

Role of low molecular weight heparin in preventing thrombosis in oncology

Yok-Lam Kwong
Department of Medicine
University of Hong Kong

Venous thromboembolism (VTE) in cancers



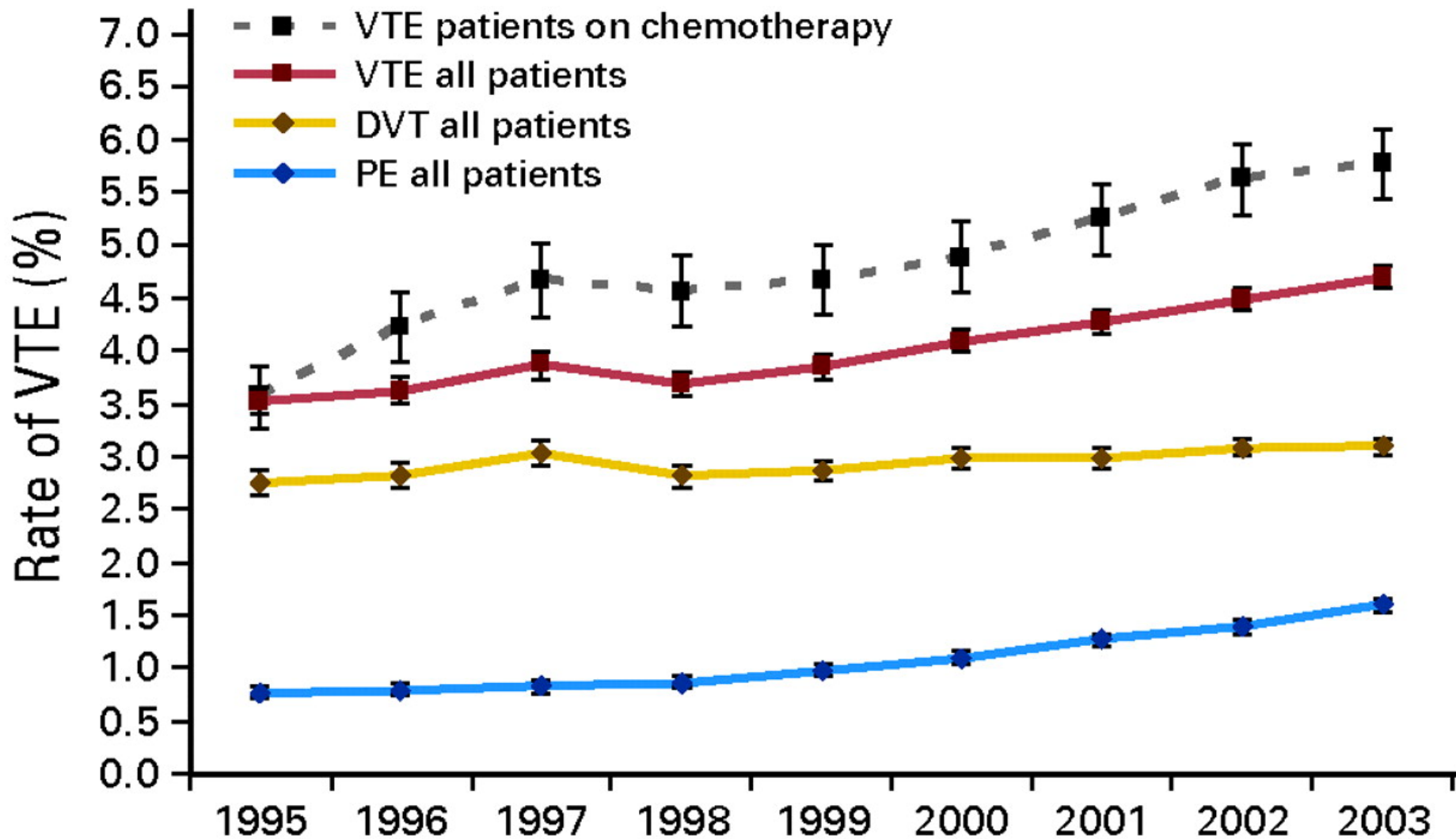
Armand Trousseau

Trousseau's sign

“I have long been struck with the frequency with which cancerous patients are affected with painful oedema of the superior or inferior extremities, whether or not either was the seat of cancer. **The frequent concurrence of phlegmasia alba dolens with an appreciable cancerous tumor, led me to the inquiry whether a relationship of cause and effect did not exist between the two, and whether the phlegmasia was not the consequence of the cancerous cachexia.** I have since that period had an opportunity of observing other cases of painful oedema in which, at autopsy, I found visceral cancer, but in which, during life, there was no appreciable cancerous tumor”.

