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Performance status and outcomes in patients with cancer receiving thromboprophylaxis: a subanalysis of the AVERT trial

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Abstract

Background The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) is central to cancer care planning and prognostication. Whether ECOG-PS also carries prognostic value in the setting of primary thromboprophylaxis for cancer-associated venous thromboembolism (VTE) remains unknown.

Objectives To evaluate the impact of ECOG-PS on clinical outcomes in ambulatory patients with cancer initiating chemotherapy.

Methods This was a post-hoc analysis of the AVERT randomized controlled trial that evaluated apixaban (2.5 mg twice daily) for thromboprophylaxis in patients at intermediate-to-high VTE risk. Multivariable survival models assessed the association between ECOG-PS (0–1 versus 2–3) and the composite primary outcome of VTE or clinically relevant bleeding (CRB), as well as its individual components and all-cause mortality, over 180 days.

Results Of 428 patients included, 368 (86.0%) and 60 (14.0%) had an ECOG-PS of 0–1 and 2–3, respectively. The primary composite outcome occurred in 12.8% ($n=47$) in those with ECOG 0–1 and 18.3% ($n=11$) with ECOG-PS 2–3 (6-month cumulative incidence: 13.0% [95% CI: 9.8%–16.7%] versus 19.9% [95% CI: 10.5%–31.4%], respectively). Worse performance status was associated with higher risks for the composite outcome (aHR: 1.76; 95% CI: 1.14–2.72; $p=0.011$), CRB (aHR: 1.58; 95% CI: 1.53–1.63; $p<0.0001$), and all-cause mortality (aHR: 5.77; 95% CI: 4.98–6.67; $p<0.0001$). In exploratory treatment-effect analyses, apixaban reduced VTE risk across ECOG-PS strata, including among participants with ECOG-PS 2–3, without clear evidence of excess CRB in this subgroup.

Conclusions ECOG-PS predicts VTE-related outcomes in ambulatory patients with cancer and may inform individualized, value-based shared decision-making regarding anticoagulant thromboprophylaxis.

Key points

- Poor ECOG performance status predicts higher bleeding, thromboembolic complications, and mortality in ambulatory cancer patients.
- In exploratory treatment-interaction analyses, apixaban appeared to reduce VTE across ECOG-PS strata, without evidence of excess bleeding among patients with worse performance status.

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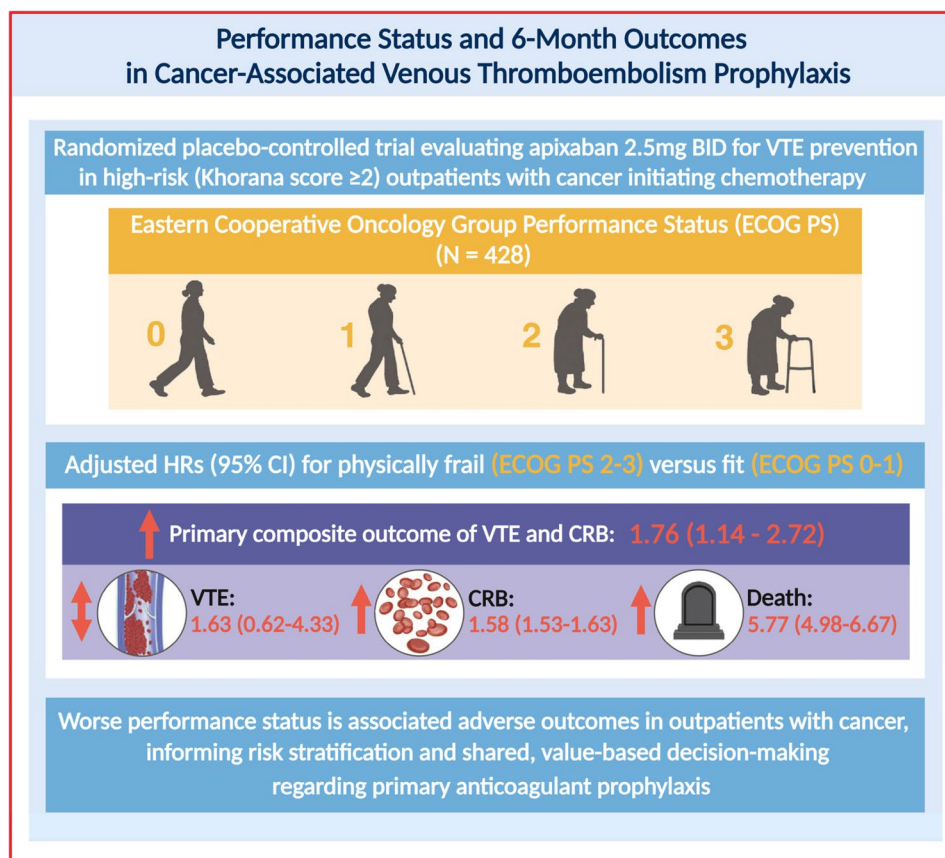
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Keywords Deep vein thrombosis, Pulmonary embolism, Anticoagulation, Thromboprophylaxis, Apixaban, Performance status, Frailty, Cardio-oncology

