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REVIEW ARTICLE

Impact of Venous Thromboembolism and Anticoagulation on Cancer and Cancer Survival

Nicole M. Kuderer, Thomas L. Ortel, and Charles W. Francis

From the Division of Hematology/Oncology and the Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, NC; and the James P. Wilmot Cancer Center and the Department of Medicine, University of Rochester, Rochester, NY.

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Corresponding author: Nicole M. Kuderer, MD, Division of Hematology, Oncology and Cellular Therapy, Duke Comprehensive Cancer Center, Duke University Medical Center, DUMC 3841, Durham, NC 27710; e-mail: nicole.kuderer@duke.edu.

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ABSTRACT

Changes in the hemostatic system and chronic hemostatic activation are frequently observed in patients with cancer, even in the absence of venous thromboembolism (VTE). VTE is a leading cause of death among patients with cancer and contributes to long-term mortality in patients with early as well as advanced-stage cancer. Mounting evidence suggests that components of the clotting cascade and associated vascular factors play an integral part in tumor progression, invasion, angiogenesis, and metastasis formation. Furthermore, there are intriguing in vitro and animal findings that anticoagulants, in particular the low molecular weight heparins (LMWHs), exert an antineoplastic effect through multiple mechanisms, including interference with tumor cell adhesion, invasion, metastasis formation, angiogenesis, and the immune system. Several relatively small randomized controlled clinical trials of anticoagulation as cancer therapy in patients without a VTE diagnosis have been completed. These comprise studies with LMWH, unfractionated heparin, and vitamin K antagonists, with overall encouraging but nonconclusive results and some limitations. Meta-analyses performed for the American Society of Clinical Oncology VTE Guidelines Committee and the Cochrane Collaboration suggest overall favorable effects of anticoagulation on survival of patients with cancer, mainly with LMWH. However, definitive clinical trials have been elusive and questions remain regarding the importance of tumor type and stage on treatment efficacy, the impact of fatal thromboembolic events, optimal anticoagulation therapy, and safety with differing chemotherapy regimens. Although the LMWHs and related agents hold promise for improving outcomes in patients with cancer, additional studies of their efficacy and safety in this setting are needed.

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INTRODUCTION

Patients with cancer have a substantially increased risk of venous thromboembolism (VTE) compared with patients without cancer.[1-8] Changes in the hemostatic system and evidence of chronic hemostatic activation, including disseminated intravascular coagulation, are frequently observed in patients with cancer, even in the absence of VTE.[9-14] There are many links between the hemostatic system and tumor cells, including fibrin or fibrinogen surrounding the tumor tissue bed.[15-18] It has been postulated that components of the clotting cascade and associated vascular factors play an integral part in tumor progression, invasion, angiogenesis, and metastasis formation.[19-23] Furthermore, intriguing in vitro and animal findings suggest that anticoagulants, in particular the low molecular weight heparins (LMWH), exert an antineoplastic effect, most likely by interfering with metastasis formation.[24-42]

ASSOCIATION OF VTE WITH MORTALITY IN PATIENTS WITH CANCER

VTE is associated with significant morbidity, including hospitalization, reduced pulmonary function, and post-thrombotic syndrome. Compared with patients without cancer, patients with cancer experience increased VTE recurrences and bleeding complications on anticoagulation therapy.[7,43] In addition, a venous thrombotic event may impact the chemotherapy schedule and potential future therapeutic choices. The most concerning sequela remains the increased risk of mortality with VTE. Several reports have shown that VTE is a leading cause of death among patients with cancer.[44,45] Sorensen et al[46] were among the first to define the worse prognosis and reduced survival of patients with cancer with VTE compared with control patients matched by age, sex, cancer type, and year of diagnosis. Chew et al[47] evaluated retrospectively the impact of VTE among patients in the California Cancer Registry and found that after adjusting for

