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Symptom Management and Supportive Care

D-dimer enhances risk targeted thromboprophylaxis in ambulatory cancer patients

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Abstract

Background. Thromboprophylaxis for ambulatory cancer patients is effective, although uncertainties remain on who should be targeted. Using D-dimer values from individuals enrolled to the AVERT trial, we sought to identify and validate a more efficient VTE risk threshold for thromboprophylaxis.

Methods. The AVERT trial compared thromboprophylaxis with apixaban to placebo among cancer patients with a Khorana Risk Score ≥ 2. The D-dimer measured at randomization was used to calculate an individualized 6-month VTE risk using the validated CATScore. A modified intention to treat analysis was used to assess efficacy (VTE) and safety (major and overall bleeding) in the a) complete cohort, b) ≥8% and <8% 6-month VTE risk thresholds.

Results. 574 patients were randomized in the AVERT trial, 466 (81%) with baseline D-dimer were included in the study. 237 subjects received apixaban, 229 received placebo. In the complete cohort, there were 13 (5·5%) VTE events in the apixaban arm compared to 26 (11·4%) events in the placebo arm (aHR-0·49 (0.25-0.95), p<0·05). Number needed to treat (NNT) to prevent one VTE=17. 82(35%) and 72(31%) patients in the apixaban and placebo arms, respectively had a 6-month VTE risk ≥8%. In this sub-group, 7 (8·4%) VTE events occurred with apixaban and 19(26·3%) events with placebo (aHR-0·33 (0·14-0·81), p<0.05), NNT=6. Individuals with a VTE risk <8% derived no benefit from apixaban thromboprophylaxis (aHR-0·89 (0·30-2·65), p=0·84). Increased rates of overall bleeding were observed with apixaban in both the complete (aHR-2·11 (1·09-4·09), p<0.05) and ≥8% predicted risk cohorts (aHR-2·87 (0·91-9·13), p=0·07).

Conclusions. A 6-month VTE risk threshold of ≥8% increases the efficiency of risk targeted thromboprophylaxis in ambulatory cancer patients. ***The Oncologist*** 2020;9999:• •

Implications for Practice: Ambulatory cancer patients receiving chemotherapy have an increased risk of venous thromboembolism (VTE). A Khorana Risk Score (KRS) ≥2 is currently the suggested threshold for thromboprophylaxis. Using baseline D-dimer values from individuals enrolled to the AVERT trial, this retrospective validation study identifies a 6-month VTE risk of ≥8% as a more efficient threshold for thromboprophylaxis. At this threshold, the number needed to treat to prevent one VTE is 6 compared to 17 in with a KRS≥2. Conversely, individuals with a predicted risk of <8% derive no clinical benefit from thromboprophylaxis. Future prospective studies should validate this threshold for outpatient thromboprophylaxis.

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Introduction

The increased incidence of venous thromboembolism (VTE) among patients with cancer is well established[1] and the

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development of VTE portends a worse prognosis in this patient population[2,3]. High quality randomized controlled trial (RCT) evidence suggests that thromboprophylaxis with either oral or parenteral anticoagulation is effective in reducing the incidence of VTE in ambulatory cancer patients[4–7]. Notably, the absolute risk reduction (ARR) in VTE achieved by thromboprophylaxis varies significantly by the treated cohort's baseline predicted risk of VTE.

The Khorana Risk Score (KRS) is the most widely used and externally validated risk prediction tool to categorize patients into low, intermediate and high risk of VTE based on tumor type, as well as clinical and hematologic parameters[8]. A KRS greater than or equal to two was an inclusion criterion in both the AVERT and CASSINI placebo-controlled RCTs that demonstrated the superiority of the direct factor Xa inhibitors, apixaban and rivaroxaban (respectively), in reducing rates of VTE in ambulatory cancer patients[6,7]. Several guidelines now encourage consideration of thromboprophylaxis among ambulatory cancer patients due to start chemotherapy who have a KRS ≥2[9–11]. Prospective comparison of several VTE risk prediction tools in cancer patients have shown that models utilizing thrombosis biomarkers, such D-dimer and soluble p-selectin, are able to better discriminate between low and high VTE risk patients[12–14].

In the most recent iteration of the Vienna VTE risk prediction score, Pabinger *et al*. combined the clinical tumor site with the baseline plasma D-dimer to develop and externally validate the 2018 Vienna 'CATScore' in two large prospective cohorts[15]. This score provides an individualized 6-month risk of VTE and demonstrated superior model performance compared to existing prediction models. In this retrospective validation study, we sought to utilize individual patient data from the AVERT study to: a) identify a more efficient VTE risk threshold for thromboprophylaxis using the CATScore; and b) perform a post hoc analysis of the AVERT study to address the safety and efficacy of risk-targeted thromboprophylaxis using the CATScore.

Methods

Study Participants

We used available data from patients enrolled in the AVERT study, a randomized, double blind placebo controlled clinical trial that assessed thromboprophylaxis with low dose apixaban, 2·5mg twice daily, in ambulatory cancer patients due to start a minimum expected course of 3 months of cytotoxic chemotherapy. Patients with a KRS ≥2 were eligible for inclusion in the study. Table S1 describes the modified KRS used for patient selection; the full trial protocol and inclusion criteria have been previously described[7]. In this analysis, we excluded 108 patients for whom baseline D-dimer measurements were not available prior to the first dose of study drug. Patients excluded from this analysis are described in Table S2. The total treatment duration for the AVERT study was 180 days and patients were followed up to 210 days or death. This study was approved by all institutional review boards at participating organizations.

D-dimer measurements

Blood samples for biomarker analyses were collected on the day of study enrollment (range day -28 to day 0 (i.e. day of chemotherapy initiation) and prior to administration of the first dose of either apixaban or placebo. Blood was drawn into 0·109M sodium citrate tubes. Within one hour of sample collection, platelet poor plasma was prepared by centrifugation for 15 minutes at 2000g. Plasma samples for D-dimer measurement were stored at -80°C after snap freezing. All D-dimer assays were performed at the Ottawa Hospital Research Laboratory using an immunoturbidimetric assay (STA-Liatest D-Di 20; Diagnostica Stago, Asnières, France). When the initial assay reading was > 4 μg/ml, the sample was diluted according to manufacturer specifications to yield a corrected assay range of 0·27-20 μg/ml.

CATScore and 6-month VTE risk prediction

The CATScore was developed and validated using data from two independent prospective cohorts designed to assess risk factors for VTE in patients with cancer. Participants in both studies had thrombosis biomarkers measured at the point of enrolment into the study and individuals receiving anticoagulation either therapeutic or prophylactic were excluded. In their model development, Pabinger et al. had maintained tumor risk site categorization as per the original KRS (Table S1), adding colorectal cancer to the 'high risk' category. Using prespecified variable selection process, the authors identified D-dimer and tumor risk categorization for inclusion into the CATScore. Using tumor type and D-dimer from the patient's in the AVERT study, we calculated the 6-month predicted risk of VTE for each individual using the published online calculator[15,16]. The individual 6-month predicted risk of VTE was calculated at 'baseline' i.e. prior to receipt of placebo or apixaban.

Outcomes

The primary efficacy outcome of the AVERT trial was the first episode of objectively documented proximal deep vein thrombosis (DVT) or pulmonary embolism (PE). VTE was defined as any symptomatic or incidentally discovered proximal DVT of the lower or upper limbs, non-fatal symptomatic or incidentally discovered, or PE-related death. The AVERT study did not perform routine ultrasonographic testing in asymptomatic patients.

The main safety outcome was major bleeding as defined by the International Society on Thrombosis and Hemostasis i.e. a) fatal bleeding, b) bleeding occurring in a critical site or, c) a decrease in hemoglobin level of 2g/dL or requiring transfusion of 2 or more units of packed red cells[17]. Clinically relevant non-major bleeding was defined as bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of the assigned treatment, or impairment in daily activities. In this analysis, safety outcomes were reported separately for a) major bleeding events and b) overall bleeding (a combination of major and clinically relevant non-major bleeding events).

Statistical Analysis

All statistical analyses were performed with R Studio Version 1.2.5001. Model discrimination was assessed using the receiver operator characteristic (ROC) curve and quantified using the area under the ROC curve (AUC), with the 95% CI calculated using the DeLong method[18]. A decision curve analysis was conducted to assess the net benefit at a range of threshold probability generated by the CATScore among patients randomized to the placebo arm[19,20]. Among patients randomized to the placebo arm, sensitivity, specificity, positive and negative predictive values were assessed at a range of 6-month VTE risk thresholds as calculated by the CATScore and KRS ≥3. No statistical comparisons were made between the baseline characteristics of the complete cohort and the cohorts stratified by the ≥8% VTE Risk threshold cutoff. Categorical variables were described numerically and as percentages, continuous variables were described using means, standard deviations and interquartile ranges. We estimated thrombosis free survival, major bleeding free survival and overall bleeding free survival (combined outcome of major and clinically relevant non-major bleeding) between individuals randomized to apixaban vs. placebo using the Kaplan-Meier method and compared results between groups using the log-rank test. We report the 180 day estimate with 95% confidence intervals for both safety and efficacy event free survival outcomes. A multivariable Cox proportional hazards model adjusting for age and sex was used to provide the adjusted Hazard Ratios (aHR) for VTE, major bleeding and all clinically relevant bleeding over the time course of the AVERT study. All safety and efficacy outcomes were calculated using the modified intention to treat analysis. The absolute risk reduction (ARR) for VTE prevention was calculated by subtracting the event rate in the placebo arm from the event rate in the apixaban arm for the complete cohort and risk stratified cohort. The number needed to treat (NNT) is the inverse of the ARR. This analysis meets the recently established consensus guidelines on the analysis and reporting of risk based variation of benefit across trial populations[21].

Results

Of 574 randomized patients in the AVERT study, 466 were included in this analysis, as 108 had no available baseline D-dimer assay. The baseline clinical characteristics of patients excluded from our study is described in Table S2. Among individuals randomized to the placebo arm (n=229), the CATScore demonstrated improved discrimination for VTE (AUC 0·75 (95% CI, 0·65-0·86)) compared to the KRS (AUC 0·56 (95% CI 0·46-0·66)) (Figure S1). The decision curve analysis demonstrates that the application of the CATScore has increased net benefit at a range of 6-month predicted VTE risk thresholds compared to a KRS ≥2 (Figure 1). A 6-month VTE risk of 8% was the optimal threshold for risk stratification, and at this threshold the CATScore had a sensitivity of 73%, specificity of 74%, positive predictive value of 26% and negative predictive value of 96% (Table S3). In comparison, a similar proportion of patients in the placebo arm had a KRS ≥3 (n=73 (32%)). However, the sensitivity was only 42% with a positive predictive value of 15% (Table S3).