Graphical Abstract



Introduction

Performance status, most commonly assessed through the Eastern Cooperative Oncology Group Performance Status (ECOG-PS), is a fundamental determinant in oncologic care pathways [1–3]. ECOG-PS measures the patient's ability to perform activities of daily living, ranging from 0 (fully functional) to 4 (bedridden) (Table 1) [1–3], and correlates with objective physical performance measures and multidimensional frailty metrics [4]. Beyond informing prognostication, ECOG-PS strongly influences treatment selection, tolerability and toxicity in routine cancer care, and its use is widely endorsed given its simplicity, feasibility, and clinical relevance [5, 6]. Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major complication and the second leading cause of death in patients with cancer [7–9]. Compared with the general population, patients with cancer receiving systemic anticancer therapies experience up to a 23-fold increase in VTE risk [10]. Major society guidelines recommend primary anticoagulant thromboprophylaxis

with low-molecular-weight heparin or factor Xa inhibitors, apixaban [11] or rivaroxaban [12], in individuals with active cancer receiving systemic anticancer therapies who are at intermediate-to-high risk for VTE (defined by Khorana score ≥ 2) and not at high bleeding risk [13–15]. However, both thrombotic and bleeding risks are heightened in cancer populations due to a complex interplay of factors, thus making the optimal selection of patient candidates for primary anticoagulant thromboprophylaxis highly challenging [7–9].

Existing thrombo-hemorrhagic risk scores exhibit sub-optimal performance in patients with cancer, especially with regard to bleeding prediction [16, 17]. Importantly, none of the currently available risk tools incorporates performance status or other frailty indicators, despite increasing recognition of their importance in multiple areas of oncology care [16, 17]. A recent European Society of Cardiology (ESC) consensus statement identified performance status as a core element of the multidimensional frailty evaluation [18], offering prognostic information that complements chronological age [19]. The ESC

Table 1 The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale

ECOG-PS score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Death

cardio-oncology guidelines further recommend assessing performance status in individuals at risk for cancer-related cardiovascular complications [20]. ECOG-PS has previously been associated with adverse outcomes in anticoagulated patients who experienced cancer-associated PE [21–23]. Whether ECOG-PS provides prognostic value among ambulatory patients with cancer at risk of VTE, particularly those eligible for primary anticoagulant thromboprophylaxis, remains unknown. To address this knowledge gap, we evaluated clinical outcomes according to ECOG-PS among participants of a large, international, randomized, placebo-controlled trial of apixaban for the primary prevention of cancer-associated VTE.

Methods

This was a post-hoc analysis of the Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients (AVERT) phase III, double-blind, randomized controlled trial, which enrolled adult outpatients with active cancer initiating chemotherapy who were at intermediate-to-high risk for VTE (Khorana score ≥ 2) [11]. Key exclusion criteria included kidney or liver insufficiency, severe thrombocytopenia (platelet count < 50,000/mm³), or life expectancy < 6 months. Patients were randomized in a 1:1 ratio to receive either apixaban 2.5 mg twice daily or matching placebo for 6 months and were followed until day 210 or death. Detailed trial procedures have been reported previously [11].

Performance status was assessed at the enrollment/randomization visit using the ECOG-PS scale by a physician within the patient’s circle of care [11]. All participants with available ECOG-PS data were included in this subanalysis. The primary outcome of this study was the composite of VTE and clinically relevant bleeding (CRB) occurring within the first 180 days after randomization. VTE included objectively-confirmed symptomatic or incidental proximal DVT and PE. CRB comprised of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB), defined according to the International Society on Thrombosis and Haemostasis criteria [24, 25]. Secondary outcomes were the individual components of the composite outcome and all-cause mortality.

All events were centrally adjudicated by an independent committee blinded to treatment allocation [11].

Analyses were performed in the modified intention-to-treat population, which included all randomized participants with an ECOG-PS score who received at least one dose of study medication on or before day 180 [11]. ECOG-PS was recorded at randomization by the local trial investigators. Baseline characteristics were summarized according to the ECOG-PS category (0–1 versus 2–3). Continuous variables were reported as mean and standard deviation when normally distributed, or as median with interquartile range when skewed. Categorical variables were summarized as counts and percentages. Between-group comparisons were made using the Wilcoxon rank-sum test for continuous variables and Fisher’s exact tests for categorical variables. Cumulative incidences of the primary and secondary outcomes were estimated with corresponding 95% confidence intervals (CIs), treating death as a competing risk, and plotted using cumulative incidence function. Cumulative incidence curves were compared using Gray’s test. Time-to-event analyses comparing ECOG-PS categories were performed using Kaplan-Meier methods and multivariable Cox proportional hazards models adjusted for age, sex, body mass index, creatinine clearance, and treatment allocation. In a sensitivity analysis, Fine-Gray subdistribution hazard models accounting for the competing risk of all-cause mortality were constructed with the same covariates. Interaction analyses were performed to assess whether the relative effect of apixaban versus placebo differed by ECOG-PS category. All statistical tests were two-sided, with a *p* value < 0.05 considered to be statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 563 patients included in the intention-to-treat analysis of the AVERT trial, 428 (76.0%) had available baseline ECOG-PS score and were included in this post-hoc analysis. Among them, 368 (86.0%) had an ECOG-PS score of 0–1 and 60 (14.0%) had an ECOG-PS score of 2–3. Baseline patient characteristics are depicted in Table 2. Compared with participants with an ECOG-PS

Table 2 Baseline characteristics of the study population according to ECOG-PS

	Overall population (n=428, 100%)	ECOG-PS 0–1 (n=368, 86.0%)	ECOG-PS 2–3 (n=60, 14.0%)	P value
Female sex	256 (59.8)	222 (60.3)	34 (56.7)	0.59
Ethnoracial background				
White or Caucasian	402 (93.9)	347 (94.3)	55 (91.7)	0.86
Non-White or non-Caucasian ^a	26 (6.1)	21 (5.7)	5 (8.3)	
Age – mean (SD), years	61.0 (11.8)	60.6 (11.9)	63.7 (10.5)	0.055
Body weight – mean (SD), kg	82.7 (22.5)	83.6 (22.8)	77.6 (20.1)	0.055
BMI – mean (SD), kg/m ²	29.7 (7.7)	30.1 (7.8)	27.3 (6.6)	0.009
CrCl – mean (SD) ^b	109.7 (43.6)	111.7 (43.5)	97.6 (42.4)	0.020
CrCl < 50 ml/min ^b	14 (3.3)	7 (1.9)	7 (11.7)	< 0.0001
Hemoglobin – mean (SD)	120.3 (19.9)	120.7 (20.2)	117.9 (17.8)	0.30
Anemia ^c	80 (18.7)	68 (18.5)	12 (20.0)	0.78
Platelets – mean (SD)	321.3 (126.1)	322.8 (127.3)	312 (119.0)	0.54
Thrombocytopenia ^d	7 (1.6)	6 (1.6)	1 (1.7)	1
Type of primary cancer				
Solid cancer	315 (73.6)	269 (73.1)	46 (76.6)	0.67
Hematological cancer	113 (26.4)	99 (26.9)	14 (23.3)	
Metastatic disease	109 (37.1)	90 (35.0)	19 (51.4)	0.055
Previous VTE	11 (2.6)	9 (2.5)	2 (3.3)	0.66
Khorana risk score				
2	288 (67.3)	251 (68.2)	37 (61.7)	0.53
3	103 (24.1)	87 (23.6)	16 (26.7)	
4	37 (8.6)	30 (8.2)	7 (11.7)	
Study treatment				
Apixaban 2.5 mg BID	215 (50.2)	184 (50.0)	31 (51.7)	0.81
Matching placebo	213 (49.8)	184 (50.0)	29 (48.3)	
Concomitant antiplatelet or NSAID use	99 (23.1)	85 (23.1)	14 (23.3)	1

Values refer to counts (percentages) if not specified otherwise; percentages may not add up to 100 due to rounding

Abbreviations: BMI body mass index, CrCl creatinine clearance, NSAID non-steroidal anti-inflammatory drug, VTE venous thromboembolism

^aComprising Black/African heritage, Asian, Hispanic/Latino, and Native Indian (aboriginal)

^bEstimated using Cockcroft-Gault equation

^cDefined as hemoglobin levels < 10 g/dL upon enrollment

^dDefined by absolute platelet count < 150,000/mm³

Table 3 Cumulative incidence of the study outcome events at 6 months of randomization, by ECOG-PS

	Overall population	ECOG-PS 0–1	ECOG-PS 2–3
Primary composite outcome:			
VTE + CRB	14.0 (10.8–17.5)	13.0 (9.8–16.7)	19.9 (10.5–31.4)
Secondary outcomes:			
VTE	6.9 (4.7–9.6)	6.5 (4.2–9.3)	9.6 (3.4–19.5)
DVT	3.8 (2.2–6.0)	3.7 (2.1–6.1)	4.1 (0.7–12.5)
PE	3.1 (1.8–5.2)	2.8 (1.4–4.9)	5.7 (1.4–14.3)
CRB	8.4 (6.0–11.4)	8.0 (5.5–11.1)	10.4 (4.2–20.0)
MB	2.4 (1.2–4.3)	2.2 (1.0–4.2)	3.6 (0.7–11.0)
CRNMB	6.3 (4.2–8.9)	6.1 (4.0–8.9)	6.9 (2.2–15.4)
All-cause mortality	10.4 (7.7–13.6)	6.4 (4.2–9.2)	35.0 (23.2–47.1)

