HHS Public Access
Author manuscript
J Thromb Haemost. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:
J Thromb Haemost. 2021 November ; 19(11): 2825–2834. doi:10.1111/jth.15519.

Overall survival with warfarin versus low-molecular-weight heparin in cancer-associated thrombosis

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Abstract

Background: When compared with warfarin, low-molecular-weight heparin (LMWH) reduces the incidence of recurrent venous thromboembolism (VTE) in cancer. However, a survival benefit of LMWH over warfarin for the treatment of cancer-associated VTE has not been established.

Methods: Using the Surveillance, Epidemiology and End Results (SEER) and Medicare linked database from 2007 through 2016, we identified Medicare beneficiaries (aged ≥66 years) who were: (1) diagnosed with primary gastric, colorectal, pancreatic, lung, ovarian, or brain cancer; (2) diagnosed with cancer-associated VTE; and (3) prescribed LMWH or warfarin within 30 days. The primary outcome was overall survival (OS). Patients were matched 1:1 using exact matching for cancer stage and propensity scored matching for cancer diagnosis, age, year of VTE, and time from cancer diagnosis to index VTE. Cox proportional-hazards regression was performed to estimate hazard ratios (HR) and 95% confidence intervals (95% CI).

Results: A total of 9,706 patients were included. Warfarin was associated with a significant improvement in OS compared to LMWH (median OS, 9.8 months [95%CI, 9.1 to 10.4] versus 7.2 months [95%CI, 6.8 to 7.8]; HR, 0.86; 95% CI 0.83 to 0.90; P<0.001). The survival advantage was most pronounced in pancreatic (HR 0.82 [95% CI, 0.74 to 0.90], P<0.001) and gastric cancers (HR

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Author contributions
Contribution: T.C. and J.I.Z. conceived and designed the study, collected data, and wrote the first draft of the manuscript; R.R. analyzed the data and created the figures; A.K., R.P., E.M. and D.N. contributed to the study design and data analysis; and all authors critically reviewed the manuscript, and approved the final version. J.I.Z. has received research funding from Incyte and Quercegen; consultancy services to Sanofi, CSL, and Parexel; and honoraria from/advisory board participation with Pfizer/Bristol Myers Squibb (BMS), Portola, and Daiichi.

disclosures
The remaining authors declare no competing financial interests.

0.82 [95% CI, 0.68 to 0.98], P=0.03). The observed differences in survival were consistent across subgroups including cancer stage, age, comorbidity burden, and year of VTE.

Conclusions: In this population-based study, warfarin was associated with improved OS compared to LMWH for the treatment of cancer-associated VTE.

Keywords

Cancer-associated thrombosis; anticoagulation; warfarin; low-molecular-weight heparin; venous thromboembolism

Introduction

Venous thromboembolism (VTE) is frequently observed in cancer patients with one out of every five cases of VTE attributed to an underlying malignancy.(1) When directly compared with vitamin K antagonists, low-molecular-weight heparin (LMWH) reduced the incidence of recurrent VTE but not the incidence of hemorrhage among patients with cancer-associated thrombosis.(2, 3) For nearly two decades, treatment guidelines have recommended the use of LMWH over vitamin K antagonists for the initial and long-term management of VTE in cancer.(4–8) VTE is considered an important contributor to mortality in cancer patients and a reduction in recurrent thrombosis presumably translates into a reduction of fatal pulmonary emboli.(9) However, a mortality benefit for LMWH compared with vitamin K antagonists for the treatment of venous thromboembolism in cancer has not been established, ostensibly due insufficient power to detect small survival differences.(10)

To investigate the mortality benefit of LMWH compared with warfarin for the treatment of cancer-associated VTE, we assessed the overall survival in cancer patients diagnosed with VTE using the Surveillance, Epidemiology and End Results (SEER) and Medicare linked databases.

Methods

Study design

This study was a retrospective cohort analysis of individuals diagnosed with primary gastric, colorectal, pancreatic, lung, ovarian, or brain cancer from January 1, 2007 to December 31, 2015 in the SEER Program linked to Medicare enrollment data and claims through December 31, 2016.(11) The study received institutional review board approval at Beth Israel Deaconess Medical Center. Data were de-identified and informed consent was not required.

Data source

The SEER-Medicare database provides individual-level linkage of SEER cancer registry data with Medicare enrollment and claims data. The SEER 18-registry program contains information on incident cancer cases including demographic data, cancer characteristics at diagnosis, and initial treatment. Its geographic coverage represents approximately 28% of the United States population.(11) Medicare is a federally funded health insurance that covers

94% of persons aged 65 or older in the United States. Medicare data contain beneficiaries' enrollment (Parts A, B, C and D coverage) data, inpatient, carrier and outpatient claims among fee-for-service beneficiaries as well as prescription drug claims. In this study, the Medicare claim data were searched through September 30, 2015 with follow-up for survival data through December 31, 2016.

