Predicting outcomes in patients with cancer and atrial fibrillation

Alejandra Gutierrez, Rushad Patell, Lisa Rybicki and Alok A. Khorana

Abstract

Background: The role of cancer-specific factors for ischemic stroke and mortality in patients with cancer and atrial fibrillation (AF) is unknown. We evaluated the utility of a previously validated risk tool for venous thromboembolism (VTE) in cancer outpatients [Khorana score (KS)] in predicting stroke and mortality in cancer patients with AF.

Methods: We conducted a retrospective cohort study of patients with cancer and AF at the Cleveland Clinic from 2008 to 2014. Outcomes, CHADS2, CHA2DS2-VASc, and KS scores were calculated from date of cancer diagnosis. Prognostic factors were identified with Fine and Gray regression (for stroke) or Cox proportional hazards analysis (for mortality).

Results: The study population comprised 1181 patients. Genitourinary (19%), lung (18%), and gastrointestinal (13%) were the most frequent cancers. Overall, 67% had CHADS2 $\geq$ 2, 57% had an intermediate KS (1–2), and 7% had a high KS ($\geq$3). Median follow up was 26.5 months (range 0.03–76). At a median of 8.2 months (range 0–61), 45 patients (3.8%) developed a stroke and 418 (35%) died. In multivariable analysis, a high KS (HR 4.5, 95% CI 3.2–6.3, $p < 0.001$) was associated with a quadruple risk of death and every point increase in CHADS2 score had a 20% increased risk of death (HR 1.19, 95% CI 1.1–1.2, $p < 0.001$). The addition of KS did not improve risk stratification for ischemic stroke to CHADS2.

Conclusion: In patients with cancer and AF, CHADS2 and CHA2DS2-VASc but not KS was predictive of ischemic stroke. A high KS represented a unique predictor of mortality beyond traditional risk scores.

Keywords: atrial fibrillation, cancer, mortality, stroke

Received: 16 January 2019; revised manuscript accepted: 10 June 2019.
common pathophysiology between VTE and arterial events in AF, we hypothesized that a validated risk score in cancer patients that predicts the development of VTE may also predict stroke and mortality.

AF is a common comorbidity in cancer patients and factors that predict outcomes in this high-risk population are unknown. Thus, we aimed to evaluate whether the addition of a validated risk score for the development of VTE in cancer patients, the KS adds prognostic information to CHADS2 and CHA2DS2-VASc for the development of ischemic stroke and mortality in cancer patients with a pre-existing diagnosis of AF.

**Methods**
The Cleveland Clinic tumor registry was queried for consecutive patients with a diagnosis of AF and cancer from 2008 to 2014. The time of cancer diagnosis was used as baseline and all patients included carried a prior diagnosis of AF as indicated by the cancer registry. An electronic query system of the electronic health records (EHRs) was used to collect additional variables not available in the registry and corroborate a diagnosis of AF by ICD-10 (International Statistical Classification of Diseases) codes. The study received approval from the institutional review board (15–1411). Informed consent was waived by the IRB given this was a retrospective study and the use of anonymous clinical data for the analysis.

The CHADS2 score (defined as one point per each: congestive heart failure, hypertension, age >75 years, diabetes mellitus [DM], and two points for a history of stroke) CHA2DS2-VASc score (defined as one point for congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, previous stroke, transient ischemic attack [TIA], vascular disease, and female sex, and two points for age >75 years and prior thromboembolism) and KS [calculated as one point per each: high-risk cancer site (lung, lymphoma, gynecologic, bladder or testicular cancer), hemoglobin <100 g/L or use of red cell growth factors, platelet count ≥250,000/mm³, leukocyte count ≥11,000/mm³ and body mass index (BMI) ≥35 kg/m²; and two points for very high-risk cancer site (stomach and pancreas)]. Patients were categorized as low risk of VTE if KS is 0, intermediate risk if KS is 1–2, and high risk if KS ≥3. All three scores were calculated with baseline characteristics at the time of cancer diagnosis. Laboratory values were obtained within 90 days of cancer diagnosis. Antiplatelet and anticoagulant therapy use within 3 months of cancer diagnosis was recorded. Manual review of the EHRs was performed by two independent authors (RP, AG) for comorbidities included in CHADS2 and CHA2DS2-VASc scores, and development of stroke.

Outcomes studied were ischemic stroke and mortality. Stroke was defined as per World Health Organization criteria as a new neurologic deficit due to a focal injury to the central nervous system by a vascular cause or imaging evidence confirmed by a neurologist. Strokes were classified as ischemic and hemorrhagic and patients with hemorrhagic strokes were excluded. Survival was determined by active follow up via chart review and appraisal of the social security death index yearly until loss to follow up or death.

Baseline characteristics are reported as mean and standard deviation or median and range for continuous variables, or as frequency counts and percentages for categorical variables. Outcomes were calculated from the date of cancer diagnosis. Ischemic stroke was estimated with the cumulative incidence method and survival was estimated by Kaplan–Meier. Univariable risk factors were identified with Fine and Gray regression for stroke and Cox proportional hazards analysis for survival. Based on Wald statistics, CHADS2, and CHA2DS2-VASc had similar association with ischemic stroke, whereas CHADS2 had a much strong association with survival than CHA2DS2-VASc. Univariable results are shown for both variables, while multivariable models included only CHADS2. Variables included in the model were: age at cancer diagnosis, gender, race, BMI, smoking status, history of hypertension, hyperlipidemia, vascular disease, diabetes, heart failure or stroke, primary cancer site, cancer stage, metastatic disease at diagnosis, baseline laboratory parameters [including hemoglobin, white blood cell count (WBC), platelet count, creatinine, blood urea nitrogen (BUN), albumin, activated partial thromboplastin time (aPTT), and prothrombin time (PT)] antiplatelet and anticoagulant therapy within 3 months of cancer diagnosis. For
each particular model variables that were part of the score being assessed (CHADS2, CHA2DS2-VASc, or KS) were excluded from the multivariable models to avoid collinearity. Multivariable analyses were performed using stepwise selection with a variable entry criterion of $p \leq 0.10$ and a variable retention criterion of $p \leq 0.05$. For overall survival two models were used. Model 1 excluded variables with $>15\%$ missing data whereas model 2 excluded variables with $>10\%$ missing data. Results are shown as hazard ratio (HR) and 95% confidence interval (CI).

**Predictors of ischemic stroke**

In univariable analysis being from a non-White race, having a history of stroke or TIA, increased serum creatinine levels, and having used antiplatelet therapy within 3 months of cancer diagnosis were significantly associated with an increased risk of ischemic stroke. In addition, a higher CHADS2 and CHA2DS2-VASc scores was associated with approximately a 40–30% increased risk of stroke per each point increase, respectively (Table 2).

KS was not associated with increased risk of ischemic stroke either analyzed as a continuous variable or as a categorical variable stratifying patients into intermediate, low, or high risk. Primary cancer site could not be analyzed given the low rate of events and the number of categories.

Three significant risk factors for ischemic stroke were identified using multivariable analysis: CHADS2 score, creatinine, and antiplatelet therapy (Table 3). When KS was added to this model to assess the effect on ischemic stroke, it was not significant analyzed either as a categorical variable (Table 3) or as a continuous variable (results not shown).

**Predictors of overall survival**

In univariable analysis multiple risk factors were associated with mortality risk, including age, gender, BMI, smoking status, hyperlipidemia, vascular disease, diabetes, heart failure, stroke/TIA, cancer stage, metastasis, hemoglobin, WBC, platelet count, and BUN (Table 2).

The three risk prediction scores were associated with overall survival in univariable analysis. For each point increase in the CHADS2 score the mortality risk increased by 22%, each point increase with the CHA2DS2-VASc score was associated with a 15% increase in mortality, and each point increase in the KS with a 58% increased mortality risk. Having an intermediate KS doubled the risk of death and a high risk quadrupled it. In univariable analysis, all KS components were statistically significant except for BMI $>35$ kg/m$^2$ (HR 0.80, 95% CI 0.61–1.05, $p = 0.11$). A high-risk cancer was associated with higher risk of death (HR 1.72, 95% CI 1.40–2.11, $p < 0.001$) and a very high-risk
cancer was associated with almost three times higher risk of death (HR 3.62, 95% CI 2.56–5.13, p < 0.001). Hemoglobin <10 g/dl was associated with higher risk of death (HR 2.84, 95% CI 2.27–3.54, p < 0.001), as were a platelet count ≥350,000/mm³ (HR 2.01, 95% CI 1.51–2.70, p < 0.001) and a leukocyte count ≥11,000/mm³ (HR 1.46, 95% CI 1.16–1.84, p = 0.002).

In multivariable analysis excluding variables with >15% missing data, KS and CHADS2 were both prognostic for mortality (Table 4). In this model, a high KS was associated with a twofold increased risk of death (HR 2.31, 95% CI 1.55–3.44, p < 0.001) while each point increase in the CHADS2 score was associated with 12% increased mortality risk (HR 1.12, 95% CI 1.02–1.22, p = 0.018). Other risk factors associated with higher mortality risk were metastatic disease at diagnosis, prolonged aPT, and higher BUN. Variables associated with a lower mortality risk included female gender and higher albumin. However, this model was based on data from 818 patients (69% of patients) and 302 deaths (72% of deaths). When KS was analyzed as a continuous variable in this model rather than a categorical variable, each point increase in the score was associated with 32% increased risk of death (HR 1.32, 95% CI 1.18–1.48, p < 0.001).

In multivariable analysis excluding variables with >10% missing data, both KS and CHADS2 remained prognostic. A high KS was associated with a fourfold increased risk of death as compared with patients with a low KS risk, and intermediate KS was associated with twofold increased risk of death. Each point increase in CHADS2 was associated with a 19% increase in risk of death. In this model having a history of vascular disease and higher BUN were associated with increased risk of death while being female and a diagnosis of hyperlipidemia were associated with a lower risk. This model was based on 99% of study patients and 99% of deaths. When KS was included in this model as a continuous variable an increase in one point in the KS was associated with 61% increased risk of death (HR 1.61, 95% CI 1.46–1.76, p < 0.001).

In multivariable analysis excluding variables with >15% missing data, KS and CHADS2 were both prognostic for mortality (Table 4). In this model, a high KS was associated with a twofold increased risk of death (HR 2.31, 95% CI 1.55–3.44, p < 0.001) while each point increase in the CHADS2 score was associated with 12% increased mortality risk (HR 1.12, 95% CI 1.02–1.22, p = 0.018). Other risk factors associated with higher mortality risk were metastatic disease at diagnosis, prolonged aPT, and higher BUN. Variables associated with a lower mortality risk included female gender and higher albumin. However, this model was based on data from 818 patients (69% of patients) and 302 deaths (72% of deaths). When KS was analyzed as a continuous variable in this model rather than a categorical variable, each point increase in the score was associated with 32% increased risk of death (HR 1.32, 95% CI 1.18–1.48, p < 0.001).

In multivariable analysis excluding variables with >10% missing data, both KS and CHADS2 remained prognostic. A high KS was associated with a fourfold increased risk of death as compared with patients with a low KS risk, and intermediate KS was associated with twofold increased risk of death. Each point increase in CHADS2 was associated with a 19% increase in risk of death. In this model having a history of vascular disease and higher BUN were associated with increased risk of death while being female and a diagnosis of hyperlipidemia were associated with a lower risk. This model was based on 99% of study patients and 99% of deaths. When KS was included in this model as a continuous variable an increase in one point in the KS was associated with 61% increased risk of death (HR 1.61, 95% CI 1.46–1.76, p < 0.001).

**Discussion**

Cancer-associated thrombosis is a leading cause of death in patients with cancer. Further, cancer patients have a higher rate of thromboembolism,
|                | Ischemic stroke          | Overall survival          |
|----------------|--------------------------|---------------------------|
|                | HR  | 95% CI   | p value | HR  | 95% CI   | p value |
| Age ≥75/<75   | 1.32| 0.73–2.37| 0.35    | 1.58| 1.31–1.92| <0.001 |
| Female        | 1.52| 0.85–2.69| 0.16    | 0.80| 0.66–0.98| 0.04    |
| White         | 0.44| 0.21–0.95| 0.04    | 0.79| 0.58–1.08| 0.15    |
| BMI           |     |          |         |     |          |         |
| Weight        |     |          |         |     |          |         |
| Overweight/obese | 1.22| 0.62–2.37| 0.57    | 1.23| 0.98–1.55| 0.07    |
| Normal/obese  | 1.17| 0.53–2.57| 0.70    | 1.45| 1.12–1.87| 0.004   |
| Underweight/obese | 1.15| 0.16–8.42| 0.89    | 3.73| 2.31–6.04| <0.001  |
| Smoking status (n = 1120) |     |          |         |     |          |         |
| Former/never  | 1.04| 0.56–1.94| 0.89    | 1.39| 1.11–1.74| 0.004   |
| Current/never | 0.22| 0.03–1.64| 0.14    | 1.87| 1.35–2.58| <0.001  |
| Hypertension  | 1.34| 0.66–2.69| 0.42    | 0.98| 0.79–1.22| 0.88    |
| Hyperlipidemia | 1.18| 0.65–2.14| 0.59    | 0.83| 0.68–1.00| 0.05    |
| Vascular disease | 1.19| 0.66–2.14| 0.56    | 1.42| 1.17–1.72| <0.001  |
| Diabetes      | 0.98| 0.50–1.94| 0.96    | 1.25| 1.01–1.55| 0.040   |
| Heart failure | 1.23| 0.63–2.37| 0.54    | 1.65| 1.34–2.04| <0.001  |
| Stroke/TIA    | 3.77| 2.03–6.99| <0.001  | 1.40| 1.08–1.83| 0.012   |
| Cancer stage (per 1 level increase) | 0.98| 0.74–1.29| 0.88    | 2.07| 1.87–2.29| <0.001  |
| Metastasis    | 0.83| 0.29–2.37| 0.73    | 5.85| 4.61–7.42| <0.001  |
| Hemoglobin (per 1 g/dl increase) | 0.91| 0.81–1.03| 0.14    | 0.81| 0.78–0.84| <0.001  |
| WBC (per 5 K/µl increase) | 1.15| 0.86–1.53| 0.33    | 1.16| 1.06–1.28| 0.002   |
| Platelets (per 25 K/µl increase) | 0.96| 0.89–1.02| 0.21    | 1.03| 1.00–1.06| 0.022   |
| Creatinine, per 1 mg/dl increase (n = 1176) | 1.14| 1.00–1.31| 0.043   | 1.02| 0.94–1.11| 0.60    |
| BUN, per 5 mg/dl increase (n = 1175) | 0.99| 0.85–1.15| 0.89    | 1.08| 1.04–1.12| <0.001  |
| Antiplatelet therapy | 2.34| 1.30–4.21| 0.004   | 1.17| 0.96–1.43| 0.13    |
| Anticoagulants | 1.16| 0.64–2.09| 0.62    | 1.04| 0.86–1.27| 0.66    |
| CHADS2 (per 1 point increase) | 1.40| 1.13–1.74| 0.002   | 1.22| 1.13–1.31| <0.001  |
| CHA2DS2-VASc (per 1 point increase) | 1.29| 1.10–1.50| 0.002   | 1.15| 1.09–1.22| <0.001  |
| KS            |     |          |         |     |          |         |
| Per 1 point increase | 0.91| 0.66–1.24| 0.55    | 1.58| 1.44–1.72| <0.001  |
| Intermediate/low | 0.81| 0.44–1.46| 0.48    | 2.07| 1.64–2.60| <0.001  |
| High/low      | 0.82| 0.25–2.74| 0.75    | 4.26| 3.04–5.98| <0.001  |

BMI, body mass index; BUN, blood urea nitrogen; KS, Khorana score; TIA, transient ischemic attack; WBC, white blood cell count.
bleeding, and mortality compared with the general population making risk stratification difficult.\textsuperscript{19–21} AF represents an additional challenge in the treatment of malignant conditions and mortality risk scores for cancer patients with AF have not been developed nor validated. This study attempts to fill this void of outcome prediction in cancer and AF patients. We found that CHADS2, CHA2DS2-VASc, and KS are associated with overall survival in cancer patients with pre-existing AF.

A high KS was associated with a quadruple increase in mortality risk representing a unique predictor of mortality beyond traditional risk scores in this population. In a recent study including 163 patients with active cancer and AF and a mean CHA2DS2-VASc of 3.2 anticoagulated with rivaroxaban the cumulative risk of death per year was 22.6\% with a risk of stroke of 1.6\%.\textsuperscript{8} The KS has been a useful mortality risk stratification tool in some cancer cohorts. In a study including 719 patients with lung cancer, having a high KS was associated with 1.7 times higher risk of death (95\% CI 1.4–2.2). This is similar to that seen in our cohort and other literature.\textsuperscript{22,23} Other reports in different cancer types are conflicting. In a retrospective single-center study of 109 patients with more than 90\% with low or intermediate KS did not predict mortality.\textsuperscript{24} In another retrospective study specific for gastric cancer including 112 patients, high KS was not associated with worse survival.\textsuperscript{25} However larger studies including solid tumors and lymphoma reiterate the value of KS for mortality prediction where a high score was associated with a HR of 3 and intermediate risk carried a HR of 2.3 for mortality.\textsuperscript{26} There are no prior reports on mortality risk assessment for patients with cancer and AF. In our study all components of the KS were associated with overall survival except BMI. Further, the sensitivity analysis confirmed a relationship between KS and overall survival.

Traditional risk factors for ischemic stroke including CHADS2 and CHA2DS2-VASc were also associated with overall survival in this cohort. Prior studies in patients with and without AF support this finding. Chen \textit{et al.} showed that in a cohort of 1311 patients with systolic heart failure with and without AF CHADS2, CHA2DS2-VASc, and R2CHADS2 which includes 2 points for renal dysfunction were all associated with overall survival.\textsuperscript{27} In a prior study including patients with and without AF who had cardiac resynchronization therapy, CHA2DS2-VASc but not CHADS2 was associated with increased mortality at a median follow up of 30 months.\textsuperscript{28} Further studies have shown that pre and post stroke CHADS2, CHA2DS2-VASc are associated with mortality even in patients without a

**Table 3.** Multivariable analysis of risk factors for ischemic stroke.

|                  | HR     | 95\% CI    | \( p \) value |
|------------------|--------|------------|---------------|
| **Model 1: significant variables and CHADS2 score**                                                                 |
| CHADS2, per 1 point increase | 1.39   | 1.11–1.73  | 0.004         |
| Creatinine, per 1 mg/dl increase | 1.16   | 1.00–1.35  | 0.045         |
| Antiplatelet therapy | 2.36   | 1.29–4.32  | 0.005         |
| **Model with the addition of the KS**                                                                                     |
| CHADS2, per 1 point increase | 1.41   | 1.13–1.76  | 0.002         |
| Creatinine, per 1 mg/dl increase | 1.16   | 0.99–1.34  | 0.06          |
| Antiplatelet therapy | 2.41   | 1.32–4.40  | 0.004         |
| KS intermediate/low risk | 0.70   | 0.38–1.27  | 0.23          |
| KS high/low risk      | 0.74   | 0.23–2.44  | 0.63          |

CI, confidence interval; HR, hazard ratio; KS, Khorana score.
diagnosis of AF. It is therefore of no surprise that in our cohort CHADS2 and CHA2DS2-VASc was associated with overall survival.

Prior studies have shown that the traditionally used scores such as the CHA2DS2-VASc should be used cautiously in patients with AF and cancer. In a study by D’Souza et al. using nationwide registries including roughly 120,000 patients those with a low CHA2DS2-VASc score of 0–1 had a higher risk of stroke than noncancer patients but in those with a score more than or equal to two the risk between cancer and noncancer patients did not differ. This finding was confirmed in a larger cohort where the impact of AF on the risk of stroke decreased in high CHA2DS2-VASc scores further emphasizing the need for better risk assessment tools in this cohort. In our study we tried to assess whether the addition of validated prediction scores for thromboembolism to the guideline standard prediction scores added prognostic information for stroke in patients with cancer and AF. We found that the KS was not associated with increased risk of ischemic stroke in univariable or multivariable analysis. This suggests the need of an interdisciplinary evaluation including oncologists/hematologists and cardiologists could be useful for the patient’s optimal management.

Our results are consistent with the existing literature showing that both CHADS2, CHA2DS2-VASc are associated with increased risk of ischemic stroke. However, in our study the use of antiplatelet therapy within 3 months of cancer diagnosis was associated with increased risk of stroke. We speculate that this might be a marker of patients who are at increased risk of stroke or embolic events and might have contraindications to anticoagulants or other confounding factors not accounted for in our adjusted analysis that may be responsible for this seemingly paradoxical effect. Interestingly, we did not find an association of female sex with increased risk of stroke finding consistent with recently published studies.

This study is limited primarily by the retrospective, single-center nature of its design. We collected information from a cancer registry and electronic medical record review but might

---

Table 4. Multivariable analysis of prognostic factors for overall survival.

|                      | Model 1 (n = 818; 302 deaths) |                      | Model 2 (n = 1175; 417 deaths) |
|----------------------|-------------------------------|----------------------|-------------------------------|
|                      | HR 95% CI p value             |                      | HR 95% CI p value             |
| Female               | 0.77 0.60–0.98 0.035          | 0.75 0.61–0.93 0.008 |
| Metastasis           | 4.28 3.30–5.56 <0.001         | NA NA NA             |
| Vascular disease     | NA NA NA                     | 1.40 1.14–1.72 0.002 |
| Hyperlipidemia       | NA NA NA                     | 0.70 0.57–0.86 <0.001|
|                      | Laboratory parameters         |                      |                               |
| PT (per 10 s increase) | 1.18 1.04–1.34 0.009         | NA NA NA             |
| BUN (per 5 mg/dL increase) | 1.07 1.02–1.12 0.003         | 1.06 1.01–1.10 0.012  |
| Albumin (per 1 g/dl increase) | 0.49 0.42–0.58 <0.001         | NA NA NA             |
|                      | Khorana score                 |                      |                               |
| Intermediate/low     | 1.23 0.92–1.64 0.16           | 1.93 1.53–2.44 <0.001|
| High/low             | 2.31 1.55–3.44 <0.001         | 4.52 3.20–6.37 <0.001 |
| CHADS2 (per 1 point increase) | 1.12 1.02–1.22 0.018         | 1.19 1.10–1.29 <0.001|

BUN, blood urea nitrogen; CI, confidence interval; HR, hazard ratio; PT, prothrombin time.
underestimate the number of ischemic events and deaths that could have presented elsewhere, lost to follow up, improperly coded, or deaths occurring overseas. Further, medication use was assessed within 3 months of cancer diagnosis and might not be representative of actual medications being used at the time of the index event. We were unable to purify data based on changes made during the actual study period that limit our ability for further data collection.

**Conclusion**

In patients with cancer and pre-existing AF, CHADS2, CHA2DS2-VASc, and KS are associated with increased mortality risk. We report here for the first time that the KS is associated with mortality with a high KS carrying a quadruple increased mortality risk representing a unique predictor of death in this cohort. Further, we demonstrate that CHADS2 and CHA2DS2-VASc predict the risk of ischemic stroke but KS is not predictive of ischemic stroke in this setting. Future research should focus on the unique factors in cancer patients with AF that impact prognostication and management.

**Authors’ Note**

Alejandra Gutierrez and Rushad Patell contributed equally to this work.

**Funding**

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Dr. Khorana acknowledges support from the National Heart, Lung, and Blood Institute (grant number 1R34HL127156), the Sondra and Stephen Hardis Chair in Oncology Research, and the Scott Hamilton CARES Initiative, the Cleveland Clinic Center of Excellence Grant. This work was supported in part by the American Society of Hematology HONORS (Hematology Opportunities for the Next Generation of Research Scientists) awarded to Rushad Patell.

**Conflict of interest statement**

The authors declare that there is no conflict of interest.

**ORCID iD**

Rushad Patell https://orcid.org/0000-0002-8426-3398

**References**

1. Hu YF, Liu CJ, Chang PM, et al. Incident thromboembolism and heart failure associated with new-onset atrial fibrillation in cancer patients. *Int J Cardiol* 2013; 165: 355–357.

2. Erichsen R, Christiansen CF, Mehnert F, et al. Colorectal cancer and risk of atrial fibrillation and flutter: a population-based case-control study. *Intern Emerg Med* 2012; 7: 431–438.

3. Farmakis D, Parissis J and Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol* 2014; 63: 945–953.

4. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. *Chest* 2010; 137: 263–272.

5. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139–1151.

6. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; 285: 2864–2870.

7. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–992.

8. Laube ES, Yu A, Gupta D, et al. Rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation and active cancer. *Am J Cardiol* 2017; 120: 213–217.

9. Marijon E, Le Heuzey JY, Connolly S, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation* 2013; 128: 1292–2201.

10. Khorana AA, Dalal M, Lin J, et al. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. *Cancer* 2013; 119: 648–655.

11. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008; 111: 4902–4907.

12. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood* 2010; 116: 5377–5382.
13. Lustig DB, Rodriguez R and Wells PS. Implementation and validation of a risk stratification method at The Ottawa Hospital to guide thromboprophylaxis in ambulatory cancer patients at intermediate-high risk for venous thrombosis. *Thromb Res* 2015; 136: 1099–1102.

14. Patell R, Rybicki L, McCrae KR, *et al.* Predicting risk of venous thromboembolism in hospitalized cancer patients: utility of a risk assessment tool. *Am J Hematol* 2017; 92: 501–507.

15. Santi RM, Ceccarelli M, Bernocco E, *et al.* Khorana score and histotype predicts incidence of early venous thromboembolism in non-Hodgkin lymphomas. A pooled-data analysis of 12 clinical trials of Fondazione Italiana Linfomi (FIL). *Thromb Haemost.* Epub ahead of print 27 April 2017. DOI: 10.1160/TH16-11-0895.

16. Santi RM, Ceccarelli M, Catania G, *et al.* PO-03 - Khorana score and histotype predict the incidence of early venous thromboembolism (VTE) in non hodgkin lymphoma (NHL). A pooled data analysis of twelve clinical trials of Fondazione Italiana Linfomi (FIL). *Thromb Res* 2016; 140(Suppl. 1): S177.

17. Stroke–1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO task force on stroke and other cerebrovascular disorders. *Stroke* 1989; 20: 1407–1431.

18. Khorana AA, Francis CW, Culakova E, *et al.* Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007; 5: 632–634.

19. Bang OY, Seok JM, Kim SG, *et al.* Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. *J Clin Neurrol* 2011; 7: 53–59.

20. D’Souza M, Carlson N, Fosbol E, *et al.* CHA2DS2-VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. *Eur J Prev Cardiol* 2018; 25: 651–658.

21. Levitan N, Dowlati A, Remick SC, *et al.* Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using medicare claims data. *Medicine (Baltimore)* 1999; 78: 285–291.

22. Mansfield AS, Tafur AJ, Wang CE, *et al.* Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. *J Thromb Haemost* 2016; 14: 1773–1778.

23. Kuderer NM, Poniewierski MS, Culakova E, *et al.* Predictors of venous thromboembolism and early mortality in lung cancer: results from a global prospective study (CANTARISK). *Oncologist.* Epub ahead print 26 September 2017. DOI: 10.1634/theoncologist.2017-0205.

24. Salazar Adum JP, Fuentes HE, Lind BB, *et al.* Predictors of active cancer thromboembolic outcomes: mortality associated with calf deep vein thrombosis. *Int Angiol.* Epub ahead print 24 May 2017. DOI: 10.23736/S0392-9590.17.03846-9.

25. Fuentes HE, Oramas DM, Paz LH, *et al.* Venous Thromboembolism is an independent predictor of mortality among patients with gastric cancer. *J Gastrointest Cancer* 2018; 49: 415–421.

26. Kuderer NM, Culakova E, Lyman GH, *et al.* A validated risk score for venous thromboembolism is predictive of cancer progression and mortality. *Oncologist* 2016; 21: 861–867.

27. Chen YL, Cheng CL, Huang JL, *et al.* Mortality prediction using CHADS2/CHA2DS2-VASc/ R2CHADS2 scores in systolic heart failure patients with or without atrial fibrillation. *Medicine (Baltimore)* 2017; 96: e8338.

28. Paoletti Perini A, Bartolini S, Pieragnoli P, *et al.* CHADS2 and CHA2DS2-VASc scores to predict morbidity and mortality in heart failure patients candidates to cardiac resynchronization therapy. *Europace* 2014; 16: 71–80.

29. Henriksson KM, Farahmand B, Johansson S, *et al.* Survival after stroke—the impact of CHADS2 score and atrial fibrillation. *Int J Cardiol* 2010; 141: 18–23.

30. Ntaios G, Lip GY, Makaritsis K, *et al.* CHADS(2), CHA(2)S(2)DS(2)-VASc, and long-term stroke outcome in patients without atrial fibrillation. *Neurology* 2013; 80: 1009–1017.

31. Tu HT, Campbell BC, Meretoja A, *et al.* Pre-stroke CHADS2 and CHA2DS2-VASc scores are useful in stratifying three-month outcomes in patients with and without atrial fibrillation. *Cerebrovasc Dis* 2013; 36: 273–280.

32. Hu WS and Lin CL. Impact of atrial fibrillation on the development of ischemic stroke among cancer patients classified by CHA2DS2-VASC score—a nationwide cohort study. *Oncotarget* 2018; 9: 7623–7630.