Abbreviations: DVT deep vein thrombosis, CRB clinically relevant bleeding, CRNMB clinically relevant non-major bleeding, MB major bleeding, PE pulmonary embolism, VTE venous thromboembolism, 95%CI 95% confidence interval

score of 0–1, those with ECOG-PS 2–3 were older, more likely to have metastatic disease, had lower body mass index and estimated creatinine clearance. Treatment allocation was balanced across ECOG-PS strata. In the ECOG-PS 0–1 group, 184 (50.0%) received apixaban and 184 (50.0%) placebo. In the ECOG-PS 2–3 group, 31 (51.7%) received apixaban and 29 (48.3%) placebo. Other baseline characteristics were generally comparable between the two groups (Table 2).

Overall, 58 (13.6%) patients experienced the primary composite outcome of VTE or CRB, including 28 (6.5%) VTE and 35 (8.2%) CRB events (5 patients had both VTE and CRB). The 6-month cumulative incidence of the primary composite outcome was 14.0% (95% CI, 10.8%–17.5%). At six months, the cumulative incidence of VTE alone was 6.9% (95% CI, 4.7%–9.6%), and that of CRB was 8.4% (95% CI, 6.0%–11.4%) (Table 3).

Composite outcome by performance status

The primary composite outcome of VTE and CRB occurred in 11 (18.3%) patients with an ECOG-PS score of 2–3, and 47 (12.8%) in those with an ECOG score of 0–1. VTE occurred in 8.3% (two DVTs, three PEs) and 6.3% (13 DVTs, 10 PEs) in patients with ECOG-PS scores of 2–3 and 0–1, respectively. CRB occurred in 10.0% (two MBs, four CRNMBs) and 7.9% (8 MBs, 22 CRNMBs) of patients with ECOG-PS scores of 2–3 and 0–1, respectively. Crude rates for all outcome components are presented in Supplementary Table 1.

The 6-month cumulative incidence of the composite outcome was higher in the ECOG-PS 2–3 group (19.9% [95% CI: 10.5%–31.4%]) than in the ECOG-PS 0–1 group (13.0% [95% CI: 9.8%–16.7%]) (Fig. 1A; Table 3). In adjusted analyses, ECOG-PS score of 2–3 was associated with a significantly increased risk to experience thrombo-hemorrhagic complications (adjusted hazard ratio [aHR]: 1.76; 95% CI: 1.14–2.72; $p=0.011$) (Fig. 2).

Thrombo-hemorrhagic components and all-cause mortality by performance status

For VTE alone, the 6-month cumulative incidence of VTE was 9.6% (95% CI: 3.4%–19.5%) in patients with

ECOG-PS 2–3 and 6.5% (95% CI: 4.2%–9.3%) in those with ECOG-PS 0–1 (Fig. 1B). The higher VTE rate in patients with worse performance status was not statistically significant (aHR: 1.63; 95% CI: 0.62–4.33; $p=0.32$). Similarly, the risks of DVT (aHR: 1.38; 95% CI: 0.35–5.50; $p=0.65$) and PE (aHR, 1.90; 95% CI: 0.74–4.87; $p=0.18$) were comparable by ECOG-PS category (Fig. 2). For CRB, the 6-month cumulative incidence was 10.4% (95% CI: 4.2%–20.0%) in the ECOG-PS 2–3 group, and 8.0% (95% CI: 5.5%–11.1%) in the ECOG-PS 0–1 group (Fig. 1C). Worse performance status was associated with a statistically significant increased risk of CRB (aHR: 1.58; 95% CI: 1.53–1.63; $p<0.0001$). Patients with ECOG-PS 2–3 also demonstrated substantially higher risks for both MB (aHR, 1.74; 95% CI: 1.68–1.80; $p<0.0001$) and CRNMB (aHR, 1.42; 95% CI: 1.37–1.48; $p<0.0001$) (Fig. 2).