Study cohort

Patients were eligible for inclusion if they met the following criteria: diagnosed with primary gastric, colorectal, pancreatic, lung, ovarian, or brain cancer between 2007 to 2015; qualifying index VTE was either contemporaneous with cancer diagnosis (within 1-month) or at any time after cancer diagnosis; were 66 years of age or older at the time of VTE diagnosis; and had prescription claims for LMWH or warfarin within 30 days, and survived at least 14 days, after the index VTE event. The six solid tumor cancer diagnoses were selected due to relatively high rates of VTE. Index VTE was determined based on the first Medicare claim (inpatient or outpatient) that contained a previously validated set of the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis codes for VTE in any diagnosis position.(12) The specific codes are listed in supplemental Table 1. LMWH (dalteparin, enoxaparin, and fondaparinux) and warfarin prescriptions were identified in Part D data using National Drug Codes. Patients were excluded if they had cancer stage 0, were entitled to Medicare due to disability or end-stage renal disease before age 65 and were not enrolled in fee-for-service Medicare Part A, B, and Part D at the time of VTE diagnosis. Eligible patients were assigned to LMWH or warfarin groups based on the first anticoagulant prescription within 30 days after the diagnosis of VTE. To account for the use of LMWH as bridging treatment while achieving the therapeutic level of warfarin, patients whose first anticoagulant prescription was LMWH but received a warfarin prescription within 14 days were classified as part of the warfarin group. To address the potential for immortal time bias related to the warfarin prescription, inclusion in both treatment groups required that patients survived at least 14 days following the index VTE. In addition, patients whose first anticoagulant prescription was LMWH but received a direct oral anticoagulants prescription within 14 days were classified as part of the direct oral anticoagulants group and were excluded from the analysis.

Variables of Interest

For each eligible patient, the following variables were extracted from the database: demographic characteristics (age at VTE diagnosis, sex, and race), cancer characteristics (primary cancer site, stage, year of diagnosis, and active anti-cancer therapy), and characteristics of the index VTE (year of diagnosis, type of VTE, and time from cancer diagnosis to index VTE). Socio-economic status (median income, poverty, and education) was assessed at patient census tract level. To assess the comorbidity burden, the summation of the Elixhauser Comorbidity Index score (range 0–31) was calculated. Elixhauser comorbidity index was developed and validated using information derived from hospitalizations;(13, 14) accordingly, the score was calculated only among those patients hospitalized at time of VTE diagnosis. Cancer staging was defined according to the staging criteria of *American Joint Committee on Cancer, 7th edition*. Lung cancer subtype was identified using the *International Classification of Diseases for Oncology, 3rd Edition* (ICD-

O-3) histology codes (S2 Table). Systemic anti-cancer therapy was identified using the ICD-9-CM diagnosis and procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes related to chemotherapy administration and prescription of approved drugs for included cancer types.(15, 16) Patients were considered to have received active systemic anti-cancer therapy if at least one Medicare claim files (inpatient, outpatient, carrier, Durable Medical Equipment, and Part D Event files) contained the corresponding codes within the 3 months preceding and after the diagnosis of index VTE. The duration of anticoagulation was determined by the total sum of days supplied from each anticoagulant prescription.

Outcome

The primary outcome was overall survival defined as the time from the diagnosis of VTE to death from any cause or alive at the time of data cut-off (December 31, 2016). The date of VTE diagnosis was determined using the date of admission (patients diagnosed in hospital) or the date of service (diagnosed in outpatient settings). Dates of death and last follow up were extracted from the Medicare Enrollment Database and were available through December 31, 2016.

Statistical analysis

The study hypothesis was that LMWH would be superior to warfarin with respect to overall survival. In previous randomized studies, the overall rate of fatal pulmonary embolism was 3.7% among the 886 patients who received vitamin K antagonists.(2, 3, 17) Assuming a 26% reduction in fatal pulmonary embolism with low-molecular-weight-heparin compared with warfarin,(2, 3, 17) target enrollment was at least 10,120 patients (two-sided α=0.05, power=0.8) with a 1:1 cohort allocation.

Matching algorithms were utilized to minimize baseline imbalances for established factors predictive of mortality in a cancer population (i.e., cancer diagnosis, stage, age, year of VTE, and length from time of cancer diagnosis until study entry).(18) Patients were exact-matched for cancer stage (stage 1–2, 3, 4, not applicable, and unknown) and propensity-score–matched based on age (<75 years *vs.* ≥75 years), primary cancer site, year of VTE diagnosis (2007 – 2010 *vs.* 2011 – 2015), and time from cancer diagnosis to index VTE (up to 3 months *vs.* more than 3 months after cancer diagnosis). Patients in the LMWH group were matched to warfarin group using 1:1 nearest neighbor matching without replacement.

The method of Kaplan and Meier was used to estimate survival distributions. Median overall survival and 95% confidence intervals (95% CI) were reported with Greenwood's formula used to estimate variance. Overall mortality rate at 90 days by treatment group was compared using Fisher's exact test. Cox proportional-hazards models were used to estimate the hazard ratio for death with 95% confidence intervals.

Prespecified subgroup analyses of the primary outcome were performed based on age at index VTE diagnosis, sex, race, Elixhauser Comorbidity Index (only for hospitalized patients which ensured requisite elements for calculation), cancer sites, lung cancer subtypes (non-small-cell vs. small-cell), cancer stages (for all cancers and non-small-cell lung cancer), and year, type (deep-vein thrombosis vs. pulmonary embolism), and setting (inpatient vs. outpatient) of index VTE diagnosis. No adjustment for multiple comparisons was planned for these subgroup analyses to minimize the potential for type II errors. Sensitivity analyses of the primary outcome were performed with the exclusion of pancreatic cancer to explore the robustness of the results. All reported *P* values are two-sided and all the analyses were performed with the use of SAS software, version 9.4 (SAS Institute) and R version 4.0.2 (R Foundation for Statistical Computing).

Results

Study cohort

A total of 11,327 eligible patients were identified. After propensity-score matching, 9,706 were included in the analysis; 4,853 received LMWH and 4,853 received warfarin (S1 Fig). The baseline characteristics of the matched cohort are presented in Table 1. The median age was 74 years (range, 66 – 99 years; Interquartile range (IQR) 70 – 80 years) and 57% were female. The median time from cancer diagnosis to index VTE diagnosis was 3.2 months (IQR, 0.7 – 10.3 months). The most common malignancies were lung (42%) and colorectal cancer (24%). There was a greater proportion of patients with pancreatic cancer patients in the LMWH group relative to the warfarin group (22% and 14%, respectively). Among hospitalized patients (N=5,582 [58%]), the median Elixhauser comorbidity index score was 5 (IQR, 3–6) in both the warfarin and LMWH group. The two groups demonstrated similar proportion of patients who received systemic anti-cancer therapy (Table 1). The socio-economic characteristics are listed in the S3 Table. Warfarin group had a higher percentage of patients with unmarried status, as well as higher percentages of patients who lived in census tracts with lower economic status (i.e., median household income in the first and second quarter range, higher proportion of adults with less than 12 years of education, and higher proportion of population living below poverty line; p-value <0.01).

Overall survival

The median follow-up was 61 months (range 0.5 – 119). Warfarin was associated with significantly improved overall survival compared to LMWH (median overall survival, 9.8 months [95%CI, 9.1 to 10.4] vs. 7.2 months [95%CI, 6.8 to 7.8]) with a hazard ratio for death of 0.86 [95% CI 0.83 to 0.90; P<0.001] (Fig 1). At 90 days, overall mortality rate was 25% in warfarin group and 30% in the LMWH group (P<0.001).

Overall survival by cancer stages

Fig 2 shows the Kaplan-Meier curves for overall survival by cancer stage (stage 1–2, 3, 4, and stage not applicable and unknown). Across all cancer stages, warfarin was associated with significantly improved overall survival compared to LMWH. The observed survival differences were greatest in earlier stage disease (stage 1–2) with median overall survival of 27.6 months [95%CI, 24.2 to 30.7 months] in the warfarin group compared with 17.1 months [95%CI, 14.7 to 20.3 months] in the LMWH group. Median overall survival in patients with stage 4 cancers were longer by 1.0 months in the warfarin group (4.8 months [95%CI, 4.3 to 5.2] versus 3.8 months [95%CI, 3.5 to 4.2]). Due to baseline imbalances of pancreatic cancer which is well established to have a poor survival, we assessed overall survival excluding this diagnosis which was again consistent with overall findings (median survival 11.3 months [95%CI, 10.6 to 12.2] versus 9.6 months [95% CI, 8.9 to 10.3], HR 0.92, 95% CI 0.87 – 0.96).

Overall survival by subgroups

Survival comparisons for warfarin versus LMWH were performed within stages for patients with non-small-cell lung cancer, the most common malignancy in the cohort and most common malignancy in the United States. Within the non-small-cell lung cancer group, a consistent trend for improved overall survival was observed across all stages (Fig 3). As shown in Fig 4, warfarin was associated with improved survival outcomes relative to LMWH across several different malignancies (i.e., lung, colorectal, pancreatic, and gastric cancers). The greatest survival benefits were noted in gastric [HR 0.82, 95% CI 0.68 to 0.98] and pancreatic cancers [HR 0.82, 95% CI 0.74 to 0.90]. The trend was consistent across all subgroups analyzed including age, sex, race, type of index venous thromboembolic event, and year of anticoagulant initiation.

The duration of anticoagulants was 136 days in warfarin group and 65 days in LMWH group. In a subgroup analysis of 3,335 patients who received warfarin (N = 2,017) or LMWH (N = 1,318) for 3 months or more, improved overall survival was consistently observed in the warfarin group (median overall survival, 24.2 months [95%CI, 22.7 to 26.5] vs. 18.9 months [95%CI, 17.3 to 20.4]) with a hazard ratio for death of 0.83 [95% CI 0.77 to 0.90, $P<0.001$] (supplemental Figure 2).

Discussion

In this population-based study that included over 9,700 patients, warfarin was associated with improved overall survival compared with LMWH among cancer patients diagnosed with VTE. The observed association with improved survival for warfarin over LMWH was consistent across different subgroups including cancer site, stage, comorbidity burden, and age.

Clinical trials have demonstrated a consistent antithrombotic benefit favoring LMWH over vitamin K antagonists in the treatment of cancer-associated thrombosis.(2, 3, 17) A systematic review and meta-analysis of 5 randomized control trials, did not rule out a beneficial or harmful effect of low molecular weight heparins compared with vitamin K antagonists on mortality.(10) The lack of survival difference between LMWH and warfarin could be expected considering the diverse cancer populations (e.g. diagnoses, stages, duration of cancer diagnoses), modest sample sizes for individual cancers, and limited duration of follow-up (3 to 12 months). The population-based approach used in our study provides the advantage of a significantly larger sample size and subsequent power than what would be possible with clinical trials. In a Finnish study that included over 6000 men with cancer, the use of warfarin was associated with a significant reduction in mortality compared with non-warfarin anticoagulation for all indications.(19)

Baseline imbalances are intrinsic limitations in retrospective cohort studies. Although the two groups were propensity-score–matched to minimize imbalances (including exact-matching for cancer stage, the strongest prognostic factor in this population), there were baseline differences between the warfarin and LMWH groups, most notably the proportions of pancreatic cancers. However, the overall survival differences remained even when excluding the pancreatic cancer diagnoses. Subgroup analyses demonstrated a consistent association for survival benefit with warfarin across principal factors known to influence cancer mortality such as cancer diagnosis, stage, age, comorbidities, and year of treatment. Survival differences were even consistent within stages even when restricted to a single cancer diagnosis (i.e., non-small-cell lung cancer). These observations are unlikely to be explained by a reduction in recurrent VTE but the diagnosis of recurrent VTE (or fatal pulmonary emboli) cannot be reliably assessed in this database. In order to address the potential for immortal time bias favoring the warfarin group (patients needed to survive the initial event in order to receive a warfarin prescription), we restricted inclusion to patients who survived at least 14 days following VTE diagnosis. Despite our extensive analyses, residual imbalances in other unmeasured confounders may have influenced the observed outcome and should be noted as one of the limitations. Such confounders may include geographical residence, patients' functional status, and access to LMWH. Interestingly, our cohort demonstrated improved overall survival in patients who received warfarin despite having lower socioeconomic status, a factor which have been shown to be associated with poorer survival outcomes in cancers. (20, 21). Another potential limitation is misclassification bias due to inaccurate coding. To minimize this bias, we utilized a validated set of diagnosis codes to identify index venous thromboembolic events.(12) This set of codes provides overall positive predictive value of 95% for identifying acute VTE. Although the positive predictive value tends to be lower for codes in the secondary diagnosis position, we implemented a second-layer confirmation by mandating anticoagulant prescription within 30 days of the VTE diagnosis. (22) The SEER-Medicare database is primarily restricted to the elderly (more than 65 years of age), thereby restricting the generalizability of our results to a younger cancer population.

In this study, the duration of treatment was considerably shorter in the LMWH group compared to warfarin group (median duration of 65 *vs.* 136 days). This is consistent with previously published data showing high discontinuation rate in LMWH. (23, 24) However, the observed increase in overall survival associated with warfarin is unlikely to be explained by the duration of treatment alone, since the subgroup analysis of patients who received treatment of 3 months or more also yield similar results. Due to the limitation of data, we were not able to determine the proportion of patients who crossed over to the other anticoagulant treatment.

The association of improved overall survival with warfarin was evident across several cancer diagnoses. The most striking survival improvement appeared in those patients with earlier stage disease. Among cancer patients with limited stage disease (stage 1–2), the median overall survival was nearly 50% longer in the warfarin group, suggesting possible anti-metastatic activity of warfarin. Warfarin has demonstrated anti-neoplastic activity in pre-clinical models(25–27), which prompted the conduct of a few randomized clinical trials in the 1980s investigating warfarin as a chemotherapeutic agent. Some trials suggested clinical benefit but the findings were inconsistent.(28–31) The U.S. Veterans Administration Cooperative Study-75, the largest of such studies, recruited 431 participants across five cancer diagnoses, which included lung and colon cancer as in the present study.(28) Their findings showed that survival doubled in patients with small-cell lung cancer (P=0.018) but survival benefit was not observed in other groups. In the Cancer and Leukemia Group B (CALGB) trial, the combination of sub-therapeutic warfarin (international normalized ratio target of 1.6 to 1.9) with chemotherapy and radiation was associated with a non-significant improvement in survival among patients with small-cell lung cancer (P=0.07).(30) The majority of these studies enrolled advanced stage disease and the trials did not specifically target enrollment to include the tumor types noted in this study to have the greatest statistical survival benefit (i.e., pancreatic and gastric cancer) and may have suffered from lack of power to more definitively characterize the antineoplastic activity of warfarin.(28, 29, 31) Moreover, in a randomized study of over 800 patients with idiopathic VTE, the administration of six months of a vitamin K antagonist compared with six-weeks, was associated with a significant 35% reduction in the subsequent diagnosis of cancer.(32) Similarly, in a Norwegian population-based study, the incidence of cancer among warfarin was significantly lower compared with non-users (incidence rate ratio [IRR] 0.84, 95%CI 0.82–0.86).(33)

In animal models, tissue factor and thrombin mediate tumor growth.(34–37) The biological bases to explain observed survival differences with warfarin compared with LMWH (i.e., factor Xa inhibition) are speculative but may be due to less thrombin generation(38), warfarin-mediated reduction in factor VII(39), or inhibition of a non-coagulation, vitamin-k dependent proteins(40). Warfarin inhibits γ-carboxylation of Gas6 (growth arrest-specific-6) protein which interrupts Gas6-dependent growth of pancreatic and lung cancers in pre-clinical models.(40, 41)

In conclusion, in this population-based study involving over 9,700 cancer patients, warfarin was associated with superior survival compared with LMWH for the treatment of cancer-associated VTE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

Role of funder: This work was supported by National Heart, Lung, and Blood Institute CLOT Consortium (U01HL143365) and Cancer Center Core Grant 5P30 CA006516. This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement # U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

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ESSENTIALS

- The survival benefit of low-molecular-weight heparin (LMWH) over warfarin in cancer is not established
- We compared overall survival for those receiving LMWH vs. warfarin for thrombosis in SEER-Medicare registry involving 9,706 cancer patients
- Warfarin was associated with a significant improvement in overall survival compared to LMWH
- Survival benefit of warfarin over LMWH was consistent across subgroups

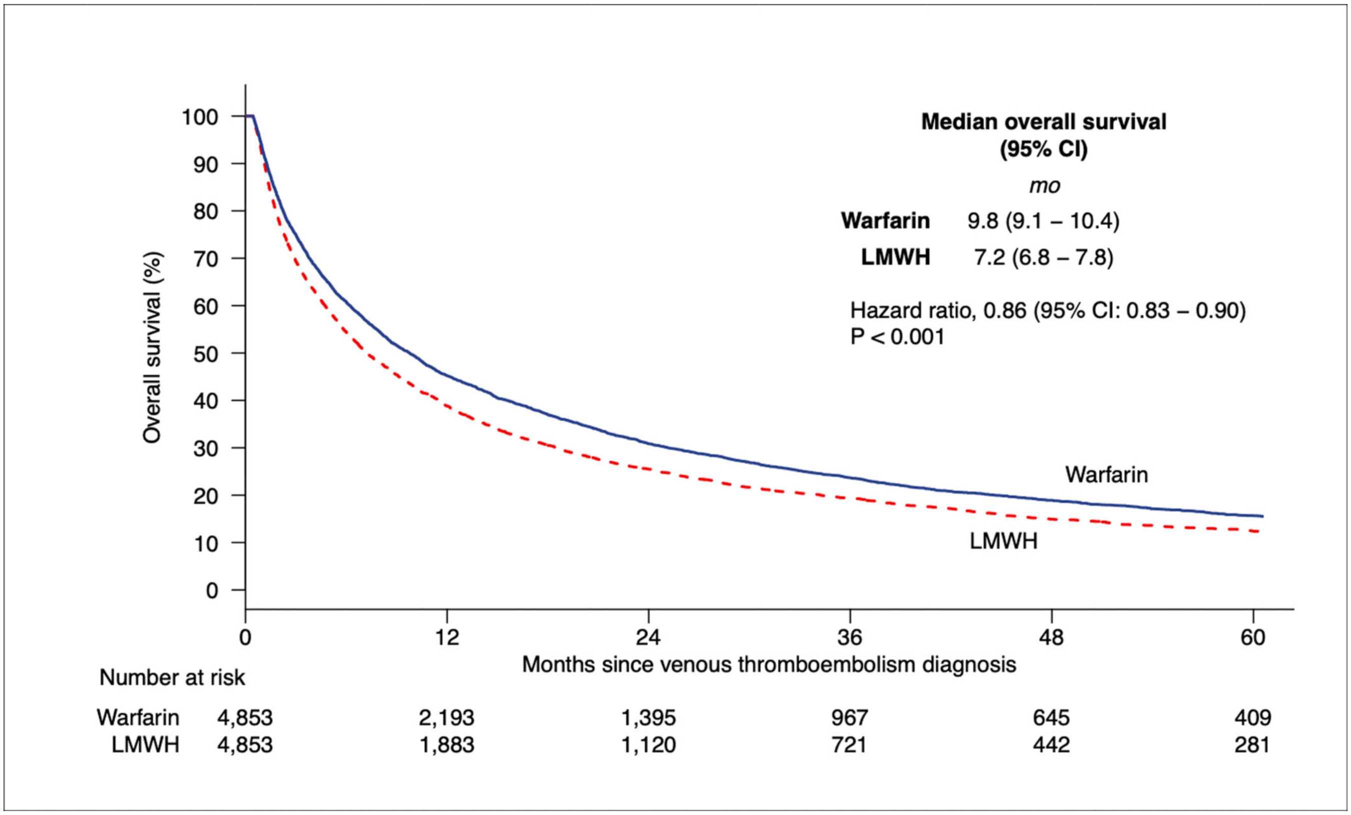

Figure 1. Overall Survival of Low-Molecular-Weight Heparin (LMWH) Compared to Warfarin in the Matched Cohort.

Shown is the Kaplan-Meier estimate of overall survival with LMWH (red dashed line) compared to warfarin (blue solid line) in the total matched cohort.

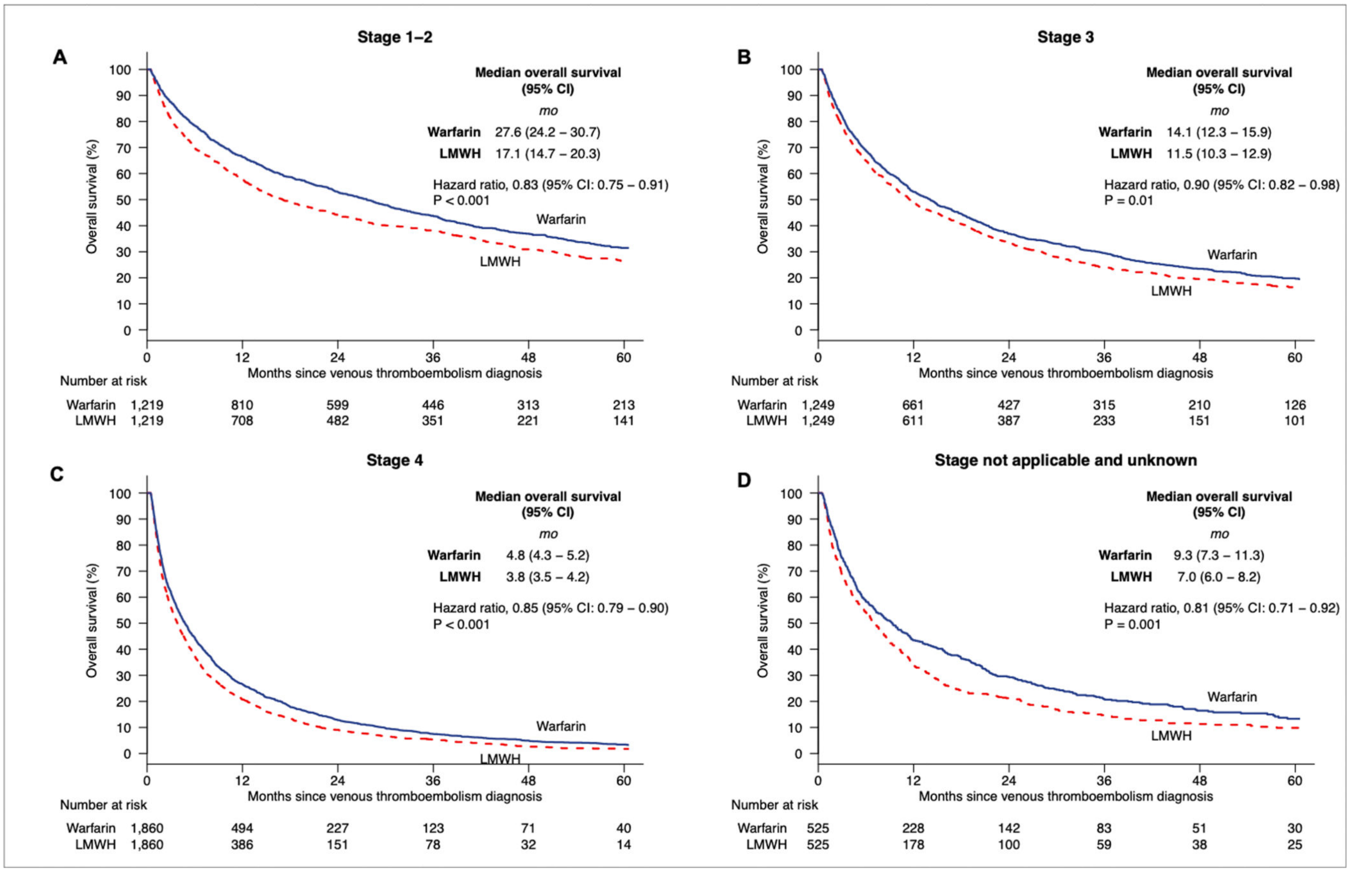

Figure 2. Overall Survival of Low-Molecular-Weight Heparin (LMWH) Compared to Warfarin According to Cancer Stages (All Cancer Population).

Shown is the Kaplan-Meier estimate of overall survival with LMWH (red dash line) compared to warfarin (blue solid line) in all cancers with stages 1–2 (Panel A), stage 3 (Panel B), stage 4 (Panel C) and stage not applicable and unknown (Panel D).