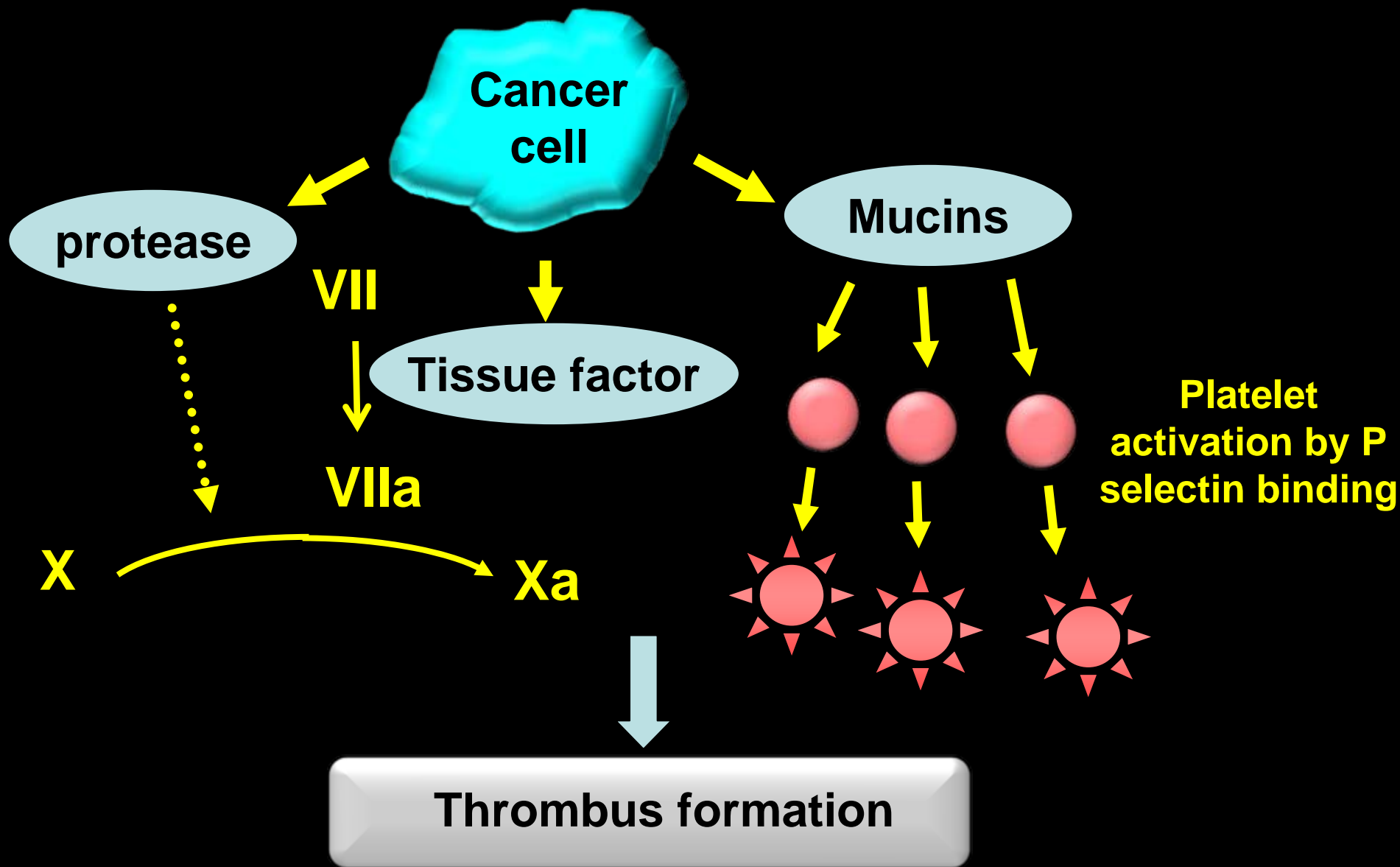
“I am lost; a phlegmasia which showed itself that night leaves me no doubt about the nature of my affliction”. **Dr Amand Trousseau developed deep vein thrombosis of his left leg a year and half afterwards, which was associated with gastric cancer from which he died.**

Increasing incidence of VTE in cancer patients



Pathogenetic mechanisms of VTE in cancers

- 1. Aberrantly glycosylated mucins**
- 2. Tissue factor / tissue factor containing membrane microvesicles**
- 3. Tumor-associated cysteine proteases**
- 4. Plasminogen-activator inhibitor (PAI)**
- 5. MET oncogene activation leading to a procoagulant state**



Risk factors for VTE in cancer patients

Patient related factors

Age

Race

Medical co-morbidities

Previous history of VTE

Elevated platelet counts

**Family history of thrombophilia or
inherited abnormalities**

Risk factors for VTE in cancer patients

Cancer related factors

Visceral and gastrointestinal cancers

Initial 3 – 6 months after diagnosis

Metastatic disease

Risk factors for VTE in cancer patients

Treatment related factors

Surgery

Hospitalization

Chemotherapy

Hormonal therapy

**Anti-angiogenic drugs, including
thalidomide, lenalidomide,
bevacizumab**

erythropoietic factors

central venous catheter

Prophylaxis of VTE in cancer patients

Randomized clinical trials of prophylaxis of VTE specifically in cancer patients not available

- 1. Treatment of VTE in cancer patients**
- 2. VTE prophylaxis in medical patients**
- 3. VTE prophylaxis in cancer surgical patients**

Lee et al 2003

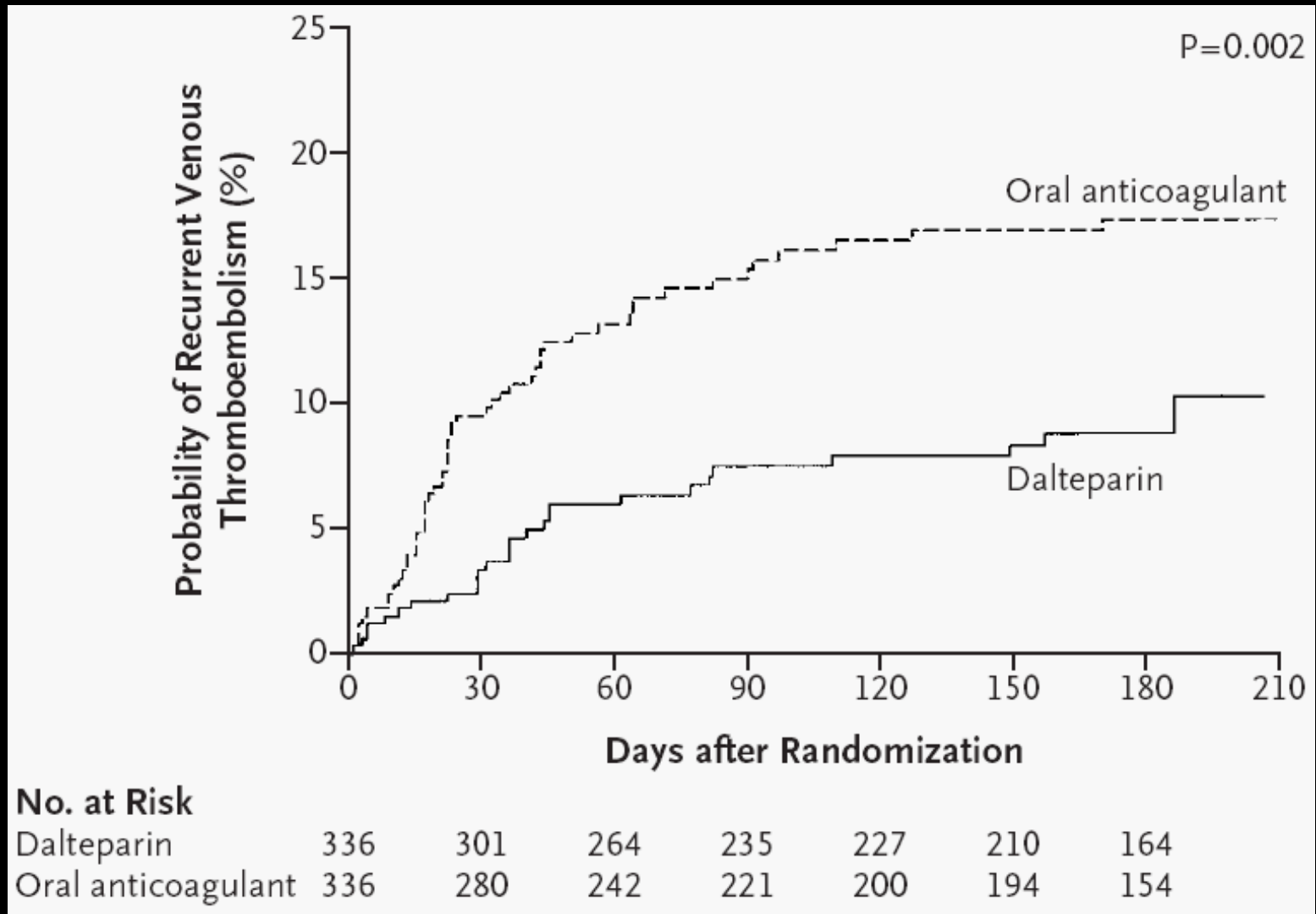
Design: cancer patients with symptomatic proximal deep-vein thrombosis, pulmonary embolism, or both

Treatment: dalteparin: 200 IU/kg once daily for five to seven days + a coumarin derivative for six months (INR: 2.5) or dalteparin alone for six months (200 IU/Kg once daily for one month, followed by a daily dose of 150 IU/Kg for five months).

Results: VTE lower in the dalteparin as compared with oral anti-coagulant group (27 / 336 versus 53 / 336 patients, hazard ratio, 0.48; P=0.002). Recurrent VTE at six months was 17% in the oral-anticoagulant group and 9% the dalteparin group. Major bleeding was similar in the dalteparin and oral-anticoagulant group (6% versus 4%), so was any bleeding (14% versus 19%). Mortality rates were 39% in the dalteparin group and 41% in the oral-anticoagulant group.

Conclusion: Dalteparin was more effective than an oral anticoagulant in decreasing VTE without increasing the risk of bleeding.

LWMH versus warfarin in preventing VTE in cancer patients



Meyer et al 2002

Design: Fixed dose of subcutaneous low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism in cancer patients.