A total of 44 (10.3%) patients died during the 6-month follow-up, none due to fatal thromboembolism or bleeding events. Mortality occurred in 23 (6.3%) patients with ECOG-PS 0–1 and 21 (35.0%) patients with ECOG-PS 2–3. Poorer performance status was strongly associated with increased all-cause mortality (aHR, 5.77; 95% CI: 4.98–6.67; $p<0.0001$). In Fine-Gray competing-risk analyses, association between ECOG-PS 2–3 and both

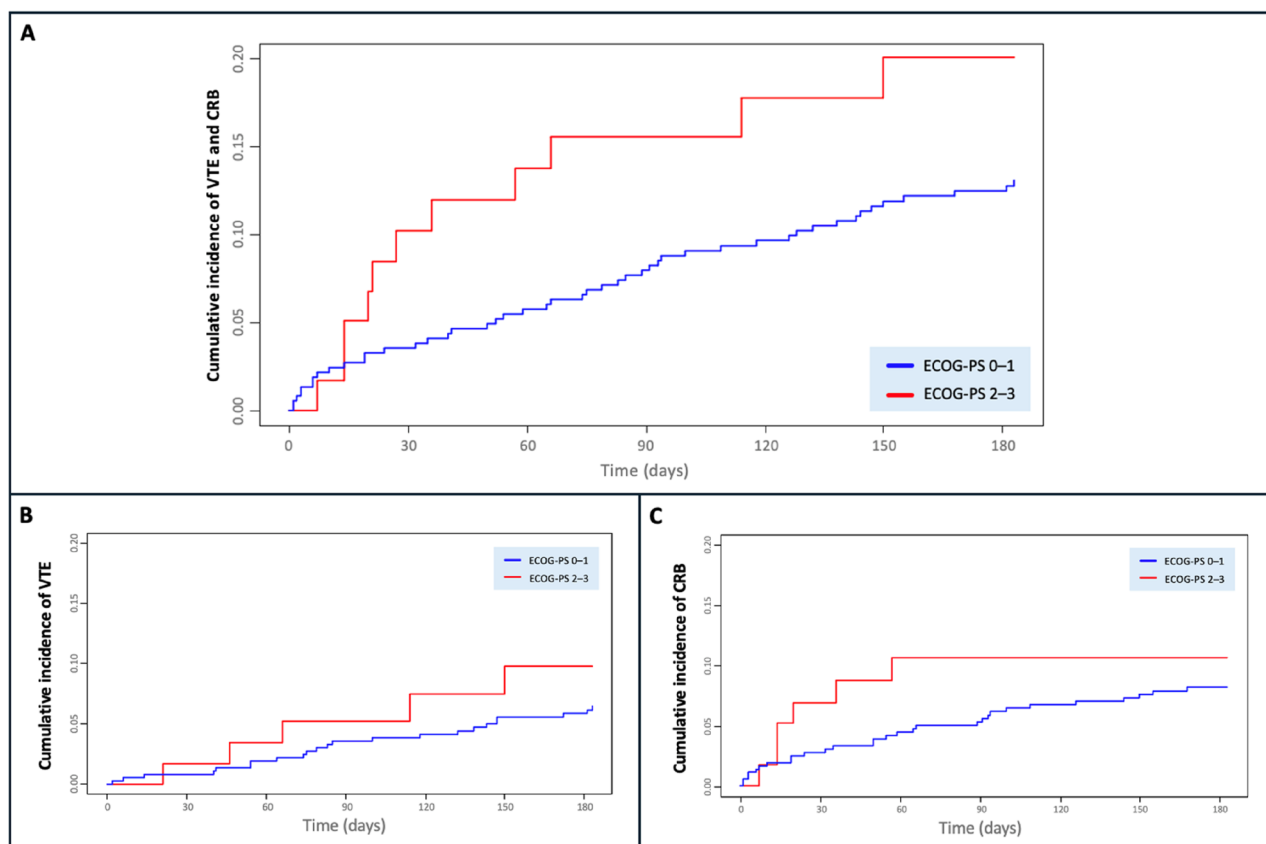


Fig. 1 Cumulative incidence function curve for: (A) the primary composite outcome of venous thromboembolism and clinically relevant bleeding, (B) venous thromboembolism alone, and (C) clinically relevant bleeding alone, by ECOG-PS

