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Major Outcomes in Atrial Fibrillation Patients with One Risk Factor:

Impact of Time in Therapeutic Range

Observations from the SPORTIF Trials

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MP and GYHL conceived the study, analysed and interpreted the data, drafted the manuscript.

Both authors had access to the data and take full responsibility of the manuscript contents.

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ABSTRACT

Background: The benefits and harms of oral anticoagulation (OAC) therapy in patients with only one stroke risk factor (*i.e.* CHA_2DS_2-VASc= 1 in males, or 2 in females) has been subject of debate.

Methods: We analysed all patients with only one stroke risk factor from the merged datasets of SPORTIF III and V trials. Anticoagulation control was defined according to time in therapeutic range (TTR).

Results: Of the original trial cohort, 1,097 patients had only one stroke risk factor. Stroke/systemic thromboembolic event had an incidence of 0.9 per 100 patient-years, with an incidence of 1.6 per 100 patient-years for all-cause death and 2.3%/patient-years for the composite outcome of stroke/systemic thromboembolic event/all-cause death. There were no significant differences in the risk for stroke/systemic thromboembolic event between sexes, nor between the different stroke risk factors amongst these atrial fibrillation patients with only one stroke risk factor. Cox regression analysis in patients treated with warfarin only found TTR to be inversely associated with stroke/systemic thromboembolic event (p=0.034) and all-cause death (p=0.015). Chronic heart failure was significantly associated with the outcome of all-cause death (p=0.0019) and the composite outcome of stroke/systemic thromboembolic event/all-cause death (p=0.021). There was a significant inverse linear association between TTR and the cumulative risk for both stroke/systemic thromboembolic event and all-cause death (both p<0.001).

Conclusions: In atrial fibrillation patients with only one additional stroke risk factor (*i.e.* CHA_2DS_2-VASc= 1 in males or 2 in females), rates of major adverse events (stroke/systemic thromboembolic event, mortality) were high, despite anticoagulation. TTR in warfarin-treated patients was inversely associated with the occurrence of both stroke/systemic thromboembolic event and all-cause death

INTRODUCTION

Oral anticoagulant (OAC) therapy is essential for stroke prevention in patients with atrial fibrillation[1]. While it is accepted that there is the need to anticoagulated all atrial fibrillation patients with a Chronic Heart Failure-Hypertension-Age 65-74-Diabetes Mellitus-Stroke-Vascular Disease-Age≥75-Sex Category (CHA$_2$DS$_2$-VASc) score ≥2[2,3], some debate remains whether to treat or not treat atrial fibrillation patients with only one additional risk factor, beyond sex (*i.e.* males with CHA$_2$DS$_2$-VASc= 1 or females with CHA$_2$DS$_2$-VASc= 2)[4].

Current European Society of Cardiology (ESC) guidelines recommend consideration of OAC treatment in male patients with CHA$_2$DS$_2$-VASc= 1, after consider bleeding risk using the Hypertesion-Abnormal Renal and Liver Function-Stroke-Bleeding-Labile INR-Elderly-Drugs or Alcohol (HAS-BLED) score (Class IIa recommendation)[3]; however, American guidelines recommend antiplatelet therapy or no therapy as an alternative to OAC in atrial fibrillation patients with CHA$_2$DS$_2$-VASc= 1[2].

Several large observational studies have consistently reported that even in atrial fibrillation patients with only one additional stroke risk factor, incidence rates for major adverse outcomes are high if non-anticoagulated[5–7], up to 2.55%/year for females and 2.75%/year for male patients for ischaemic stroke, and even higher if systemic embolic event and all-cause death are considered [6]. OAC reduces stroke and all cause mortality, and OAC treatment improves prognosis even in atrial fibrillation patients with one additional stroke risk factor[5] with a positive net clinical benefit (NCB) when compared to both antiplatelet treatment or no treatment[8,9]. Conversely, other cohorts have suggested lower event rates in atrial fibrillation patients with only one additional risk

factor, with ischaemic stroke rates below 1%/year both for males and females[10], hence questioning the necessity to treat such patients[11].

In this study, our objective was to describe the rates of stroke/systemic thromboembolic event, all-cause death and their composite outcome in a large clinical trial cohort of anticoagulated non-valvular atrial fibrillation patients with one additional risk factor (*i.e.* CHA_2DS_2-VASc= 1 in males or 2 in females). Second, we analysed the impact of individual stroke risk factors on outcomes. Third, we describe the relationship between the time in therapeutic range (TTR) and outcomes in the subgroup of atrial fibrillation patients with CHA_2DS_2-VASc= 1 in males or 2 in females, who were treated with warfarin.

METHODS

For the present study, we analysed the pooled datasets from the Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) III and V studies[12–14]. The SPORTIF trials were two global multicentre phase III clinical trials, one open label (SPORTIF III) and one double blinded (SPORTIF V) comparing the efficacy and safety of the direct thrombin inhibitor ximelagatran, compared to warfarin, in preventing thromboembolic stroke in non-valvular atrial fibrillation patients.

For this analysis, we considered all the patients with only one additional risk factor for stroke beyond the sex category, according to CHA_2DS_2-VASc score[15]; that is, male atrial fibrillation patients with CHA_2DS_2-VASc = 1 and female atrial fibrillation patients with CHA_2DS_2-VASc = 2.

TTR was calculated, in all patients treated with warfarin, according to the standardized Rosendaal interpolation method[16], by assigning an INR value to each day between two successive observed INR values. After that, the percentage of time that the interpolated INR remained between 2 and 3 was used to establish the TTR value.

Study Outcomes

Outcomes considered for the present study, defined and adjudicated by an independent events committee according to the original SPORTIF trials, were stroke/systemic thromboembolic event, all-cause death and the composite outcome of stroke/systemic thromboembolic event/all-cause death. Stroke was defined according as the acute onset of a focal neurological deficit in any of the carotid, vertebral or cerebral artery distribution territories lasting>24 hours. Systemic

thromboembolic event was recorded for the abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of another likely mechanism. Mortality was related to the reported occurrence of death by any investigator.

Statistical Analysis

All continuous variables were tested for normality. Variables with normal distribution were expressed as means and standard deviations (SD). Non-parametric variables were expressed as median and interquartile range (IQR). Categorical variables, expressed as counts and percentages, were analysed by chi-squared test.

Survival analysis, assessed by an intention-to-treat approach, was performed according both to sex and risk factor; differences in survival were analysed using the log-rank test and Kaplan-Meier curves were drafted according to the different groups. Evaluation of clinical characteristics significantly associated with outcomes was explored using a Cox proportional-hazards analysis. All variables with a p-value <0.10 for the association in the univariate analysis, were included in the forward stepwise multivariate model.

A regression analyses were performed between TTR and cumulative risk derived from the Cox multivariable models, in relation to the different outcomes. Scatterplot graphs with regression line were also drafted. A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA).

RESULTS

Among the 7,329 patients enrolled in the original SPORTIF trials, 1,097 (15.0%; median [IQR] age 61 [56-64] years; 212 (19.3%) female) had only one additional stroke risk factor, beyond sex. Of these, 578 (52.7%) were assigned to warfarin, while 519 (47.3%) were assigned to ximelagatran arm. Baseline characteristics of this cohort are summarised in Table 1. Of the stroke risk factors, hypertension was the most prevalent (719 patients, 65.5%), chronic heart failure in 182 (16.6%); and age 65-74 years in 196 (17.9%).

Study outcomes

After a median follow-up of 566 days [IQR 495-653], stroke/systemic thromboembolic event occurred in 15 (1.4%), all-cause death in 28 (2.6%) and the composite outcome of stroke/systemic thromboembolic event/all-cause death in 40 (3.6%). Cumulative incidences in these anticoagulated patients were 0.9 per 100 patient-years for stroke/systemic thromboembolic event, 1.6 per 100 patient-years for all-cause death and 2.3% patient-years for the composite outcome, respectively. In the *warfarin-treated subgroup*, stroke/systemic thromboembolic event incidence was 0.9 per 100 patient-years, 2.0 per 100 patient-years for all-cause death and 2.7 per 100 patient-years for the composite outcome.

The *crude incidences* of various study outcomes were summarised in Table 2. No death events were reported in diabetic patients, nor any study endpoints amongst patients age 65 to 74 years. The highest event rate for stroke/systemic thromboembolic event was reported in diabetic patients, while patients with chronic heart failure reported the highest rates for all-cause death and the composite outcome.

Kaplan-Meier survival analyses found no significant difference in the risk for stroke/systemic thromboembolic event between male and female patients [Figure 1, Panel A] or between the different stroke risk factors for the whole cohort [Figure 1, Panel B]. For all-cause death, there was a significant difference between risk factor type for predicting events, but not for sex (Log-Rank: 2.748, p=0.097) [Figure 1, Panel C and D]. No significant difference was found for the composite outcome between sex (Log-Rank: 0.519, p=0.471) or risk factor type (Log-Rank: 6.901, p=0.141). In the *warfarin-treated subgroup*, Kaplan-Meier survival analyses found that no significant difference for sex was evident for stroke/systemic thromboembolic event (Log-Rank: 0.310, p=0.578), all-cause death (Log-Rank: 0.662, p=0.416) and composite outcome (Log-Rank: 0.013, p=0.908). Similarly, no significant difference for risk factor type was evident for stroke/systemic thromboembolic event (Log-Rank: 1.394, p=0.845), all-cause death (Log-Rank: 7.816, p=0.099) or composite outcome (Log-Rank: 7.540, p=0.110).

Impact of individual risk factors and TTR in the warfarin subgroup

Taking hypertension as the reference (being the most prevalent risk factor), none of the risk factors emerged as a significant predictor compared to the others for either stroke/systemic thromboembolic event or the composite outcome [Figure 2]. For all-cause death, only chronic heart failure emerged as significant predictor (hazard ratio: 2.68, 95% confidence interval: 1.09-6.60; p=0.032) [Figure 2].

On multivariate Cox regression analysis performed in the *warfarin-treated subgroup* (Table 3), only TTR expressed as continuous variable was inversely associated with the occurrence of stroke/systemic thromboembolic event (p=0.034). For all-cause death, there was a significant

relationship for chronic heart failure (p=0.019), while TTR was inversely associated (p=0.015). For the composite outcome, TTR was significantly associated on univariate analysis (p=0.041), but on multivariate analysis, only chronic heart failure was significant (p=0.021).

There was a significant linear inverse association between TTR (as a continuous variable) and the cumulative risk for both stroke/systemic thromboembolic event and all-cause death (standardized beta: -0.876, p<0.001 and standardized beta: -0.512, p<0.001, respectively) [Figure 3].

When considering TTR quartiles, numerically higher event rates for all the study outcomes were seen in the lowest TTR quartile (poor anticoagulation control) compared to the highest quartile of TTR [stroke/systemic thromboembolic event: 3.5% vs 0.7%; all-cause mortality: 5.6% vs 2.8%; composite outcome: 6.9% vs 3.5%, respectively; full data not shown].

DISCUSSION

In this clinical trial cohort of non-valvular atrial fibrillation patients with only one additional stroke risk factor (*i.e.* CHA_2DS_2-VASc= 1 in males or 2 in females), rates of major adverse events (stroke/systemic thromboembolic event, mortality) were high despite anticoagulation. Second, there was no significant difference in the risk for stroke/systemic thromboembolic event between males or females, nor between the different stroke risk factors amongst these patients with only one stroke risk factor. Third, TTR in the subgroup of warfarin-treated patients was inversely associated with the occurrence of both stroke/systemic thromboembolic event and all-cause death.

Among the several stroke risk factors considered, none emerged as a significant predictor for the occurrence of stroke/systemic thromboembolic event and composite outcome in this anticoagulated cohort. Only for the occurrence of all-cause death, chronic heart failure was found as a significant predictor among the other risk factors. These results strengthen the concept that in atrial fibrillation patients with only one additional stroke risk factor (beyond sex), the risk for major adverse events remains consistently higher, despite anticoagulation. For example, Chao et al. reported that in untreated atrial fibrillation patients with one stroke risk factor, ischaemic stroke risk was 2.75% per year[6]. In an European population, Lip et al. reported that with one stroke risk factor, ischaemic stroke was 1.5%/year and all-cause death was 11.3%/year in untreated patients[7]. Beyond the risk of stroke, atrial fibrillation patients are exposed to significant higher risks for an adverse clinical outcomes, as reported in other large contemporary real world studies, despite high percentage of patients treated with OAC[17,18]. Whilst we tend to focus on stroke reduction, we should remember that OAC also significantly reduces stroke/SE (by 64%), ischaemic stroke (by 67%) and all-cause mortality (by 26%) compared to control or placebo[19].

10

In the large nationwide study from Danish registries, patients with one additional risk factor beyond sex (*i.e.* CHA_2DS_2-VASc= 1 in males or 2 in females) had significant reduced rate of events, in particular all-cause death, with anticoagulation[7]. An even larger study, comprising more than 120,000 atrial fibrillation patients, reported that the NCB of patients with one additional risk factor treated with warfarin was consistently positive independent of risk factor NCB weights used whether at 1 and 5 years follow-up[8]. The Loire Valley Atrial Fibrillation Project also showed that in atrial fibrillation patients with one risk factor, use of OAC was inversely associated with occurrence major adverse events (p=0.002 for the composite outcome of death, stroke/systemic thromboembolic event and p=0.01 for the secondary outcome of death, stroke/systemic thromboembolic event and major bleeding)[5]. Our current study therefore underscores the important role of OAC in non-valvular atrial fibrillation patients with only one additional stroke risk, in reducing major adverse outcomes. