 6.2 |

Legend: * unknown primary tumour.
was compared to placebo in the prevention of venous thromboembolism [18]. Venous thromboembolism (between day 1 and day 14) was defined as deep vein thrombosis, clinical suspicion of deep vein thrombosis, (fatal) pulmonary embolism. A total of 18.6% of patients (22 out of 118 patients with cancer) experienced VTE during the observation, but no data were presented on the relative efficacy of enoxaparin vs. placebo in the subgroup of patients with cancer.

Although bleeding complications were not statistically different between treatment groups, there was a nominal decrease in minor (1.50 vs. 6.38%; OR 0.22; 95%CI 0.05-1.06) bleeding complications in the certoparin group. This might somewhat relate to the mode of application, because UFH was administered as a subcutaneous injection three times daily, while certoparin was administered once daily. It appears however to translate into a patient related benefit. Bleeding rates overall were well comparable with previous trials [15-18].

VTE and bleeding complications in patients with or without cancer

Patients with cancer have a sixfold increased risk of venous thromboembolism (VTE) compared to those without, but this risk increase has been documented for patients without prophylaxis [1,2]. The additional risk can almost be abolished by heparin prophylaxis (UFH or LMWH) as demonstrated in the present analysis, where VTE rates (Incidence of proximal DVT, symptomatic non-fatal PE and death from any cause) were not increased in patients with cancer versus those without (5.29 vs. 4.13%; p = 0.4097), reinforcing the need for an effective prophylaxis. In agreement with data from previous trials [15-18], the bleeding risk and complications rates observed were low, justifying the use of pharmacologic thromboprophylaxis in hospitalized patients with cancer.

Limitations

Despite the high relevance of the present data for clinical practice, there are some inherent limitations to the present subgroup analysis. 1) There are considerable differences in VTE risk between patients with different cancer types and we have not captured these in sufficient detail to account for differences in patient characteristics, in particular for the comparison of certoparin and UFH. 2) The subgroup of patients with cancer was small compared to the overall sample size of CERTIFY. The power of the analysis was therefore limited in this subgroup as illustrated by numerically large differences between the groups which could not be statistically validated. 3) There is no possibility to explore the absolute efficacy of either heparin in comparison to patients receiving no prophylaxis, but there are a number of studies documenting this [15,19-23].

### Table 5 Event rates in patients with and without cancer

|                          | All patients | Pts with cancer at admission | Pts without cancer at admission | OR (95%CI) | p-value* |
|--------------------------|--------------|-----------------------------|-------------------------------|------------|----------|
|                          | n/avail.     | %                           | n/avail.                      | %          |          |
| Thromboembolic events    |              |                             |                               |            |          |
| Combined endpoint        | 12/227       | 5.29                        | 104/2516                      | 4.13       | 1.29 (0.70-2.39) | 0.4097 |
| Proximal DVT             | 10/225       | 4.44                        | 98/2516                       | 3.90       | 1.15 (0.59-2.23) | 0.6851 |
| Symptomatic non-fatal PE | 1/257        | 0.39                        | 9/2827                        | 0.32       | 1.22 (0.15-9.69) | 0.8488 |
| VTE related death        | 1/263        | 0.38                        | 0/2852                        | 0          | -        |          |
| Distal DVT               | 17/207       | 8.21                        | 178/2270                      | 7.84       | 1.05 (0.63-1.77) | 0.8495 |
| Proximal or distal DVT   | 21/207       | 10.14                       | 218/2280                      | 9.56       | 1.07 (0.67-1.71) | 0.7851 |
| Symptomatic DVT          | 2/253        | 0.79                        | 7/2814                        | 0.25       | 3.20 (0.66-15.46) | 0.1488 |
| Death from any cause     | 8/263        | 3.04                        | 33/2852                       | 1.16       | 2.68 (1.22-5.86) | 0.0136 |

Legend: Pts, patients; UFH, unfractionated heparin; DVT, deep venous thrombosis; PE, pulmonary embolism; OR, odds ratio; CI, confidence interval, * two-sided p-value for null-hypothesis: difference = 0 or odds ratio = 1.

### Table 6 Bleeding complications in patients with or without cancer (safety population)

|                          | All patients | Pts with cancer at admission | Pts without cancer at admission | OR (95%CI) | p-value* |
|--------------------------|--------------|-----------------------------|-------------------------------|------------|----------|
|                          | n/avail.     | %                           | n/avail.                      | %          |          |
| Bleeding complications   |              |                             |                               |            |          |
| with major bleeding      | 2/274        | 0.73                        | 15/2965                       | 0.51       | 1.45 (0.33-6.36) | 0.6254 |
| with minor bleeding      | 9/274        | 3.28                        | 101/2965                      | 3.41       | 0.96 (0.48-1.93) | 0.9152 |

Legend: Pts, patients; SD, UFH, unfractionated heparin; OR, odds ratio; CI, confidence interval, * two-sided p-value for null-hypothesis: difference = 0 or odds ratio = 1.
Table 7 Safety data for patients with or without cancer (safety population)

|                           | Pts with cancer at admission | OR (95%CI) | Total (n = 274) | OR (95%CI) vs. pts. with cancer (n = 2965) |
|---------------------------|-----------------------------|------------|-----------------|------------------------------------------|
|                           | Certoparin (n = 133)        | UFH (n = 141) |                 |                                          |
| Patients with AEs, n (%)  | 79 (59.4)                   | 95 (67.4)  | 0.71 (0.43-1.16) | 174 (63.5)                               |
| Suspected drug relation   | 5 (3.8)                     | 6 (4.3)    | 0.88 (0.26-2.95) | 11 (4.0)                                 |
| Dose adjustment or study drug interruption | 1 (0.8) | 2 (1.4) | 0.53 (0.05-5.88) | 3 (1.1)                                 |
| Study drug discontinuation | 6 (4.5)                     | 7 (5.0)    | 0.90 (0.30-2.76) | 13 (4.7)                                 |
| Concomitant medication/non-drug therapy | 56 (42.1) | 76 (53.9) | 0.62 (0.39-1.00) | 132 (48.2)                              |
|                           | 10 (7.5)                    | 18 (12.8)  | 0.56 (0.25-1.25) | 28 (10.2)                                |
| Deaths from any cause     | 2 (1.5)                     | 6 (4.3)    | 0.34 (0.07-1.73) | 8 (2.9)                                  |
| Suspected drug relation   | 0 (0)                       | 1 (0.7)    | -               | 1 (0.4)                                  |
| Study drug discontinuation | 1 (0.8)                     | 3 (2.1)    | 0.35 (0.04-3.39) | 4 (1.5)                                  |

Patients with SAEs, n (%)

- 10 (7.5)
- 18 (12.8)
- 0.56 (0.25-1.25)
- 28 (10.2)
- 172 (5.8)
- 1.85 (1.21-2.81)
- 1.85 (1.21-2.81)
- 2.67 (1.22-5.84)
- 1.08 (0.14-8.49)

Authors’ contributions

SH, SMS, UT, HEG, RB, CA, CS and HR have been involved in the conception and design of the study. CS was responsible for the integrity of the data and the accuracy of the data analyses.

Competing interests

All authors have declared no competing interests.

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Conclusions

Certoparin, 3,000 UaXa o.d. and 5,000 IU UFH t.i.d. were equally effective and safe with respect to bleeding complications in patients with cancer. There were no statistically significant differences in the risk of thromboembolic events in patients with or without cancer receiving adequate anticoagulation.

References

1. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O’Fallon WM, Melton LJ: Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000, 160(6):809-815.
2. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR: Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost 2006, 4(3):529-533.
3. Heit JA, O’Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, Melton LJ: Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med 2002, 162(11):1245-1248.
4. Sörensen HT, Mellemkjaer L, Olsen JH, Baron JA: Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000, 343(25):1846-1850.
5. Acalay A, Wun T, Khati Y, Chew HK, Harvey D, Zhou H, White RH: Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol 2006, 24(7):1112-1118.
6. Chew HK, Wun T, Harvey D, Zhou H, White RH: Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006, 166(4):458-464.
7. Prandoni P, Lensing AW, Piccioni A, Bernardi E, Simioni P, Gliori B, Marchioni A, SABBIONI P, PRINS MH, NOVENTA F, GLIOLEMI R: Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002, 100(10):3484-3488.
8. Krauth D, Holden A, Knipic N, Liepmann M, Ansell J: Safety and efficacy of long-term oral anticoagulation in cancer patients. Cancer 2007, 109(5):1846-1850.
9. HUTTEN BA, PRRS MH, GENT M, GNSBERG J, TISSEN JG, BULLER HR: Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000, 18(17):3078-3083.
10. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, COLWELL CW: Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008, 133(Suppl):381S-455S.
11. AWHP. 2010 [S3-Guideline: Prophylaxis of venous thromboembolism (VTE)][http://www.awhp.org/getlendervdetail/8003-001.html].
12. Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, Kakkar A, Kuderer NM, Levine MI, Mendelson D, Raskob G, Sonmerfield MR, Thodyl P, Trent D, Francis CW: American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007, 25(34):5490-5505.
13. Wagner LD, Baird MF, Bennett CL, Bockenstedt PL, Cataland SR, Fankos J, Fogarty PF, Goldhaber SZ, Grover TS, Haire W, Hassoun H, HANJANEK S, Liebman H, MD, LEUNG LL, LINENBERGER ML, MILLER T, Oreti L, Salem R, Smith JL, STREIFF MB: Venous thromboembolic disease. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2006, 4(9):838-869.
14. Mandala M, Falanga A, Rola F. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guidelines for the management. Ann Oncol 2010, 21(Suppl 5):v274-276.

15. Samama MM, Cohen AT, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, Weiskinger N. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999, 341(11):793-800.

16. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004, 110(7):874-879.

17. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowksi W, Turpie AG, Egberts JF, Lensing AW. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006, 332(7537):325-329.

18. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Olsson CG, Turpie AG. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med 2004, 164(9):963-968.

19. Kakkar AK, Levine MH, Kadziola Z, Lemoine NR, Low V, Patel HK, Rustin G, Thomas M, Quigley M, Williamsson RC. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). J Clin Oncol 2004, 22(10):1944-1948.

20. Klerk CP, Smaerenburg SN, Otten HM, Lensing AW, Prins MH, Piovella F, Prandoni P, Bos MM, Richel DJ, van Tienhoven G, Buller HR. The effect of low molecular weight heparin on survival in patients with advanced malignancy. J Clin Oncol 2005, 23(10):2130-2135.

21. Albinas M, Coskun HS, Ert O, Ozdan M, Eser B, Unal A, Cetin M, Soyuer S. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. J Thromb Haemost 2004, 2(8):1266-1271.

22. Sideras K, Schaefer PL, Okuno SH, Sloan JA, Kutteh L, Fitch TR, Dakhil SR, Levitt R, Alberts SR, Morton RF, Novotny PJ, Loprinzi CL. Low-molecular-weight heparin in patients with advanced cancer: a phase 3 clinical trial. Mayo Clin Proc 2006, 81(6):758-767.

23. Lazo-Langner A, Coos GD, Spaans JN, Rodger MA. The effect of low-molecular-weight heparin on cancer survival. A systematic review and meta-analysis of randomized trials. J Thromb Haemost 2007, 5(4):729-737.

24. Riess H, Haas S, Tebbe U, Abletshauser C, Sieder C, Bramlage P, Schellong S. Certoparin versus unfractionated heparin to prevent venous thromboembolic events in acutely ill, non-surgical patients; The CERTIFY Study. J Thromb Haemost 2009, 7(6):1209-1215.

25. Tebbe U, Schellong SM, Haas S, Gerlach HE, Abletshauser C, Sieder C, Bramlage P. Certoparin versus unfractionated heparin to prevent venous thromboembolic events in patients hospitalized because of heart failure: A subgroup analysis of the randomized, controlled CERTIFY study. Am Heart J 2011, 161(2):322-328.

26. Rousson V, Steffen B. A mixed approach for proving non-inferiority in clinical trials with binary endpoints. Biometrics 2008, 64(2):190-204.