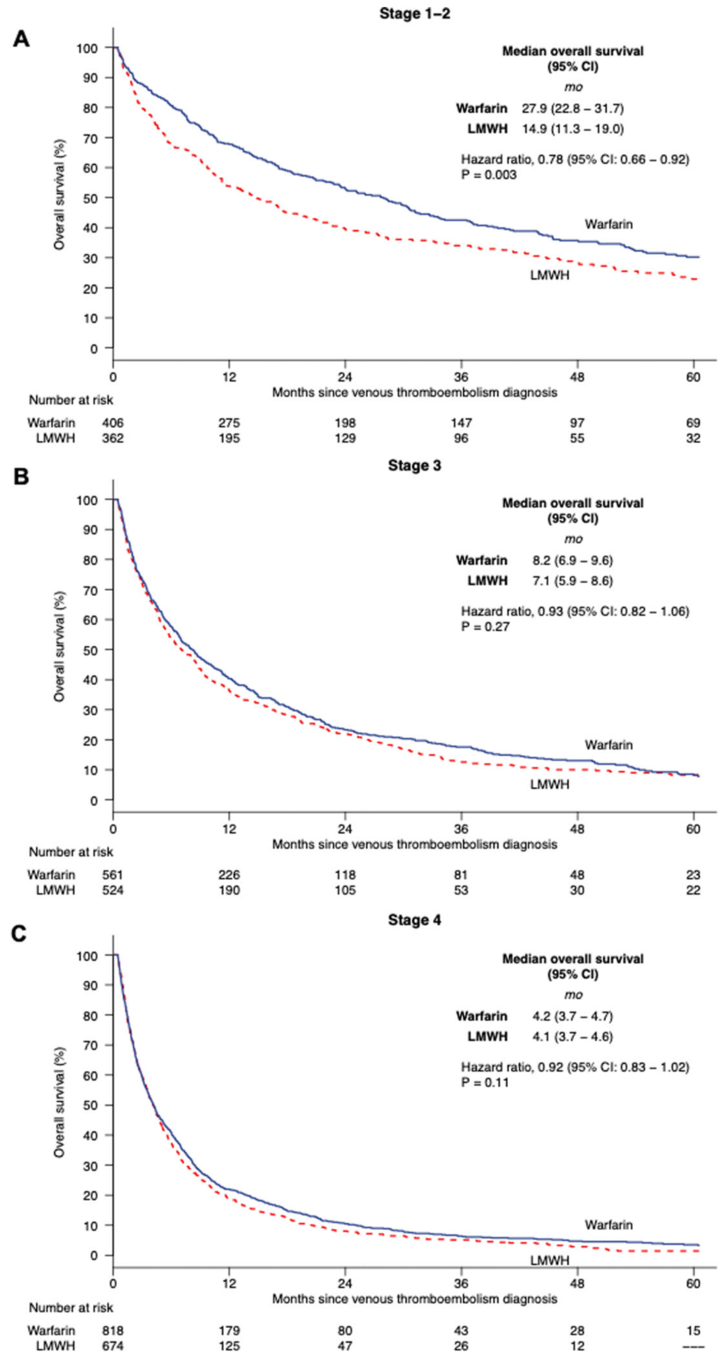

Figure 3. Overall Survival of Low-Molecular-Weight Heparin (LMWH) Compared to Warfarin According to Cancer Stages (Non-Small-Cell Lung Cancer Population).

Shown is the Kaplan-Meier estimate of overall survival with LMWH (red dahsed line) compared to warfarin (blue solid line) in non-small-cell lung cancer for stages 1–2 (Panel A), stage 3 (Panel B) and stage 4 (Panel C). Numbers at risk are not reported for the entire study period to comply with the Cell Size Suppression Policy of the Centers for Medicare and Medicaid Services.

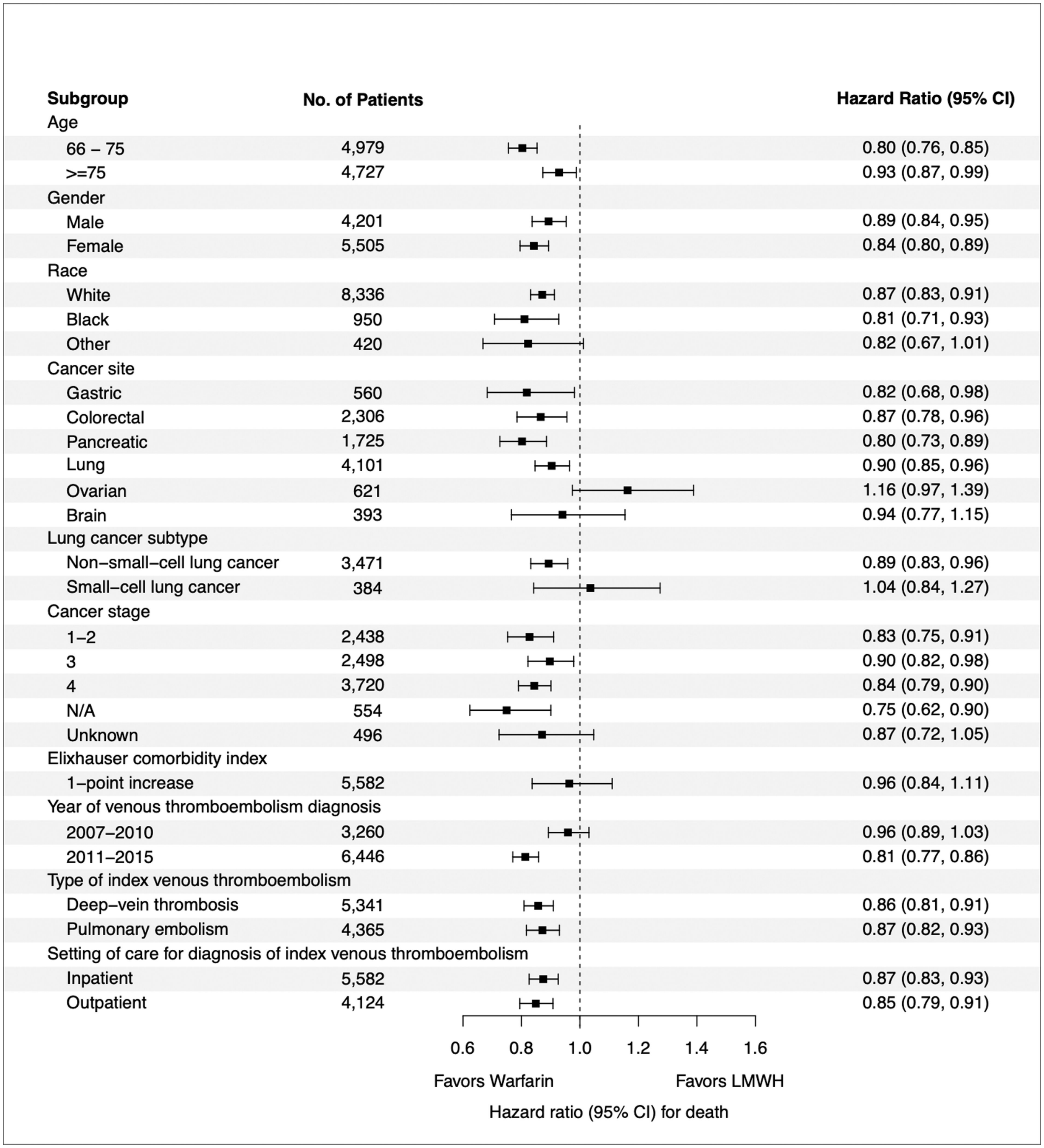

Figure 4. Subgroups Analyses of Overall Survival.

Shown is a forest plot of the subgroup analyses using a multivariable Cox proportional-hazards model that included the anticoagulant group, the subgroup covariate of interest, and the subgroup-by-treatment interaction.

Table 1.

Demographic and Clinical Characteristics of Study Cohort at Baseline after Propensity-Score Matching.

Characteristics	**Total (N = 9,706)**	**Warfarin (N = 4,853)**	**LMWH (N = 4,853)**
Age at index VTE diagnosis			
Median (IQR) — yr	74 (70 – 80)	75 (70 – 80)	74 (70 – 79)
66 – 74 yr — no. (%)	4,979 (51)	2,424 (50)	2,555 (53)
≥75 yr — no. (%)	4,727 (49)	2,429 (50)	2,298 (47)
Female sex — no. (%)	5,505 (57)	2,779 (57)	2,726 (56)
Race — no. (%) *			
White	8,059 (83)	4,052 (83)	4,007 (83)
Black	983 (10)	500 (10)	483 (10)
Other	629 (6)	288 (6)	341 (7)
Unknown	35 (0)	13 (0)	22 (0)
Median Elixhauser Comorbidity Index score, Median (IQR)	5 (3 – 6)	5 (3 – 6)	5 (3 – 6)
Elixhauser Comorbidity Index score (Inpatient claims only) — no./total no. (%) †			
0	45/5,582 (<1)	28/2,770 (1)	17/2,812 (<1)
1–2	593/5,582 (11)	305/2,770 (11)	288/2,812 (10)
≥3	4,944/5,582 (89)	2,437/2,770 (88)	2,507/2,812 (89)
Cancer stage at diagnosis — no. (%) ‡			
Stage 1–2	2,438 (25)	1,219 (25)	1,219 (25)
Stage 3	2,498 (26)	1,249 (26)	1,249 (26)
Stage 4	3,720 (38)	1,860 (38)	1,860 (38)
Not applicable	554 (6)	277 (6)	277 (6)
Unknown	496 (5)	248 (5)	248 (5)
Primary cancer site — no. (%)			
Gastric	560 (6)	262 (5)	298 (6)
Colorectal	2,306 (24)	1,172 (24)	1,134 (23)
Pancreatic	1,725 (18)	676 (14)	1,049 (22)
Lung	4,101 (42)	2,210 (46)	1,891 (39)
Ovarian	621 (6)	349 (7)	272 (6)
Brain	393 (4)	184 (4)	209 (4)
Systemic anti-cancer therapy within 3 months — no. (%)	2,556 (26)	1,210 (25)	1,346 (28)
Year of index VTE diagnosis			
2007 – 2010	3,260 (34)	1,664 (34)	1,596 (33)
2011 – 2015	6,446 (66)	3,189 (66)	3,257 (67)
Type of index VTE			

Characteristics	Total (N = 9,706)	Warfarin (N = 4,853)	LMWH (N = 4,853)
Deep-vein thrombosis	5,341 (55)	2,731 (56)	2,610 (54)
Pulmonary embolism	4,365 (45)	2,122 (44)	2,243 (46)
Time from cancer diagnosis to index VTE			
Median months	3.2	3.4	3.0
(IQR)	(0.7 – 10.3)	(0.8 – 11.1)	(0.7 – 9.5)
Total duration of anticoagulation after VTE diagnosis, Median days (IQR)	100 (30 – 270)	136 (60 – 336)	65 (25 – 201)

IQR indicates interquatile range; LMWH low-molecular-weight heparins; and VTE, venous thromboembolism.

[*]Race was abstracted from the Medicare Enrollment Database. Other included Other, Asian, Hispanic, and North American Native.

[†]The Elixhauser Comorbidity Index scores range from 0 to 31, with higher scores indicating a higher number of chronic coexisting conditions. The scores were calculated only for inpatient claims.

[‡]Based on the staging criteria of American Joint Committee on Cancer, 7th edition.