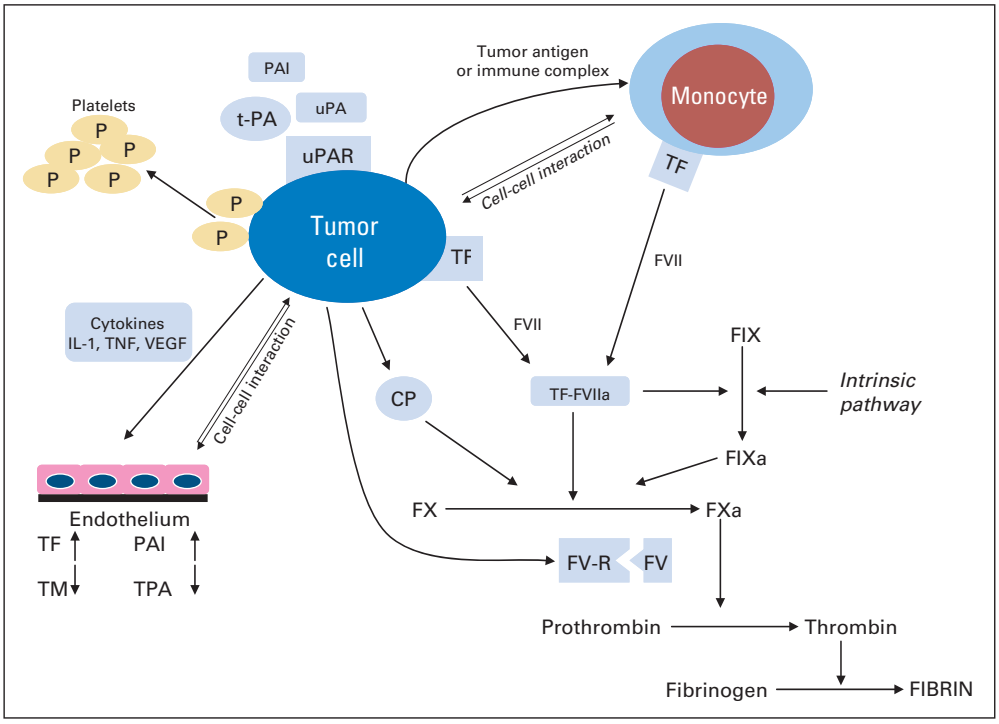

Fig 1. The tumor cell promotes a hypercoagulable state and activates the hemostatic system, utilizing cell surface proteins such as tissue factor (TF), cancer procoagulant (CP), tissue plasminogen activator (t-PA), urokinase plasminogen activator (uPA), as well as plasminogen activator inhibitor 1 (PAI-1) and 2 (PAI-2). Interaction with other blood cells (eg, monocytes, platelets, endothelial cells) occurs (A) directly by cell-cell interaction; or (B) indirectly by cytokine release promoting prothrombotic endothelial changes. IL, interleukin; P, protein; F, factor; TM, thrombomodulin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; R, receptor; FV-R, factor V receptor. Adapted from Falanga.[5]

stage, VTE patients with cancer continue to experience increased mortality. In a subsequent analysis restricted to patients with breast cancer, increased mortality again was observed even after adjusting for comorbid conditions. This appeared most pronounced in early-stage patients and the first few months after VTE diagnosis.[48] Based on a prospectively accrued, and closely followed cancer cohort, including more than 4,000 patients with solid tumor and lymphoma starting a new chemotherapy regimen at 115 oncology practices throughout the United States, Kuderer et al[49] determined that VTE is an independent risk factor for mortality during the initial months of chemotherapy in patients with cancer of all stages. This remained the case after adjusting for all major risk factors including age, sex, ethnicity, cancer type and stage, chemotherapy type and relative dose intensity, performance status, body mass index, comorbid conditions, and major laboratory abnormalities.[49] Additional research is needed to clarify if excess death in VTE patients with cancer is mainly due to more aggressive disease versus due to the occurrence of fatal thromboembolic events.

PROTHROMBOTIC MECHANISMS DUE TO CANCER

Evidence of hemostatic activation is a common finding in most patients with cancer.[10,12,50,51] Patients with cancer exhibit numerous patient-, disease-, and treatment-related predisposing factors for venous thrombosis. There are many ways that the tumor may contribute to a hypercoagulable state, including acute phase reactions, hemodynamic changes, tissue necrosis, and aberrant protein metabolism.[51,52] However, probably the most important factors contributing to the general prothrombotic state in patients with cancer derive from the tumor cells themselves. Their specific prothrombotic properties and their ability to further induce a hypercoagulable environment have been reviewed previously, in particular by Falanga et al[51,52] (Fig 1), and will be addressed in further detail elsewhere in this special issue.