Treatment: subcutaneous enoxaparin (1.5 mg/kg once a day) versus warfarin given for 3 months in 146 cancer patients with venous thromboembolism.

Results: VTE in 15 of 71 evaluable patients receiving warfarin (21.1%; 95% confidence interval [CI], 12.3%-32.4%) versus 7 of 67 patients receiving enoxaparin (10.5%, 95% CI, 4.3%-20.3%; $P = .09$). Death due to hemorrhage in 6 patients receiving warfarin, versus none in patients receiving enoxaparin. Death from other causes occurring in 17 patients (22.7%) receiving warfarin (95% CI, 13.8%-33.8%) versus 8 (11.3%) receiving enoxaparin (95% CI, 5.0%-21.0%; $P = .07$). No difference was observed regarding the progression of the underlying cancer or cancer-related death.

Conclusion: Treatment with enoxaparin is as effective as warfarin, and may be safer with respect to bleeding.

Hull et al 2006

Design: Cancer patients with VTE received once daily tinzaparin or warfarin.

RESULTS: VTE occurred in 7/100 patients receiving tinzaparin versus 16/100 patients receiving warfarin (P=.044; risk ratio=.44; absolute difference -9.0; 95% confidence interval [CI], -21.7 to -0.7). Minor bleeding occurred in 27/100 patients receiving tinzaparin and 24/100 patients receiving warfarin (absolute difference -3.0; 95% CI, -9.1 to 15.1). Mortality at 1 year was high, reflecting the severity of the cancers; 47% in each group died.

Conclusion: Low-molecular-weight heparin is more effective than warfarin for preventing VTE in cancer patients

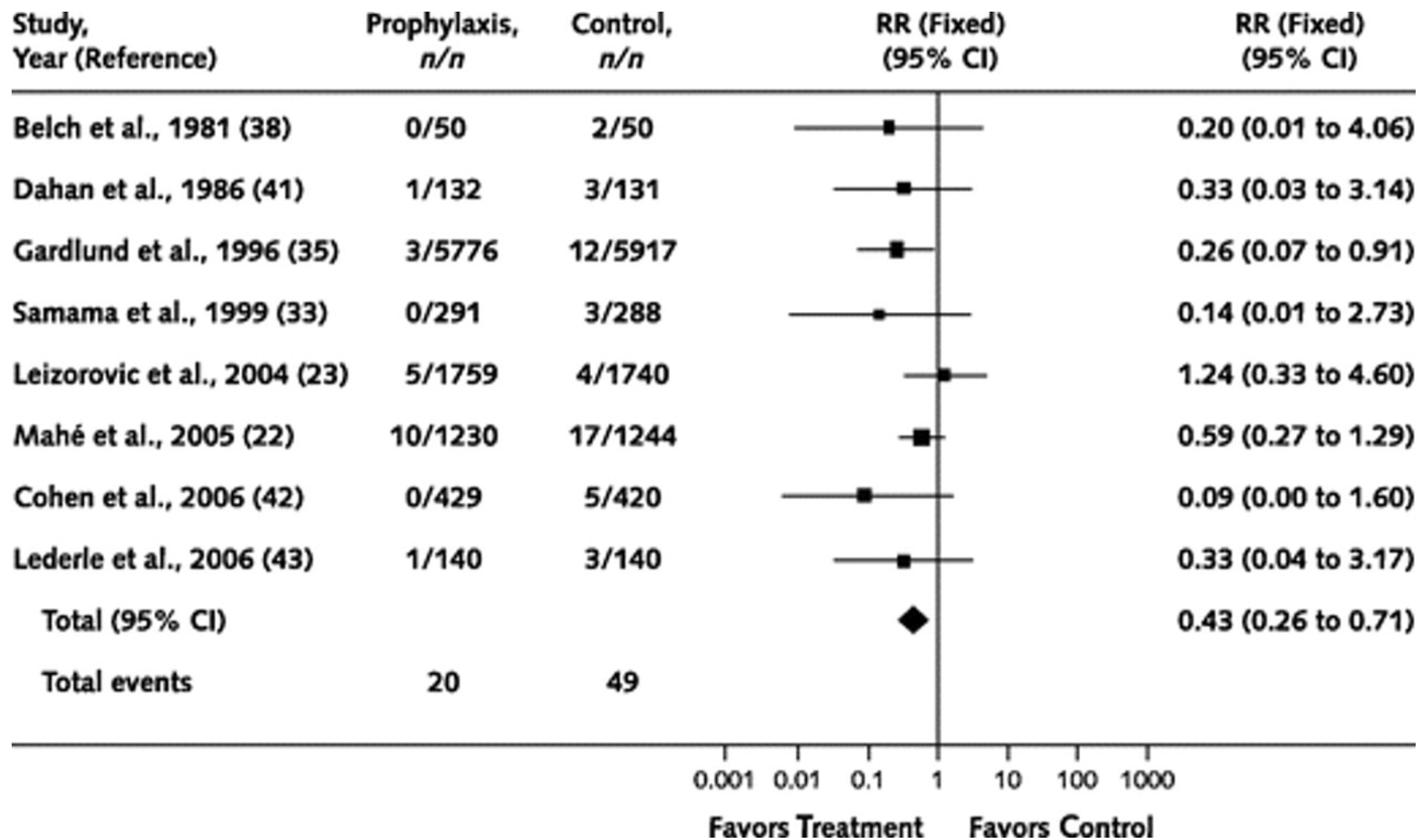
VTE treatment in cancer patients: conclusions

- 1. LWMH is the preferred agent, because of its efficacy, safety and convenience**
- 2. Other drugs have undesirable limitations, and may have poor efficacy and safety.**

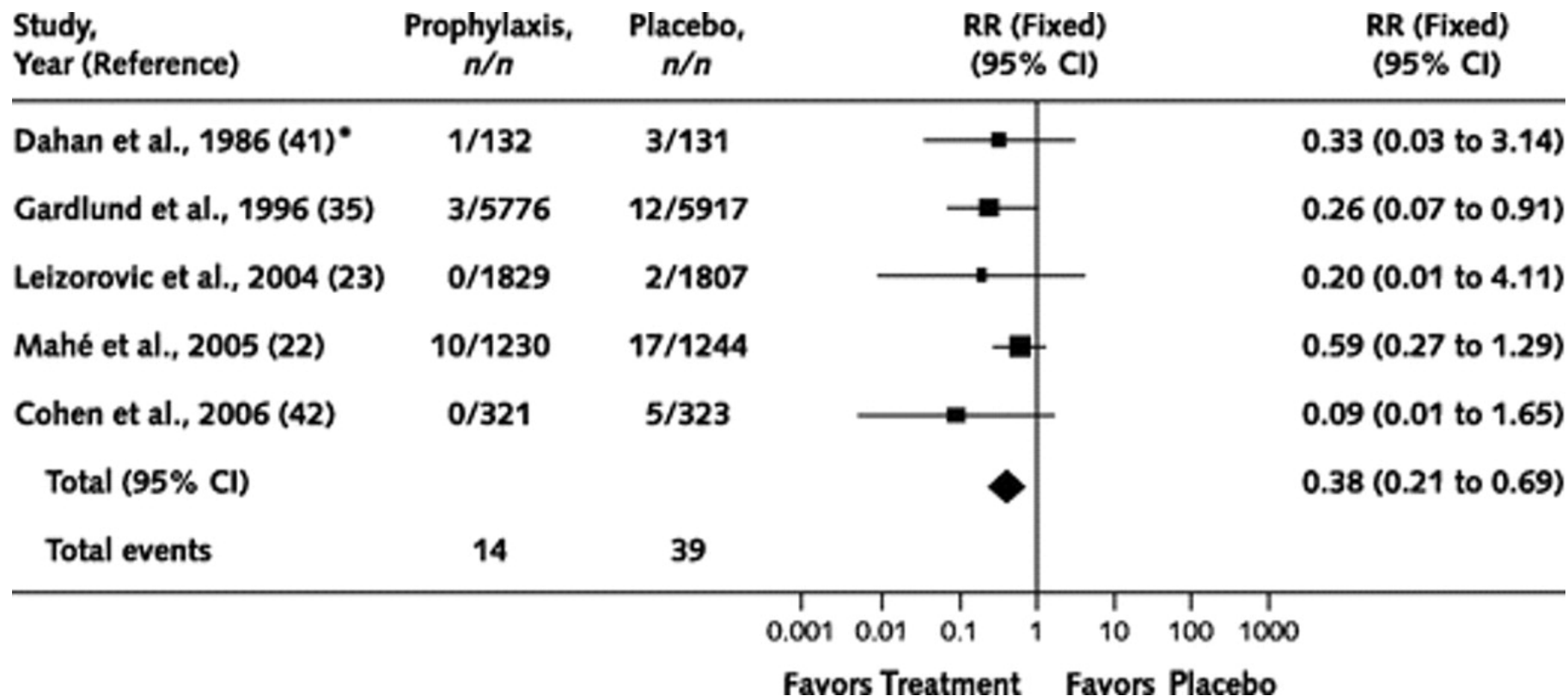
Prevention of VTE in cancer patients

- 1.No randomized controlled trials**
- 2.Efficacy and need inferred from studies of patients without cancer, and without a previous history of VTE**

Pulmonary embolism during anticoagulant prophylaxis of hospitalized medical patients



Fatal pulmonary embolism during anticoagulant prophylaxis in hospitalized medical patients



Anticoagulant prophylaxis for VTE in hospitalized medical patients

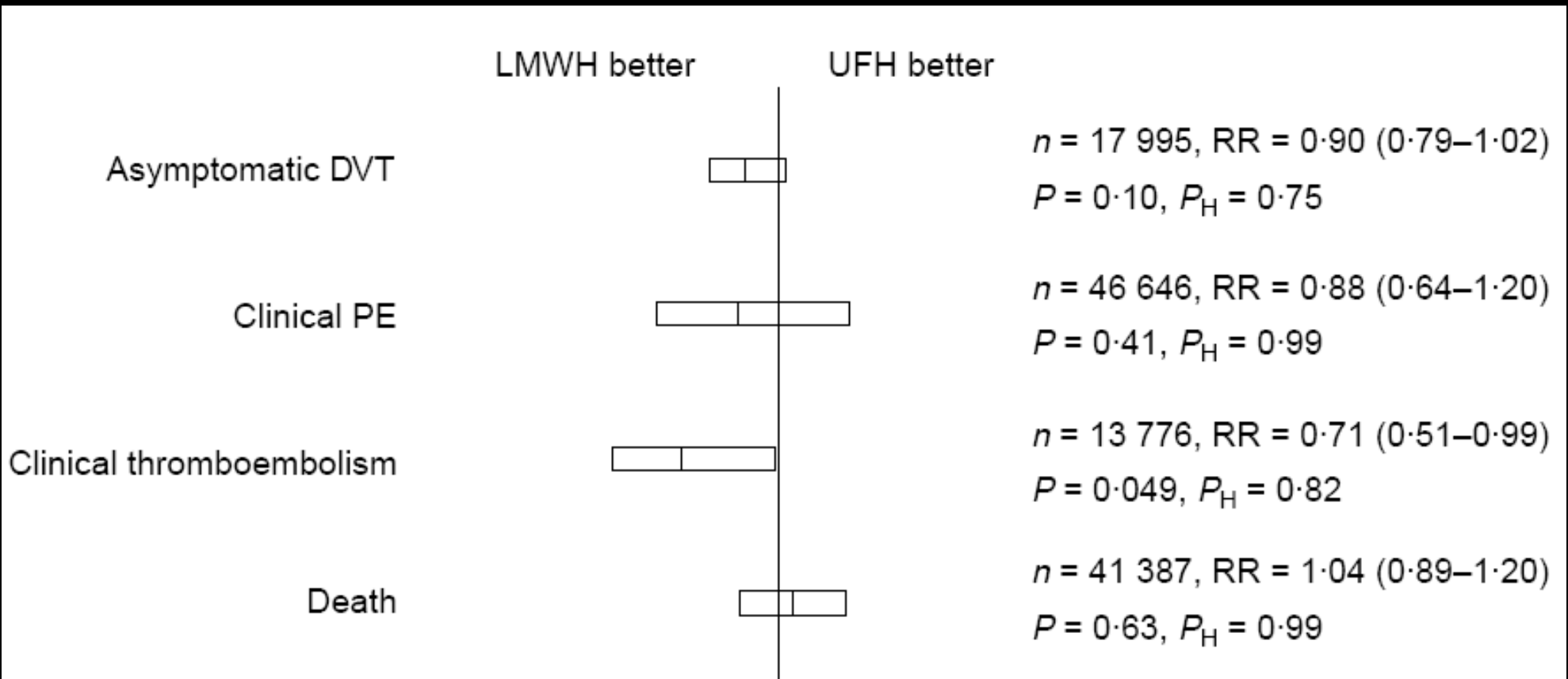
Study	Total No. of Patients	Patients With Cancer		Placebo Events		Treatment Events		Relative Risk	95% CI	P
		No.	%	No./Total No.	%	No./Total No.	%			
MEDENOX	579*	72	12.4	43/288	<u>14.9</u>	16/291	<u>5.5</u>	0.37	0.22 to 0.63	< .001
PREVENT	3,706	190	5.1	73/1,473	<u>4.96</u>	42/1,518	<u>2.77</u>	0.55	0.38 to 0.8	.0015
ARTEMIS	849 [†]	131	15.4	34/323	<u>10.5</u>	18/321	<u>5.6</u>	0.47	0.08 to 0.69	.029