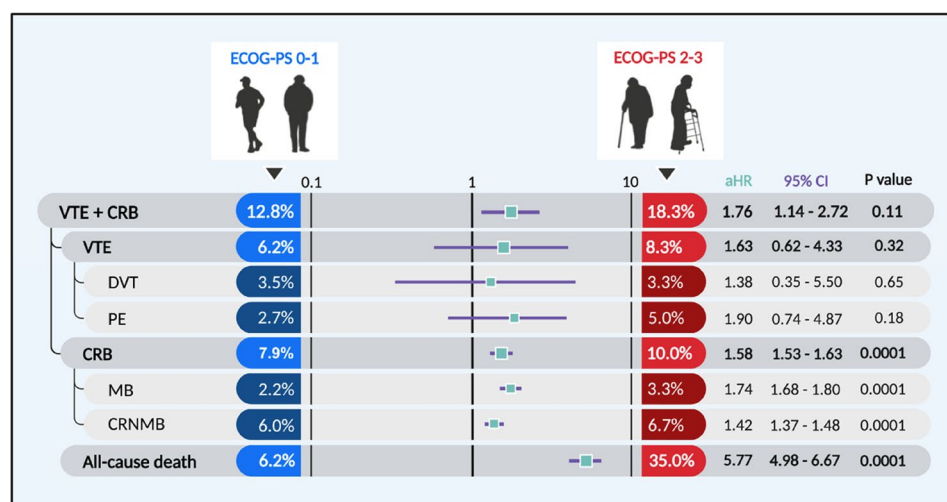


Fig. 2 Risk for the primary and secondary study outcomes according to ECOG-PS. Notes: HRs refer to ECOG-2/3 vs ECOG-0/1 (reference); aHRs are controlled for age, gender, treatment allocation, body mass index, and creatinine clearance. Abbreviations: aHR, adjusted hazard ratio; DVT, deep vein thrombosis; CRB, clinically relevant bleeding; CRNMB, clinically relevant non-major bleeding; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism; 95% CI, 95% confidence interval

Table 4 Associations of ECOG-PS score (2–3 vs. 0–1) with the study outcomes in multivariable regression models

	Crude HR (95%CI)	P value	Adjusted HR (95%CI) ^a	P value	Subdistribution aHR (95% CI) ^b	P value
Primary composite outcome:						
VTE + CRB	1.70 (1.11–2.60)	0.014	1.76 (1.14–2.72)	0.011	1.75 (1.13–2.69)	0.012
Secondary outcomes:						
VTE	1.58 (0.61–4.08)	0.35	1.63 (0.62–4.33)	0.32	1.57 (0.60–4.15)	0.34
DVT	1.18 (0.29–4.73)	0.82	1.38 (0.35–5.50)	0.65	1.33 (0.34–5.22)	0.69
PE	2.09 (0.85–5.12)	0.11	1.90 (0.74–4.87)	0.18	1.84 (0.71–4.74)	0.21
CRB	1.47 (1.42–1.52)	<0.0001	1.58 (1.53–1.63)	<0.0001	1.58 (1.53–1.63)	<0.0001
MB	1.75 (1.70–1.80)	<0.0001	1.74 (1.68–1.80)	<0.0001	1.73 (1.67–1.80)	<0.0001
CRNMB	1.28 (1.23–1.32)	<0.0001	1.42 (1.37–1.48)	<0.0001	1.41 (1.36–1.47)	<0.0001
All-cause mortality	6.82 (6.01–7.75)	<0.0001	5.77 (4.98–6.67)	<0.0001	–	–

Abbreviations: aHR adjusted hazard ratio, DVT deep vein thrombosis, CRB clinically relevant bleeding, CRNMB clinically relevant non-major bleeding, MB major bleeding, PE pulmonary embolism, VTE venous thromboembolism, 95% CI 95% confidence interval

^aCox proportional hazard model with censoring at death, adjusted for age, gender, treatment allocation, body mass index, and creatinine clearance

^bFine-Gray multivariable subdistribution hazard model accounting for the competing risk of all-cause death, adjusted for the same confounders used in the Cox proportional hazard model

the primary composite outcome and CRB remained consistent (adjusted subdistribution HRs 1.75 [95% CI, 1.13–2.69]; $p=0.012$, and 1.58 [95% CI, 1.53–1.63]; $p<0.0001$; respectively) (Table 4).

Treatment interaction by performance status

Exploratory analyses examined whether the effects of apixaban differed by performance status. A statistically significant interaction was observed for the primary composite outcome (p for interaction = 0.0052) (Table 5). Apixaban was associated with reduced risk for thrombohemorrhagic events in participants with ECOG-PS 2–3 (aHR 0.49; 95% CI: 0.28–0.85; $p=0.012$), whereas the net effect was close to neutral in those with ECOG-PS 0–1 (aHR 1.06; 95% CI: 1.04–1.09; $p<0.0001$). Apixaban

reduced VTE risk across ECOG-PS strata, including among participants with ECOG-PS 2–3, although the interaction for VTE did not reach statistical significance (p for interaction = 0.084). For CRB, apixaban was associated with increased bleeding risk among patients with ECOG-PS 0–1, whereas no clear excess bleeding was detected among those with ECOG-PS 2–3.

Discussion

In this post hoc analysis of the AVERT randomized controlled trial evaluating primary VTE prophylaxis with apixaban [11], performance status, assessed through the ECOG-PS, was a strong and independent predictor of 6-month clinical outcomes in ambulatory patients with active cancer initiating systemic chemotherapy

Table 5 Exploratory treatment-effect analyses of apixaban vs. placebo according to ECOG-PS category

	aHR (95% CI)	P-value for HR	P-value for interaction
VTE or CRB			
Apixaban vs. Placebo in ECOG 0–1 group	1.06 (1.04–1.09)	< 0.0001	0.0052
Apixaban vs. Placebo in ECOG 2–3 group	0.49 (0.28–0.85)	0.012	
VTE			
Apixaban vs. Placebo in ECOG 0–1 group	0.54 (0.52–0.55)	< 0.0001	0.084
Apixaban vs. Placebo in ECOG 2–3 group	0.21 (0.01–0.62)	0.0046	
CRB			
Apixaban vs. Placebo in ECOG 0–1 group	1.46 (1.42–1.50)	< 0.0001	< 0.0001
Apixaban vs. Placebo in ECOG 2–3 group	0.89 (0.77–1.03)	0.12	

Estimates are derived from exploratory post hoc interaction analyses and should be interpreted cautiously given the modest number of outcome events, particularly within the ECOG-PS 2–3 subgroup

Abbreviations: aHR adjusted hazard ratio, CRB clinically relevant bleeding, VTE venous thromboembolism, 95% CI 95% confidence interval.

and at intermediate-to-high thrombotic risk. Patients with ECOG-PS 2–3 had up to a 1.7-fold higher risk for the primary composite outcome of VTE and CRB compared with those with ECOG-PS of 0–1. Although the increased VTE risk associated with ECOG-PS 2–3 did not reach statistical significance, poorer performance status demonstrated an association with bleeding complications, conferring a 60% higher risk of CRB and a 75% higher risk of MB.

Prior observational studies have suggested a relationship between higher ECOG-PS scores and incident cancer-associated VTE [26, 27], a pattern not confirmed in this interventional trial, although VTE rates were directionally higher in patients with poorer performance status. Differences in study design, lack of adjustment for anticoagulant exposure in earlier cohorts, and evolving guideline-based use of thromboprophylaxis may partly explain these discrepancies. Collectively, the available evidence might point toward an important role of physical vulnerability and multidomain frailty, beyond tumor and treatment factors, in shaping bleeding susceptibility in cancer, a concept supported by data from non-cancer patients receiving direct oral anticoagulants for VTE or atrial fibrillation [28–32]. Future studies should elucidate the molecular and clinical determinants linking impaired functional status, frailty phenotypes, and thrombotic-hemorrhagic risk profiles in cancer populations [33, 34].

Consistent with prior studies in patients with cancer-associated PE, we observed markedly increased all-cause mortality among individuals with poorer performance status [21, 22], nearly a 6-fold higher risk at 6 months. These findings highlight the importance of incorporating ECOG-PS into shared, value-based decision-making, ensuring that thromboprophylaxis strategies align with patient preferences, quality-of-life considerations and goals of care.

Our results complement those from recent analyses including the Hokusai-VTE Cancer subanalysis by Farmakis et al., in which ECOG-PS predicted the 12-month composite of recurrent VTE and MB (aHR: 2.13; 95% CI:

1.24–3.67) in patients with cancer-associated PE [23]. ECOG-PS deterioration over time, rather than baseline ECOG-PS, was most prognostic in that study [23]. Differences in trial populations, endpoints and durations notwithstanding, the aggregate data highlight the prognostic relevance of both baseline and interval changes in ECOG-PS, and suggest that a 6-month assessment window may be clinically informative for thrombo-hemorrhagic outcomes in ambulatory cancer populations. Similarly, the CARAVAGGIO trial demonstrated that ECOG-PS 2 predicted MB risk during apixaban treatment for cancer-associated VTE (aHR: 2.31; 95%CI: 1.24–4.29) [35]. A recent meta-analysis further identified ECOG-PS ≥ 2 as one of the strongest predictors of bleeding in cancer-associated VTE, second only to prior bleeding and brain cancer [36]. The present study extends these observations by demonstrating prognostic value of performance status in the setting of primary thromboprophylaxis.

These findings, which require confirmation, have potentially important implications. Future studies should evaluate whether incorporation of ECOG-PS, or broader multidimensional frailty assessments, into risk prediction models enhance the identification of patients at elevated thrombo-hemorrhagic risk [33]. Importantly, both performance status and multidimensional frailty are potentially modifiable targets amenable to multimodal interventions [37]. Exercise-based rehabilitation and structured supportive-care pathways have demonstrated benefits across diverse cancer populations [38]. Whether interventions aimed at improving physical or multidomain frailty can translate into improved vascular outcomes or reduce thrombo-hemorrhagic events warrants prospective evaluation [37, 39].

Frailty measures have previously been linked with anticoagulation safety and efficacy in non-cancer patients with VTE or atrial fibrillation [28–32]. Despite overall poorer thrombo-hemorrhagic outcomes in the ECOG-PS 2–3 stratum, the exploratory treatment-interaction analysis suggested that apixaban may retain a net clinical benefit in this more vulnerable subgroup, while suggesting a

relatively neutral net effect in those with ECOG-PS 0–1. Apixaban reduced VTE risk across ECOG-PS strata, with numerically greater relative benefit in participants with poorer performance, though this interaction did not reach statistical significance. Regarding bleeding, apixaban increased CRB among ECOG-PS 0–1 participants but did not increase bleeding in the ECOG-PS 2–3 group. These findings suggest that poorer performance status alone should not necessarily preclude consideration of apixaban thromboprophylaxis in otherwise eligible patients, while individualized assessment of bleeding risk, cancer status, treatment regimen, and goals of care remains essential.

These interaction data must be interpreted cautiously given their exploratory nature, modest event rates, and potential for residual confounding. It remains plausible that the high baseline bleeding risk in patients with poor performance status may attenuate observable treatment differences. Nevertheless, the overall results suggest that physically frail participants did not experience disproportionate harm from apixaban prophylaxis, consistent with emerging evidence showing preserved or even favorable apixaban safety profiles across frailty strata in non-cancer populations [28, 29, 40].

Our study has several limitations. First, the number of outcome events was relatively small, and a modest proportion of participants had ECOG-PS 2–3, although this proportion is comparable to or higher than in several other cancer-associated VTE trials [23, 35, 41]. Notably, unlike many trials that excluded patients with ECOG-PS > 2, the AVERT trial had no such restriction, broadening representation of more vulnerable patients. However, patients unable to attend ambulatory visits, as well as those with life expectancy < 6 months, were excluded by design [11]. Thus, findings cannot be extrapolated to hospitalized, bed-bound community-dwelling or end of life patients (ECOG-PS of 4). The ongoing Towards Cancer Patient Empowerment for Optimal Use of Antithrombotic Therapy at the End of Life (SERENITY) study will provide valuable information for these populations [42]. Second, randomization in AVERT was not stratified by ECOG-PS; although analyses were adjusted for baseline differences, residual confounding cannot be excluded, including from tumor-related factors such as cancer stage or metastatic disease, as well as treatment-related factors such as anticancer therapy type and chemotherapy regimen. Third, ECOG-PS, while simple, pragmatic, and widely used, has inherent limitations including interobserver variability and the inability to capture multidimensional frailty, which is better assessed using validated tools such as gait speed, handgrip strength, the Short Physical Performance Battery, the Geriatric-8, and the Vulnerable Elders Survey-13 [4, 43–47]. Integrating ECOG-PS with dedicated frailty measures

is recommended in onco-geriatric care and may refine prognostication and clinical decision-making in cancer-associated VTE [37, 39]. Nevertheless, the AVERT study was a randomized, placebo-controlled trial with central blinded adjudication and minimal loss of follow up, minimizing bias for secondary analyses.

Conclusions

In this post-hoc analysis of the AVERT randomized trial, ECOG-PS emerged as a strong independent predictor of thrombo-hemorrhagic outcomes and all-cause mortality in ambulatory patients with cancer initiating chemotherapy and at intermediate-to-high risk for VTE. The findings identify the clinical value of incorporating performance status, and potentially broader frailty-based assessment, into risk stratification and shared decision-making in the setting of primary anticoagulant thromboprophylaxis, potentially enhancing individualized, value-based care pathways and improve selection of patients most likely to benefit from cancer-associated VTE prevention strategies.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40959-026-00542-7>.

Supplementary Material 1: Supplementary Table 1. Description and crude rates of the study primary and secondary outcome events, by ECOG-PS.

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Authors' contributions

N. Potere, Y. Xu and M. Carrier contributed to study design, data interpretation, and wrote the manuscript draft. R. Mallick performed the statistical analyses. M. Carrier and P. Wells were responsible for the study conception, planning and supervision. All authors critically reviewed and provided key contributions to the manuscript.

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None.

Data availability

The data underlying this study may be available from the corresponding author, Dr. Marc Carrier, upon reasonable request and subject to approval by the AVERT trial steering committee.

Declarations

Ethics approval and consent to participate

The AVERT trial (ClinicalTrials.gov number, NCT02048865) was approved by the institutional research ethics board or ethics committee at each participating center, and all participants provided written informed consent before enrollment. The present study is a post hoc analysis of previously collected AVERT trial data and did not involve additional patient contact or study procedures.

Competing interests

N. Potere has received, outside of the present work, research fellowships and awards from the International Society on Thrombosis and Haemostasis (ISTH), the Canadian Venous Thromboembolism Research Network (CanVECTOR) and the Italian Society for the Study on Thrombosis and Haemostasis, and research funding, paid to his institution, from the International Network of Venous Thromboembolism Clinical Research Networks (INVENT) and the ISTH Scientific and Standardization Committee. M.D.N. reports personal fees as invited speaker from Werfen, Mylan, Leo Pharma and Pfizer, and institutional funding from Leo Pharma outside of the present work. A Lazo-Langner has received research funding from Regeneron Pharmaceuticals. M. Carrier has received research funding from BMS, Pfizer, and Leo Pharma, and honoraria from Bayer, Pfizer, BMS, Servier, and Leo Pharma. The other authors have no relevant conflicts of interest to disclose.

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