Briefly, tissue factor (TF), cancer procoagulant (CP), and to a lesser extent tumor mucins are the best described tumor procoagulants. TF is a transmembrane protein that forms a macromolecular complex with factor VII to activate both factor IX and X.[53] CP is mainly found in malignant tissue and is a 68kDa cysteine protease that activates factor X directly, independent of factor VII.[54] Both TF and CP are expressed in large numbers in human and animal tumors including leukemic cells, particularly the promyelocytic leukemic subtype.[54-62]

Most components of the fibrinolytic system are found to be expressed in tumor cells. These include tissue plasminogen activator (t-PA), urokinase plasminogen activator (u-PA), as well as plasminogen activator inhibitor 1 (PAI-1) and 2 (PAI-2).[63-65] In addition to their role in hemostasis, fibrinolytic factors participate in the process of tumor invasion necessary for metastasis formation and may contribute to the increased risk of bleeding.[55,64,65] Tumor cells also release cytokines, such as tumor necrosis factor (TNF), interleukin-1(IL-1), and vascular endothelial growth factor (VEGF), which in turn promote prothrombotic endothelial changes and angiogenesis.[18,66-69] IL-1β and TNF-α together with bacterial lipopolysaccharides (endotoxins) increase the endothelial expression of TF and PAI-1, while downregulating thrombomodulin (TM), with resulting decrease in protein C activation, one of the principal anticoagulant defense systems.[18,66,67,69-73] Cytokine release and endotoxins can also rapidly increase t-PA, which tends to be followed by an even larger rise in PAI-1, resulting in an overall procoagulant state.[68] At the same time, endothelial activation by IL-1β and TNF-α leads to increases in expression of endothelial adhesion molecules. These enable tumor-endothelial cell binding and likely facilitate tumor cell extravasation

and invasion.[74-77] In addition, tumor cells have the ability to interact either directly or through soluble mediators with other blood cells, especially monocytes, macrophages, and platelets, which mainly promote thrombosis through the clotting cascade or platelet activation.

IMPACT OF HEMOSTATIC SYSTEM ON CANCER GROWTH AND PROGRESSION

Patients presenting with idiopathic venous thrombosis are at increased risk of developing cancer in subsequent years.[78-81] Thrombosis may be an early manifestation of an occult tumor. However, there is mounting evidence that the hemostatic system itself contributes to tumor cell survival and cancer progression. Several mechanisms have been implicated, in which various factors of the hemostatic system may aid in cancer cell survival, proliferation, invasion, metastasis formation, and tumor blood vessel formation (Fig 2).[21,82,83]

Fibrin deposits surrounding tumors and tumor cells may not only protect against immunologic attack,[15-17] but also form a necessary matrix or support stroma for tumor tissue,[21,22,84,85] and stimulate angiogenesis.[86] Next to its dual role in fibrin formation and platelet activation, thrombin appears to contribute in concert with TF to tumor cell invasion and metastasis formation.[87,88] Furthermore, thrombin is believed to act as an autocrine growth and proinflammatory stimulant through cleavage and activation of protease activated receptors (PARs), and can induce the expression of c-*myc* protooncogene and TF.[21,89-96]

In its role as primary initiator of hemostasis, TF results in thrombin and fibrin matrix formation. Furthermore, TF contributes to angiogenesis, tumor cell migration, and tumor progression by various pathways that include clotting-dependent and clotting-independent mechanisms and can result in direct or indirect induction of growth hormones, for example, vascular endothelial growth factor (VEGF).[83,97,98] TF and VEGF closely colocalize and correlate with microvessel density, disease progression, and more advanced disease in breast and other cancers.[97,99-102] The TF-VIIa complex directly induces tumor production of VEGF, other growth factors, and cytokines through signaling, mainly via PARs as well.[103-106] TF expression and activity is an important determinant of tumor metastatic potential and TF inhibition decreases metastasis development in animal models.[99,107-110] The TF-VIIa complex inhibits apoptosis and prolongs tumor cell survival through thrombin-independent cellular pathways, including signaling via p44/42 MAPK and Jak/STAT pathways.[111,112]

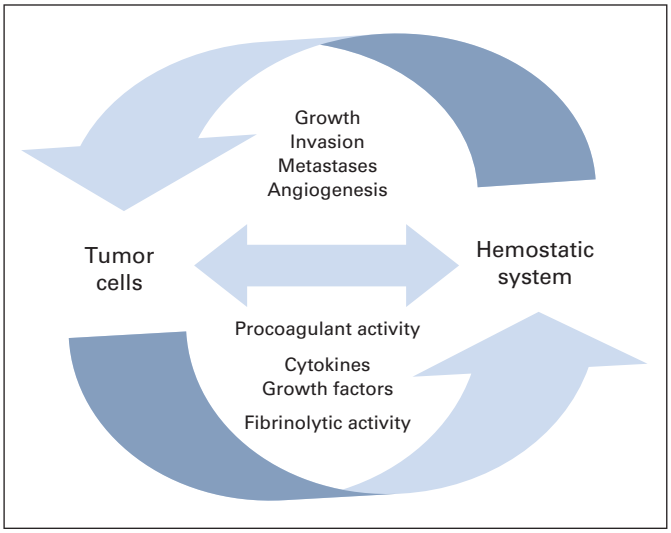

Fig 2. Positive feedback loop between tumor and the hemostatic system: tumor can promote a procoagulant state. Components of the activated hemostatic system, in particular the platelet-fibrin–rich tumor microthrombi, also promote tumor growth, angiogenesis, invasion, and metastasis formation.

Platelets may contribute to tumor cell survival in the bloodstream and overall tumor growth. Tumor cells entering blood vessels quickly recruit platelets to form tumor-platelet aggregates and later microthrombi that also include fibrin and leukocytes.[113,114] These tumor microthrombi help cancer cells survive the hostile environment in blood vessels and facilitate lodging at distant sites.[113,114] Platelets also contribute to angiogenesis and potentially to tumor growth by secreting a variety of growth and stimulatory factors, including VEGF, platelet-derived growth factor, transforming growth factor, thrombin, and fibrinogen.[113-115]

P- and L-selectins play a critical role in cancer cell interaction with endothelial cells, platelets, and leukocytes and are important for adhesion and metastasis formation.[30,35,82,116-118] Neutrophils and monocytes that are commonly found around tumor blood vessels contribute to metastasis formation by facilitating tumor cell extravasation.[119,120] More importantly, knockout mice for P- or L-selectin demonstrate a marked attenuation of metastasis formation, and double-deficient mice have a near abrogation of metastases.[30,82,116-118]

ANTINEOPLASTIC EFFECTS OF ANTICOAGULANTS IN PRECLINICAL STUDIES

As early as the 1930s, heparins were reported to interfere with several vital steps of tumor progression and in particular metastasis formation in laboratory animals, including tumor growth, tumor cell motility, migration, invasion, metastases development, and cancer survival.[26,121-127] Numerous studies confirmed that heparins prolong survival of laboratory animals after tumor cell inoculation.[26-34,36] This antineoplastic effect of heparin likely involves multiple mechanisms, as has been investigated by numerous preclinical studies.

Antiangiogenic Effect of Heparins and Impact on Growth Factors

In addition to inhibiting or decreasing fibrin and thrombin formation and their secondary stimulatory effects,[21,84,128] heparins have significant antiangiogenic properties.[129-136] In vitro studies have shown that LMWHs in contrast to heparin can inhibit the activity of VEGF and basic fibroblast growth factor (bFGF), resulting in reduced endothelial cell growth.[132,133,136] This phenomenon appears to be dependent on the specific molecular weight of heparins and was not observed with the pentasaccharide fondaparinux.[132,133,136] Heparins also interfere with angiogenesis indirectly by reducing TF expression.[137]

Antiproliferative Effects of Heparins

In most preclinical studies, the antiproliferative effects of LMWH and unfractionated heparin (UFH) did not directly affect primary tumor growth,[31,33,34] but rather interfered with metastasis formation.[26,28-31,33-36] Heparins' main antiproliferative effect is on

noncancer cells, such as endothelial cells, epithelial cells, fibroblasts, and vascular smooth muscles.[133,138-140] Heparins also have been implicated in inducing differentiation and apoptosis in in vitro studies.[32,37,141]

Effects of Heparins on the Metastatic Process: Cancer Cell Adhesion and Migration

Tumor cell migration and vascular adhesion is an integral part of metastasis development. Heparins intervene in several steps of the metastatic process. For any cellular movement through tissue and endothelial cell layers, the extracellular matrix needs to be modulated and degraded. The cancer cell achieves this with the secretion of heparinases and other proteolytic enzymes. Heparins reduce tumor invasiveness by inhibiting heparinases and other extracellular matrix components.[36,142,143] The binding and inhibition of P- and L-selectins by heparin is a key mechanism by which it interferes with crucial cancer cell interactions with endothelium, platelets, and leukocytes, vital for metastasis development as previously discussed.[30,35,82,116-118,144]

Effects of Heparins on the Immune System

Natural killer (NK) cells are key players in the destruction of circulating tumor cells before lodging at a distant site. The NK cell tumoricidal activity appears to be enhanced by both LMWH and UFH through increased activity of TNF and interferon in mice experiments.[145] As mentioned previously, heparin also blocks crucial selectin binding for leukocyte-mediated tumor cell extravasation.[82,117]

Antineoplastic Effects of Warfarin

There is less evidence to suggest that vitamin K antagonists exert an antineoplastic effect. Nevertheless, some evidence indicates that warfarin may reduce metastasis formation in part by activating macrophages.[146] Warfarin may also have an inhibitory effect on carcinoma-induced and bFGF-associated angiogenesis.[100,147]

CLINICAL TRIAL EVIDENCE OF ANTICOAGULATION IMPACT ON CANCER SURVIVAL

While heparins have been implicated in potentially enhancing the therapeutic effects of surgery and chemotherapy,[38,148-153] this has never been conclusively confirmed. Evidence in support of the hypothesis that anticoagulation may improve cancer survival comes otherwise from two major types of clinical studies. The first category was of patients treated for established VTE with different anticoagulants to determine which agent was most effective in preventing recurrent thrombosis. In these trials, survival was either not assessed at all or evaluated as a secondary outcome. In the second category of studies, the primary goal was to study the impact of anticoagulants on cancer survival in patients without a diagnosis of VTE. The results of both types of studies support the hypothesis that the administration of anticoagulants may improve survival independent of thrombosis.

Clinical Trials of Anticoagulation As VTE Therapy in Patients With Cancer With VTE

Clinical trials of anticoagulation in patients with documented VTE also included patients with cancer. Subgroup analyses of patients with cancer in these trials have suggested that initial LMWH can improve survival compared with UFH. Prandoni et al[154] compared initial treatment of patients with proximal deep vein thrombosis (DVT) with either LMWH or UFH. During the 6 months of follow-up, 44% of the patients with cancer in the UFH group died compared with 7% of patients on LMWH ($P = .02$). Meta-analyses of this and several subsequent randomized trials of symptomatic VTE demonstrated improved survival in patients with cancer on LMWH compared with UFH.[155-158] Hettiarachchi et al[157] compared the mortality rates of LMWH versus UFH treatment for DVT in patients with cancer across nine randomized controlled trials in general medical patients with cancer representing 18% of the trial population. Among patients with cancer receiving LMWH, fewer deaths were reported in the first 3 months than in those receiving UFH (odds ratio, 0.61; 95% CI, 0.40 to 0.93). However, it is surprising that such a difference would occur with only brief initial exposure differences to either LMWH or UFH, which were both subsequently followed by the same vitamin K antagonist. Given the post hoc analyses of cancer subgroups in these trials, their results remain hypothesis generating only.

The CLOT study, a large randomized controlled trial of VTE treatment in patients with cancer, was conducted comparing LMWH (dalteparin) for 6 months to dalteparin for a brief initial period followed by a vitamin K antagonist.[159] Whereas the primary outcome of this trial was recurrent thrombosis, survival was assessed as a secondary outcome and not found to be improved in the dalteparin arm compared with controls. A post hoc subgroup analysis, focusing only on the patients with nonmetastatic disease, reported the 12-month all-cause mortality at 20% in the dalteparin group compared with 35% in vitamin K antagonist treated patients ($P = .04$).[160] However, in patients with metastatic cancer, no survival difference was observed between dalteparin (72%) and oral anticoagulant (69%) study arms ($P = .46$).

Clinical Trials of Anticoagulation As Cancer Therapy in Patients With Cancer Without VTE

Several randomized controlled trials have been undertaken to directly study the impact of anticoagulant therapy (LMWH, UFH, and warfarin) on overall survival in patients with cancer without VTE.

Small-Cell Lung Cancer Trials

In an early anticoagulation survival study, Zacharski et al[161] randomly assigned patients with lung, colon, head and neck, and prostate cancer to standard treatment with or without the addition of warfarin for an average of 26 weeks. Significant improvements in time to tumor progression and in overall survival were reported among the 50 patients with small-cell lung cancer, while no difference in survival was observed in other tumor types. In another study, 328 patients with small-cell lung cancer receiving chemotherapy were randomly assigned to concurrent warfarin or not.[162] A significant improvement in objective tumor response was observed with a trend toward improved overall survival. A subsequent study of warfarin in 347 patients with limited-stage small-cell lung cancer demonstrated no significant improvement in response rate, disease-free, or overall survival.[163] A recent randomized controlled trial of LMWH in 84 patients with small-cell lung cancer demonstrated median progression-free survival of 10 months with LMWH compared with 6 months in chemotherapy control patients ($P = .01$) with improvements observed in patients with both limited and extensive disease.[164] In a multicenter trial of 277

patients with small-cell lung cancer randomly assigned to chemotherapy alone or with UFH for 5 weeks,[165] patients receiving UFH experienced improved response rates ($P = .04$), and median survival ($P = .01$) with greatest benefit in limited-stage disease. Whereas most studies of anticoagulants as cancer treatment have demonstrated improved survival in small-cell lung cancer, such studies have been limited by small sample size, heterogeneous cancer patient populations potentially leading to an imbalance of important prognostic factors between randomization arms, outdated chemotherapy, and limited data on thromboembolic and bleeding complications.

Trials in Other Cancer Types

The impact of LMWH on survival in other tumor types has also been studied in randomized trials. In a study of 385 patients with advanced malignancy receiving standard treatment with or without dalteparin or placebo for 1 year, Kakkar et al[166] observed no significant differences in survival up to 3 years. However, in a post hoc landmark analysis of 102 patients still alive at 17 months, significant improvement in survival was found for patients receiving dalteparin. Although the improved outcome in patients with less advanced cancer is consistent with studies discussed above, these results must be interpreted with caution. In another LMWH trial, 302 patients with locally advanced or metastatic solid tumors were randomly assigned to nadroparin or placebo for 6 weeks.[167] With a mean follow-up of 1 year, a significant improvement in overall survival was observed (relative risk, 0.75; 95% CI, 0.59 to 0.96; $P = .02$) among patients receiving nadroparin. Sideras et al[168] could not confirm these findings in a trial with 144 advanced solid tumor patients randomly assigned to standard treatment with or without dalteparin, but results were limited by small sample size.

Meta-Analyses of Anticoagulation Therapy

Before 2004, there were several meta-analyses suggesting improved survival in patients with cancer on anticoagulation therapy in the absence of venous thrombosis.[169-172] However, results of these studies were confounded by including nonrandomized studies or favorable post hoc subgroup analyses from trials in general medical patients. They also preceded the publication of several more recent trials,[164,167,168,173-175] and reporting on bleeding events was limited.

As part of the activities of the American Society of Clinical Oncology Venous Thromboembolism Guidelines Panel, Kuderer et al[176] performed a meta-analysis and systematic review of all RCTs of the efficacy and safety of anticoagulant trials (LMWH, UFH, vitamin K antagonists) in the treatment of patients with cancer without venous thrombosis. Across the 11 eligible trials, anticoagulation significantly decreased overall 1-year mortality with a relative risk of 0.905 (95% CI, 0.85 to 0.97; $P = .003$; Fig 3). For LMWH, the relative risk for mortality was 0.88 (95% CI, 0.79 to 0.98; $P = .015$), compared with a nonsignificant effect of warfarin, resulting in an absolute risk reduction in mortality of 8% for LMWH. Major bleeding episodes occurred

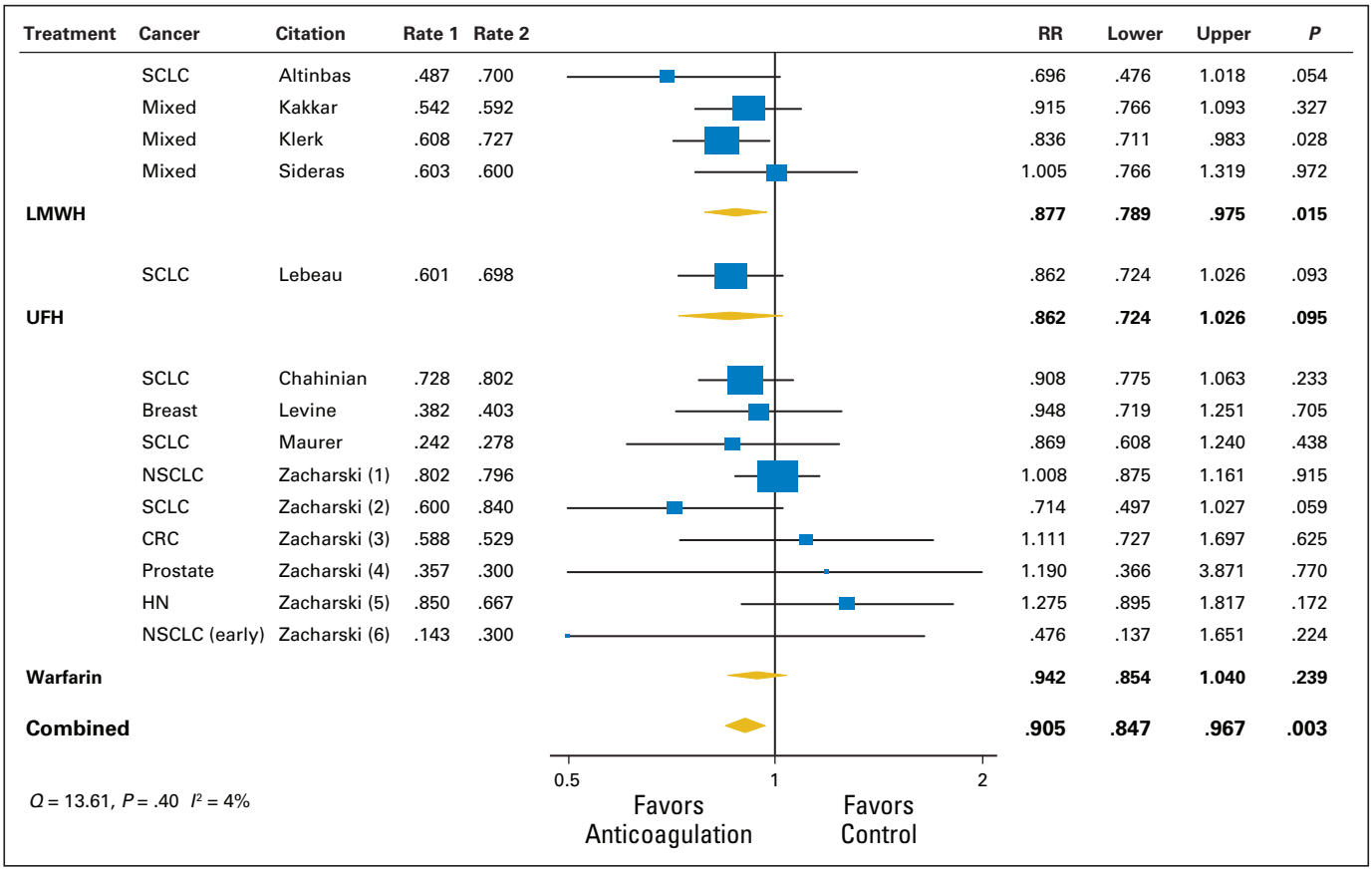

Fig 3. Meta-analysis of anticoagulation studies evaluating the impact on mortality in cancer patients without venous thrombosis: 1-year overall mortality by type of anticoagulation. SCLC, small-cell lung cancer; LMWH, low molecular weight heparin; UFH, unfractionated heparin; NSCLC, non–small-cell lung cancer; CRC, colorectal cancer; HN, head and neck cancer. Adapted from Kuderer et al.[176]

less frequently in patients who received LMWH compared with those who received warfarin (Fig 4), with an absolute risk increase of 1% in bleeding with LMWH therapy compared with 11.5% with warfarin. Although this difference in major bleeding between LMWH and warfarin could be in part a result of differences in study design and trial population, these results are consistent with previous findings.[159,177-181] Overall, fatal bleeding was a rare event. Most trials did not report on thrombosis outcomes.[176] These findings were confirmed in subsequent reviews, including the Cochrane Collaboration with their separate reports on heparins and vitamin K antagonists.[182-184]

CONCLUSIONS AND FUTURE RESEARCH

Mounting evidence suggests that components of the clotting cascade play an integral part in tumor progression, invasion, angiogenesis, and metastasis formation. Furthermore, there are intriguing experimental findings suggesting that especially LMWHs exert an antineoplastic effect through multiple mechanisms. When combined in meta-analyses, available randomized controlled trials of anticoagulation as cancer therapy in patients without VTE suggested favorable effects of LMWH on mortality of patients with cancer. However, definitive large clinical trials remain elusive. Only one relatively small trial with unfractionated heparin has been reported, not allowing any firm conclusions. Numerous additional questions remain regarding the importance of tumor type and stage on treatment efficacy, the impact of prevention of fatal venous and arterial thromboembolic events, optimal anticoagulation therapy, bleeding complications with differing chemotherapy regimens, and potential special patient monitoring needs.

To better elucidate the clinical benefits of anticoagulation therapy in patients with cancer, ongoing and future trials should focus on homogenous patient populations with the same tumor type, extent of disease, and treatment regimen, modeled after other well-designed cancer trials. In addition, these trials should report on standard survival and treatment response outcomes as well as clinically relevant thromboembolic events and bleeding complications. Despite some remaining hurdles, LMWH and related agents hold promise for improving cancer outcomes.