MEDENOX: enoxaparin

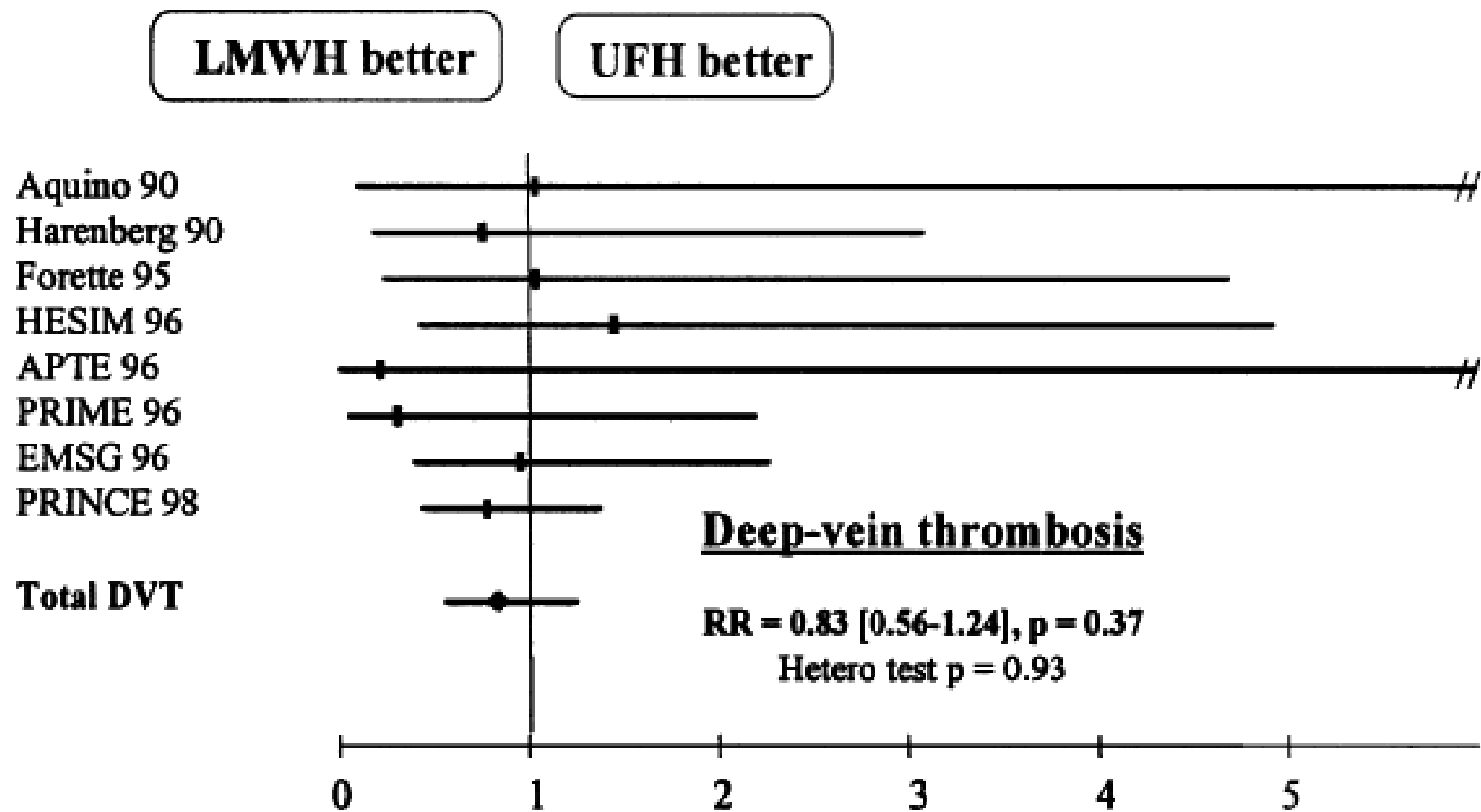
PREVENT: dalteparin

ARTEMIS: fondaparinux

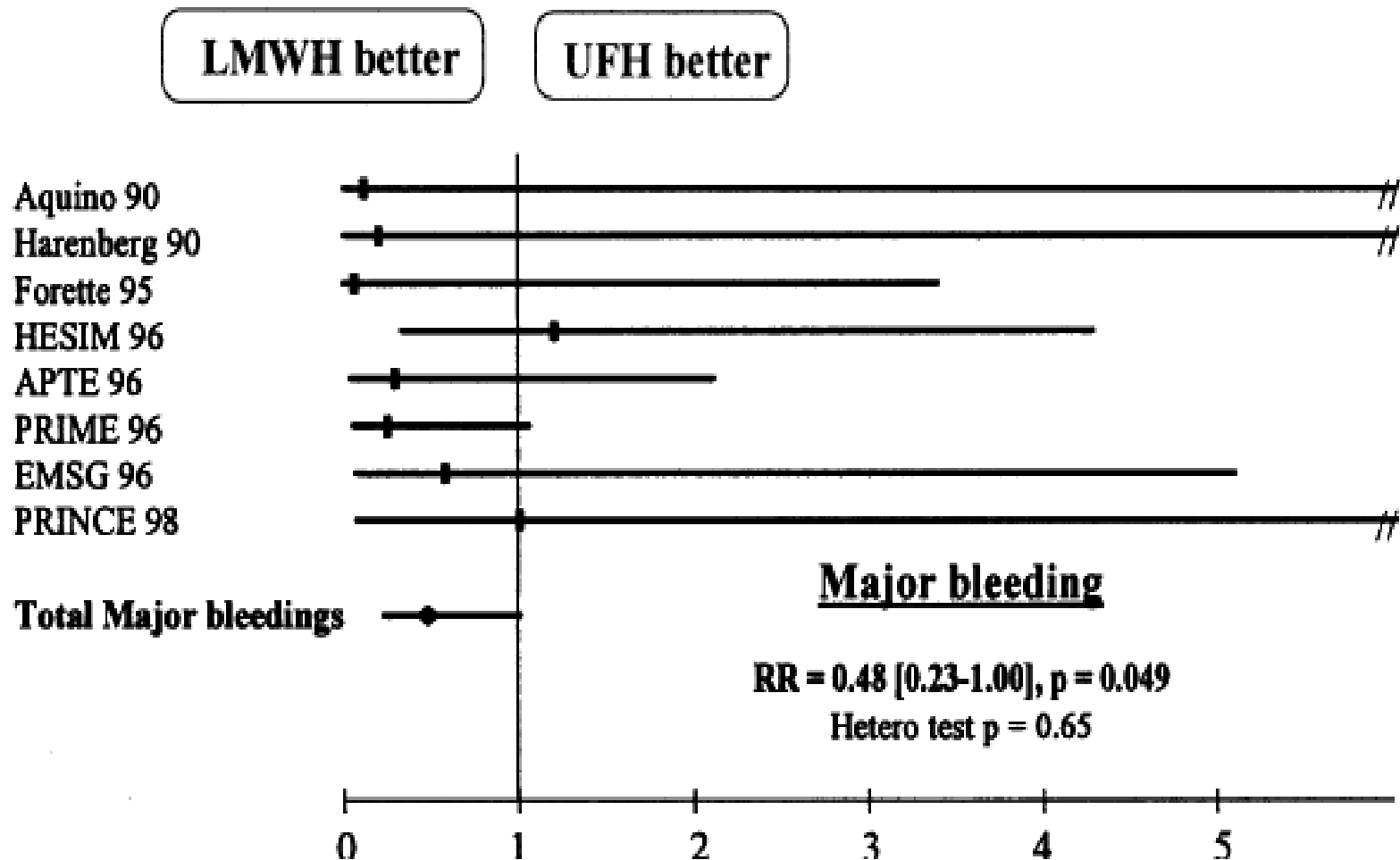
LMWH versus UFH in VTE prophylaxis in surgical patients