The baseline clinical characteristics of individuals included in this analysis are summarized in Table 1. The mean 6-month predicted VTE risk was 10·9% (95% CI 10·5%-11·3%) in the ≥8% risk cohort compared to 5.4% (95% CI 5·3-5·5%) in the <8% risk cohort, with a mean D-dimer of 4·0 μg/ml (95% CI, 3·2-4·9 μg/ml) in the ≥8% risk cohort vs. 1·2 μg/ml (95% CI, 1·1-1·3 μg/ml) in the <8% risk cohort. Individuals in the ≥8% cohort were more likely to be male 59% vs. 33% and have a lower BMI (27.9 kg/m^2 (95% CI, 26.0-27.9) vs. 30.7kg/m^2 (95% CI, 29.8-31.6)). All patients with a very high-risk tumor type for VTE i.e. pancreatic, gastric and primary brain had a predicted 6-month VTE risk ≥8%.

VTE outcomes by risk cohorts

The median duration of follow up was 196 days (IQR 188-204 days) in the complete cohort and was identical in the ≥8% and <8% risk cohorts. In the complete cohort, there were 13 (5·5%) VTE events in the apixaban arm and 26 (11·4%) events in the placebo arm (aHR 0·49: 95% CI, 0·25-0·95, p<0·05) (Table 2). The 180-day thrombosis free survival in the apixaban arm was 95% (95% CI 92-98%) compared to 89% (95% CI 85-93%) in the placebo arm (Figure 2). When selecting patients for thromboprophylaxis based on a KRS ≥2 (i.e. the complete cohort), the absolute risk reduction (ARR) of 5·9% equates to a corresponding number needed to treat (NNT) with apixaban of 17 to prevent one VTE.

In the ≥8% 6-month VTE risk cohort, there were 7 (8·4%) VTE events in the apixaban arm and 19 (26·3%) in the placebo arm (aHR 0·33 (0·14-0·81), p<0·05) and the corresponding 180-day thrombosis free survival was 93% (95% CI 87-98%) in the apixaban arm versus 74% (95% CI 65%-85%, p<0·01) in the placebo arm. When selecting patients for thromboprophylaxis using a CATScore 6-month VTE risk threshold of ≥8%, the ARR is 17·9% with a corresponding NNT with apixaban of 6.

In the <8% risk cohort, there was no significant difference in the VTE events between patients treated with apixaban (n=6 (3·9%)) versus placebo (n=7 (4·5%)) (aHR 0·89 (0·30-2·65), p=0·84) (Table 2). In this cohort, the 180-day thrombosis free survival was 96% (95% CI 94-100%) in the apixaban arm compared to 95% (95% CI 92-99%) in the placebo arm (Figure 2).

Bleeding outcomes by risk cohort

In the complete cohort, there were no significant differences in major bleeding events in the apixaban arm (n=9 (3·8%)) compared to the placebo arm (n=5 (2·2%)) (aHR 1·83 (95% CI, 0·61-5·45), p=0·28). Patients receiving apixaban had increased overall bleeding rates compared to placebo (n=27 (11·4%) vs. 13 (5·7%)) (aHR 2·11 (95% CI 1·09-4·09), p<0·05) (Table 2). Patients receiving apixaban in the complete cohort had a 180-day major bleeding free survival of 96% (95% CI 94-99%) and 180-day overall bleeding free survival of 88% (95% CI 84-92%) (Figure 3).

In the ≥8% risk cohort, there was no significant difference in major bleeding between apixaban and placebo (n=5

(6%) vs. 3 (4·2%)) (aHR 1·91 (95% CI 0·44-8·19) p=0.39). However, while the rates of overall bleeding were increased in the apixaban arm (n=11 (13%) vs. 4 (5·6%) in the placebo arm), this was not statistically significant (aHR 2·87 (95% CI, 0·91-9·13), p=0·07) (Table 2). In the ≥8% cohort, patients receiving apixaban had a 180-day major bleeding free survival of 94% (95% CI 88-99%) and 180-day overall bleeding free survival of 86% (95% CI 79-94%) (Figure 3).

In the <8% risk cohort, major and overall bleeding events were lower compared to the ≥8% risk cohorts. There was no significant difference in major bleeding events between apixaban and placebo (n=4 (2.6%) vs. n=2 (1.3%)) (aHR 2.07 (95% CI 0·38-11·3) p=0·40). Although there were increased rates of overall bleeding in the apixaban arm (n=16 (10·3) vs. 9 (5·7%)) this was not statistically significant (aHR 1·89 (95% CI 0·83-4·27), p=0·13). In the <8% cohort, patients receiving apixaban had a 180-day major bleeding free survival of 97% (95% CI 95-100%) and 180-day overall bleeding free survival of 89% (95% CI 84-94%) (Figure 3).

Discussion

Despite the longstanding and robust evidence on the utility of thromboprophylaxis in reducing the VTE burden among ambulatory cancer patients[4–7], methods for identifying the appropriate 'high-risk' population for the most efficient use of thromboprophylaxis continues to generate much debate[22]. In this study, we retrospectively validated the 2018 Vienna CATScore[15] in a cohort of ambulatory cancer patients with a Khorana Risk Score ≥2 who were enrolled into the placebo controlled AVERT thromboprophylaxis trial[7]. We confirm the excellent discrimination of the CATScore for VTE prediction; furthermore, we propose a 6-month VTE risk cutoff of ≥8% as a risk threshold for consideration of thromboprophylaxis among ambulatory cancer patients. At this threshold, the NNT to prevent one VTE with apixaban thromboprophylaxis is only 6, compared to an NNT of 17 when using a KRS ≥2. Patients with a 6-month predicted risk of VTE <8% appear to derive no benefit in terms of VTE prevention from thromboprophylaxis with apixaban. Patients in the ≥8% and <8% cohorts do not experience increased rates of major bleeding. Similar rates of overall clinically relevant bleeding with apixaban was seen in the complete and risk stratified cohorts.

The Khorana Risk Score was published in 2008 and was developed from a prospective cohort of patients enrolled in the Awareness of Neutropenia Study Group Registry [8]. A significant advantage and key to the initial popularity of the KRS is the readily available clinical and hematologic parameters required at the time of risk stratification, without the need for additional measurements of thrombotic biomarkers. However, subsequent prospective validation studies and systematic reviews have demonstrated the limitation of the KRS in terms of positive predictive value for VTE and that the key component for risk prediction of the KRS is the categorization and weighting of the primary tumor type[12,22,23]. When developing and validating the 2018 Vienna 'CATScore', Pabinger *et al*. maintained the tumor type categorization as per the KRS and added D-dimer on a continuous scale for improved risk prediction[15]. In their external validation cohort, the CATScore had an AUC of 0·68 (95% CI 0·62-0·74) versus 0.56 (95% CI 0.50-0.63) for the KRS in the same cohort. Similarly, we demonstrate the excellent discrimination of the CATScore when applied to the placebo arm of the AVERT study. This is in contrast to the poor sensitivity of the KRS that has been previously highlighted[23]. Although the sensitivity of a KRS ≥3 in the placebo arm of the AVERT of 42% is an improvement from previously published figures[22,23], it does not compare favorably to 73% sensitivity seen with a CATScore at a threshold of ≥8%.

At our recommended 6-month VTE risk threshold of ≥8%, similar to a KRS ≥2, all patients categorized with 'very high risk' tumor types would receive thromboprophylaxis. The measurement of D-dimer and evaluation of CATScore would thus have limited utility in the decision to provide thromboprophylaxis in this patient population. However, as the CATScore has not been widely adopted into clinical practice and still needs further validation, we would advocate the ongoing calculation of the CATScore even among very high risk tumor types. Future studies, ideally including patients with KRS 0 or 1, may identify a higher 6-month VTE risk threshold, which would thus necessitate measurement of D-dimer and calculation of the CATScore in all tumor types.

D-dimer is a global marker of fibrinolysis and is a key component of the CATScore. It is widely available in clinical laboratories, and commonly used for its negative predictive value to exclude low risk VTE[24,25]. D-dimer is now also being used to assess the risk of VTE recurrence on cessation of oral anticoagulation [26]. Most prior risk prediction tools utilize D-dimer as a dichotomous variable i.e. either normal or elevated[13,24–26], however dichotomization is known to result in significant loss in vital clinical information[27]. By maintaining D-dimer on a continuous scale, Pabinger et al. are better able to utilize this thrombotic biomarker for risk prediction[15]. Interestingly, the Vienna Prediction Model for VTE recurrence, similar to the CATScore, utilized D-dimer on a continuous scale also and demonstrated improved discrimination between high and low risk patients[28].

Unlike the KRS, the requirement for a D-dimer assay for the CATScore poses additional practical hurdles in real world implementation of risk-targeted thromboprophylaxis in ambulatory cancer patients. Additionally, increasing efforts will need to be placed on the operating characteristics of the large variety of commercially available D-dimer assays, as the results from the nomogram generated by Pabinger *et al*. may not translate directly to all D-dimer assays[29]. Despite these potential limitations, prior quality improvement strategies that incorporate electronic health records to provide personalized VTE prophylaxis to ambulatory cancer patients have been shown to be an effective tool to increase thromboprophylaxis uptake rates [30].

Limitations

There are several important limitations in our study. First, the model performance of the CATScore was assessed in a cohort of patients with a KRS ≥2 enrolled in the AVERT trial. It remains uncertain if the risk discrimination will be as robust when applied to a wider cohort of ambulatory

cancer patients with lower baseline predicted risks of VTE. Notably, the low risk group (i.e. KRS of 0 or 1) accounted for greater than 50% of the individuals enrolled into the prospective cohorts used for the development and validation of the CATScore[15]. However, our study is not able to evaluate the proportion of patients with a KRS<2 who would be categorized as having a CATScore ≥8%. Second, in this post-hoc analysis we excluded 108 randomized patients due to the omission of baseline D-dimer measurement. Although there does not appear to be a systematic etiology for this omission and the excluded patients had similar baseline clinical characteristics, the possibility of an inadvertent selection bias and confounding remains. Third, given the exclusion of patients at high risk of bleeding from clinical trials evaluating thromboprophylaxis and the caveats of translating trial results into real world practice[6,7,31], most societal guidelines still recommend an individualized patient-centered approach when deciding on thromboprophylaxis[9,10]. Interestingly, similar to the evolution of primary and secondary prevention in cardiovascular disease, an individualized risk percentile as generated by the CATScore may aid in this shared decision making process[32]. Fourth, we are mindful to highlight that the inclusion criteria for the AVERT study required patients to have a minimum intent of 3-month of outpatient cytotoxic chemotherapy. The role of thromboprophylaxis among those receiving immunotherapy, targeted therapy or hormonal therapy alone has not been fully outlined. Finally, we demonstrate that there are increased rates of overall bleeding with apixaban in the complete cohort analysis; however, the rates of overall bleeding were not statistically significant in the cohorts stratified by the CATScore. With the reduced sample size, we would be mindful for the possibility of a type II error in this instance.