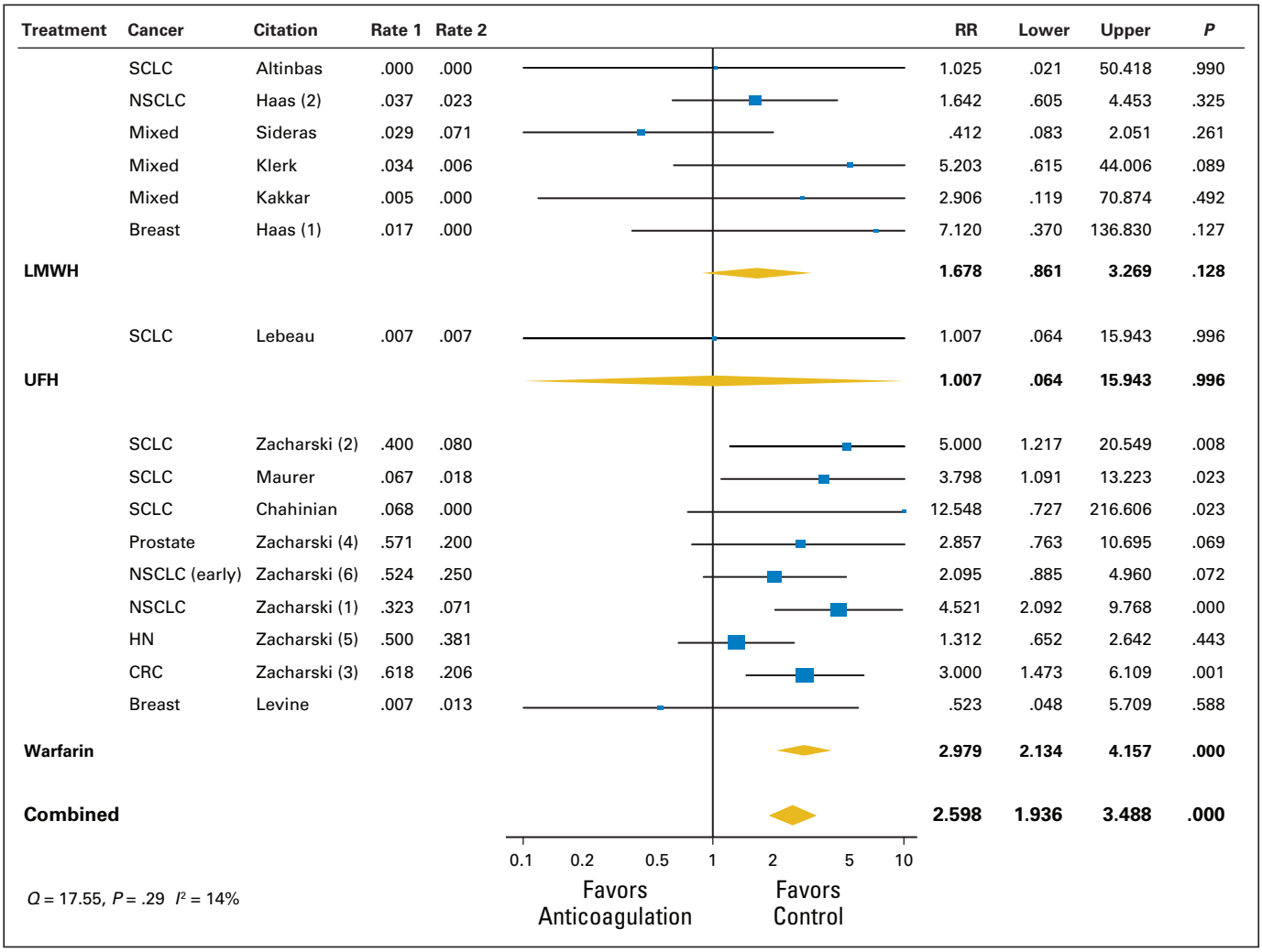

Fig 4. Meta-analysis of anticoagulation studies evaluating the impact on mortality in cancer patients without venous thrombosis: major bleeding complications by type of anticoagulation. SCLC, small-cell lung cancer; NSCLC, non–small-cell lung cancer; HN, head and neck cancer; CRC, colorectal cancer. Adapted from Kuderer et al.[176]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Nicole M. Kuderer, Thomas L. Ortel, Charles W. Francis
Administrative support: Thomas L. Ortel, Charles W. Francis
Provision of study materials or patients: Nicole M. Kuderer
Collection and assembly of data: Nicole M. Kuderer, Charles W. Francis
Data analysis and interpretation: Nicole M. Kuderer, Thomas L. Ortel, Charles W. Francis
Manuscript writing: Nicole M. Kuderer, Thomas L. Ortel, Charles W. Francis
Final approval of manuscript: Nicole M. Kuderer, Thomas L. Ortel, Charles W. Francis

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