LMWH versus UFH in VTE prophylaxis in all types of patients



LMWH *versus* UFH in VTE prophylaxis in all types of patients



VTE prophylaxis in at-risk patients

- 1. Unfractionated heparin and low molecular weight heparin are equally effective**
- 2. LMWH is more convenient, and may be safer with respect to bleeding**
- 3. LMWH is considered the standard in VTE prophylaxis in medical and surgical patients**

VTE prophylaxis in cancer patients: considerations

- 1.Cancer patients have an increased incidence of VTE**
- 2.VTE treatment is more effective with LMWH**
- 3.VTE prevention in severely ill medical patients and patients undergoing major surgery is beneficial and needed**
- 4.VTE prevention is more effective and safer with LMWH**

ASCO recommendations of VTE prophylaxis for cancer patients

- 1. Hospitalized patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants**
- 2. Ambulatory patients with cancer should not receive routine antithrombotic prophylaxis**
- 3. Patients receiving thalidomide or lenalidomide together with chemotherapy or dexamethasone should receive antithrombotic prophylaxis**

ASCO recommendations of VTE prophylaxis for cancer patients

- 1. All patients undergoing major surgical intervention for malignant diseases should be considered for thromboprophylaxis**
- 2. Cancer patients undergoing operation lasting > 30 minutes should receive thromboprophylaxis**
- 3. Prophylaxis should be started preoperatively or as early as feasible postoperatively**
- 4. Mechanical methods should be considered in combination with thromboprophylaxis**
- 5. Thromboprophylaxis should be continued for 7 – 10 days, and extended to 4 weeks when other serious risk factors are present**

ASCO recommendations of VTE prophylaxis for cancer patients

- 1. LMWH is preferred for the initial 5 – 10 days for cancer patients with established VTE**
- 2. LMWH is also preferred for at least 6 months for long-term anticoagulation**
- 3. After 6 months, continued treatment may be considered for selected patients with metastases**
- 4. The insertion of a vena cava filter may be considered if prophylaxis is contraindicated, or recurrent VTE develops despite treatment**

Thromboprophylaxis in cancer patients without VTE: impact on the cancers

Background

- 1. Alterations in the hemostatic system and chronic hemostatic activation are frequent in cancer patients, although VTE may not have occurred.**
- 2. VTE is an important cause of death in cancer patients and contributes to long-term mortality in early-staged and advanced cancers.**
- 3. Evidence suggests that the clotting cascade and other vascular factors may play an important role in cancer progression, invasion, angiogenesis, and metastasis.**

Thromboprophylaxis in cancer patients without VTE: impact on the cancers

Anticoagulants, particularly the low molecular weight heparins (LMWHs), exert an antineoplastic effect through multiple mechanisms, including interference with

- 1. tumor cell adhesion**
- 2. Invasion**
- 3. metastasis formation**
- 4. Angiogenesis**
- 5. the immune system**

Thromboprophylaxis in cancer patients without VTE: impact on the cancers

- 1. Studies with LMWH, unfractionated heparin, and vitamin K antagonists, show encouraging but nonconclusive results.**
- 2. Meta-analyses suggest overall favorable effects of anticoagulation on survival of patients with cancer, mainly with LMWH.**
- 3. Issues remain regarding**
 - A. the importance of tumor type and stage**
 - B. the impact of fatal thromboembolic events**
 - C. optimal anticoagulation therapy**
 - D. safety with differing chemotherapy regimens.**

Acknowledgement

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