In summary, thromboprophylaxis in cancer patients due to start outpatient chemotherapy has been shown to be effective. Using baseline D-dimer from individuals enrolled into the AVERT thromboprophylaxis trial, we demonstrated the improved efficiency of risk targeted thromboprophylaxis using the 2018 Vienna CATScore. We propose a 6-month VTE risk of ≥8% as a threshold for patient selection, where the number needed to treat to prevent one VTE is only 6. Future prospective studies should aim to further validate the CATScore and our recommended threshold.

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References

1. Blom JW, Vanderschoot JPM, Oostindiër MJ, Osanto S, Van Der Meer FJM, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66 329 cancer patients: Results of a record linkage study. J Thromb Haemost 2006; 4: 529–35.

2. Sørensen HT, Mellemkjær L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000; 343: 1846–50.

3. Wun T, White RH. Epidemiology of cancer-related venous thromboembolism. Best Pract. Res. Clin. Haematol. 2009; 22: 9–23.

4. Agnelli G, Gussoni G, Bianchini C, *et al*. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol 2009; 10: 943–9.

5. Agnelli G, George DJ, Kakkar AK, *et al*. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 2012; 366: 601–9.

6. Khorana AA, Soff GA, Kakkar AK, *et al*. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med 2019; 380: 720–8.

7. Carrier M, Abou-Nassar K, Mallick R, *et al*. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med 2019; 380: 711–9.

8. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008; 111: 4902–7.

9. Key NS, Khorana AA, Kuderer NM, *et al*. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2019; 38: 496–523.

10. Wang TF, Zwicker JI, Ay C, *et al*. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: Guidance from the SSC of the ISTH. J Thromb Haemost 2019; 17: 1772–8.

11. Farge D, Frere C, Connors JM, *et al*. 2019 International Clinical Practice Guidelines for the Treatment and Prophylaxis of Venous Thromboembolism in Patients With Cancer. Lancet Oncol 2019; 20: e566–81.

12. van Es N, Di Nisio M, Cesarman G, *et al*. Comparison of risk prediction scores for venous thromboembolism in cancer patients: A prospective cohort study. Haematologica 2017; 102: 1494–501.

13. Ay C, Dunkler D, Marosi C, Chiriac A, Pabinger I. Prediction of venous thromboembolism in cancer patients. Blood 2010; 116: 5377–83.

14. Alexander M, Ball D, Solomon B, *et al*. Dynamic Thromboembolic Risk Modelling to Target Appropriate Preventative Strategies for Patients with Non-Small Cell Lung Cancer. Cancers (Basel) 2019; 11: 50.

15. Pabinger I, van Es N, Heinze G, *et al*. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. Lancet Haematol 2018; 5: e289–98.

16. catscore: Cancer-associated VTE – clinical prediction model. https://cemsiis.meduniwien.ac.at/en/kb/science-research/software/clinical-software/cancer-vte/ (accessed Jan 13, 2020).

17. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J. Thromb. Haemost. 2005; 3: 692–4.

18. Robin X, Turck N, Hainard A, *et al*. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics 2011; 12: 77.

19. Vickers AJ, Elkin EB. Decision curve analysis: A novel method for evaluating prediction models. Med Decis Mak 2006; 26: 565–74.

20. Biostatistics: Decision Curve Analysis | Memorial Sloan Kettering Cancer Center. https://www.mskcc.org/departments/epidemiology-biostatistics/biostatistics/decision-curve-analysis (accessed Feb 14, 2020).

21. Kent DM, Paulus JK, Van Klaveren D, *et al*. The Predictive Approaches to Treatment effect Heterogeneity (PATH) statement. Ann Intern Med 2020; 172: 35–45.

22. Mulder FI, Bosch FTM, Es N Van. Primary Thromboprophylaxis in Ambulatory Cancer Patients : Where Do We Stand ? Cancers (Basel) 2020; 12: 1–17.

23. Mulder FI, Candeloro M, Kamphuisen PW, *et al*. The khorana score for prediction of venous thromboembolism in cancer patients: A systematic review and meta-analysis. Haematologica 2019; 104: 1277–87.

24. Wells PS, Anderson DR, Rodger M, *et al*. Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism

presenting to the emergency department by using a simple clinical model and D-dimer. Ann Intern Med 2001; 135: 98–107.

25. Wells PS, Anderson DR, Rodger M, *et al*. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003; 349: 1227–35.

26. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of Venous Thromboembolism Recurrence: High Negative Predictive Value of D-dimer Performed after Oral Anticoagulation Is Stopped. Thromb Haemost 2002; 87: 7–12.

27. Altman DG, Royston P. The cost of dichotomising continuous variables. Br. Med. J. 2006; 332: 1080.

28. Eichinger S, Heinze G, Kyrle PA. D-dimer levels over time and the risk of recurrent venous thromboembolism: an update of the Vienna prediction model. J Am Heart Assoc 2014; 3: e000467.

29. Linkins L-A, Takach Lapner S. Review of D-dimer testing: Good, Bad, and Ugly. Int J Lab Hematol 2017; 39: 98–103.

30. Ades S, Gilchrist A, Holm A, Libby K, Cushman M, Douce D. Venous thromboembolism prevention in the ambulatory cancer clinic (VTE-PACC): A Systems-based, personalized, multidisciplinary program to increase venous thromboembolism (VTE) risk assessment, education and anticoagulant prophylaxis in cancer outpatients. Blood 2017; 130: 217–217.

31. Najafzadeh M, Schneeweiss S. From trial to target populations - Calibrating real-world data. N. Engl. J. Med. 2017; 376: 1203–5.

32. Lloyd-Jones DM, Braun LT, Ndumele CE, *et al*. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Special Report From the American Heart Association and American College of Cardiology. Circulation 2019; 139: e1162–77.

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Table 1. Baseline clinical characteristics

Characteristics	Complete Cohort		2018 CATScore ≥ 8%		2018 CATScore < 8%	
	Apixaban	Placebo	Apixaban	Placebo	Apixaban	Placebo
	N=237	N=229	N=83	N=72	N=154	N=157
Age - year						
Mean +/- SD	60·6 +/- 12·6	61·0 +/- 11·8	59·5 +/- 11·7	61·8 +/- 9·9	61·2 +/- 13·0	60·6 +/- 12·6
Interquartile Range	54-70	55-69	54-67	55 - 67	54-71	54-70
Sex						
Male (%)	98 (41)	98 (43)	48 (58)	44 (61)	50 (32)	54 (34)
CrCl (ml/min)						
Mean +/- SD	109 +/- 42	107 +/- 44	107 +/- 40	104 +/- 35	110 +/- 43	109 +/- 48
Interquartile Range	80-133	76-129	81-117	83-119	78-139	73-133
Weight - kg						
Mean +/- SD	81 +/- 23	83 +/- 22	76 +/- 19	78 +/- 18	83 +/- 24	85 +/- 23
Interquartile Range	62-96	67-95	61-87	63-87	64-98	68-97
BMI kg/m^2						
Mean +/- SD	29·3 +/- 7·8	29·6 +/- 7·4	27·0 +/- 6·5	27·0 +/- 5·6	30·6 +/- 8·1	30·9 +/- 7·8
Interquartile Range	23-36	24-35	23-30	24-29	24-37	25-36
Tumor Type N - (%)						
Brain	13 (5·4)	8 (3·5)	13 (15·7)	8 (11·1)	0 (0)	0 (0)
Lung	24 (10·1)	23 (10·0)	2 (2·4)	2 (2·8)	22 (14·2)	21 (13·4)
Stomach	23 (9·7)	16 (7·0)	23 (27·7)	16 (22·2)	0 (0)	0 (0)
Pancreatic	27 (11·4)	30 (13·1)	27 (32·5)	30 (41·7)	0 (0)	0 (0)
Lymphoma	62 (26·1)	58 (25·3)	9 (10·8)	4 (5·6)	53 (34·4)	54 (34·3)
Gynecologic	65 (27)	61 (26·6)	8 (9·6)	10 (13·9)	57 (37·0)	51 (32·5)
Other	23 (9·8)	33 (14·4)	1 (1·2)	2 (2·8)	22 (14·2)	31 (19·7)
Khorana Risk Score (%)						
2	151 (63·7)	156 (68·1)	45 (54·2)	44 (61·1)	106 (68·8)	112 (71·3)
3	65 (27·4)	57 (24·9)	26 (31·3)	20 (27·8)	39 (25·3)	37 (23·5)
4	21 (8·9)	16 (7·0)	12 (14·4)	8 (11·1)	9 (5·8)	8 (5·1)
D-dimer µg/ml						
Mean +/- SD	2·2 +/- 3·5	2·1 +/- 3·5	3·9 +/- 5·3	4·1 +/- 5·5	1·3 +/- 1·0	1·2 +/- 1·0
Interquartile Range	0·6-2·4	0·4-2·0	0·6-4·9	0·5-6·7	0·5-1·7	0·4-1·6
6-month predicted risk (%)						
Mean +/- SD	7·4 +/- 3·1	7·1 +/- 3·3	10·9 +/- 2·5	11·0 +/- 3·0	5·5 +/- 1·0	5·3 +/-1·1
IQR	5·1 – 9·6	4·9 – 8·9	9·3-11·6	9·1-11·8	4·9-6·1	4·7-6·0

Abbreviations: CATScore (Risk Prediction tool used to calculate 6 month predicted VTE[15]), *CrCl* – Creatinine Clearance, *BMI* – Body Mass Index

Table 2. Efficacy and safety data of complete and risk stratified populations

	Complete Analytic AVERT cohort			CATScore ≥8%*			CATScore <8%*		
Outcome	**Apixaban**	**Placebo**	**Hazard Ratio**	**Apixaban**	**Placebo**	**Hazard Ratio**	**Apixaban**	**Placebo**	**Hazard Ratio**
	N=237	N=229	(95% CI)	N=83	N=72	(95% CI)	N=154	N=157	(95% CI)
VTE - N (%)	13 (5·5)	26 (11·4)	0·49 (0·25-0·95)$	7 (8·4)	19 (26·3)	0·33 (0·14-0·81)$	6 (3·9)	7 (4·5)	0·89 (0·30-2·65)
Major Bleeding - N (%)	9 (3·8)	5 (2·2)	1·83 (0·61-5·45)	5 (6·0)	3 (4·2)	1·91 (0·44-8·19)	4 (2·6)	2 (1·3)	2·07 (0·38-11·3)
Overall bleeding - N (%)	27 (11·4)	13 (5·7)	2·11 (1·09-4·09)$	11 (13)	4 (5·6)	2·87 (0·91-9·13)	16 (10·3)	9 (5·7)	1·89 (0·83-4·27)

The complete analytic cohort comprises of all patients enrolled into the AVERT study for whom baseline D-dimer was available.
*- Each patient was stratified by their individualized 6-month predicted risk of venous thromboembolism (VTE)[15]
$-adjusted Hazard Ratios p<0.05 (adjusted for age and sex)
Abbreviations: CATScore – 2018 Vienna CATScore, VTE – Venous thromboembolism

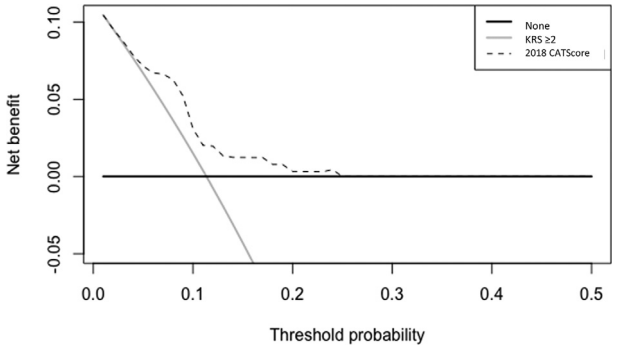

Figure 1. Decision Curve Analysis
A decision curve analysis among participants randomized to the placebo arm of the AVERT study. The net benefit (y-axis) is calculated as the true positive rate minus the weighted false positive rate for venous thromboembolism (VTE) and is demonstrated at a range of risk threshold probabilities (x-axis – right truncated at 0.5). The dashed line demonstrates the net benefit for the use of the CATScore based selection for thromboprophylaxis, whereas the grey and black lines represents the net benefit of alternative strategies of the Khorana risk score (KRS) of greater than or equal to 2 (grey) or treating no one (black).

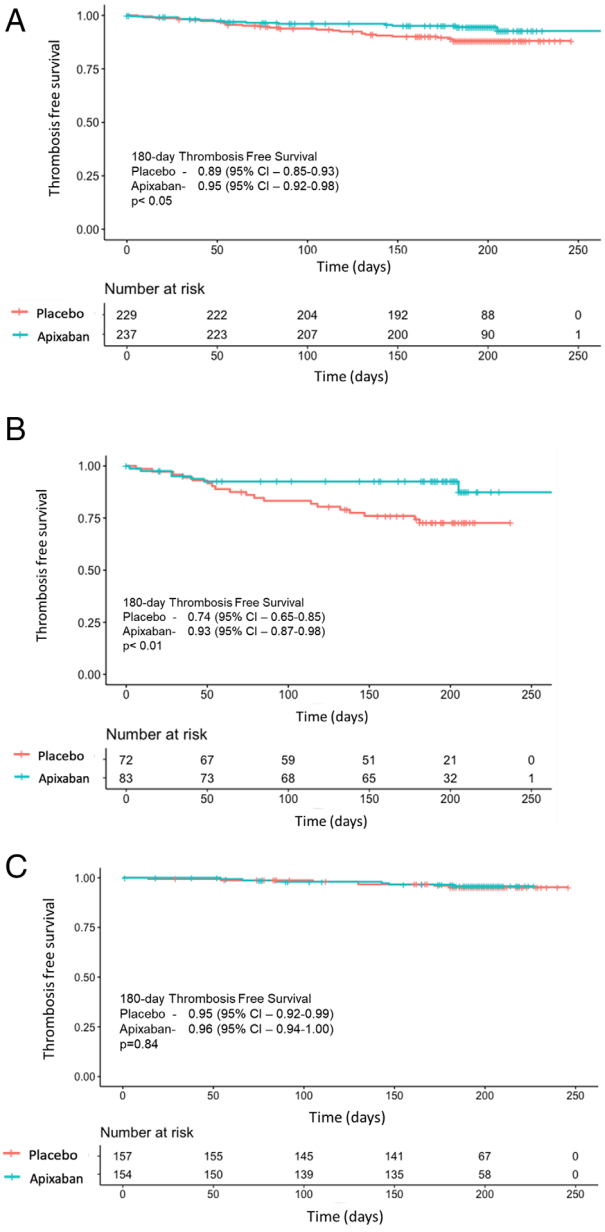

Figure 2. Kaplan-Meier analysis of thrombosis free survival

A Kaplan-Meier analysis with log rank test was used to compare the thrombosis free survival between twice daily apixaban 2.5mg versus placebo for A) all patients enrolled into the AVERT study for whom baseline D-dimer values were available B) individuals in the AVERT study with a 6-month predicted risk of VTE (venous thromboembolism) greater than or equal to 8% or C) 6-month predicted risk of less than 8%. A) Thromboprophylaxis with apixaban led to an improved thrombosis free survival compared to placebo with an absolute risk reduction (ARR) of 5·9% at 180-days (number needed to treat (NNT) = 17) p<0·05. B) Among patients with a 6-month predicted risk $\geq$ 8%, apixaban had a 180-day ARR of 17·9% (NNT = 6), p<0·01. C) Individuals with a 6-month predicted risk < 8% derived no benefit in thrombosis free survival when receiving prophylaxis with apixaban compared to placebo (p=0·84).

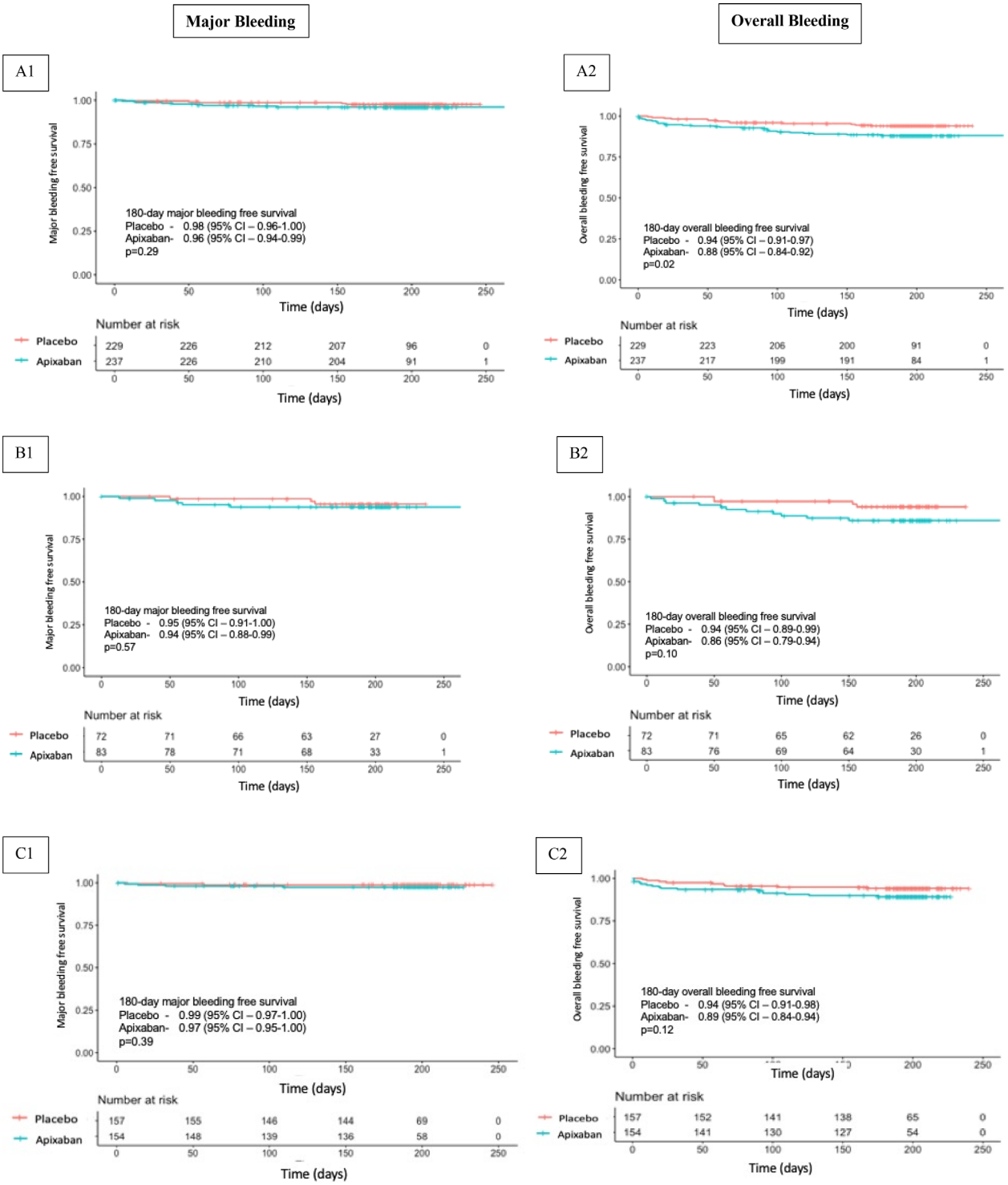

Figure 3. Kaplan-Meier analysis of major and overall bleeding events
A Kaplan-Meier analysis with log rank test demonstrated no difference in major bleeding events in patients randomized to thromboprophylaxis with apixaban 2·5mg twice daily versus placebo in A1) all patients enrolled into the AVERT study for whom baseline D-dimer was available (p=0·29) B1) individuals with a 6-month predicted VTE (venous thromboembolism) rate of ≥ 8%, p=0·57 or C1) individuals with a 6-month predicted VTE rate < 8%, p=0·39. There was an increased rate of overall bleeding (composite of major and clinically relevant non-major bleeding) in all patients randomized to apixaban 2.5mg BID versus placebo, this was significant in the complete analytic cohort (p=0·02) with no significance in patients with a 6-month predicted VTE risk ≥ 8% (B2) p=0·10 or those with a 6-month predicted VTE risk <8% (C2) p=0·12.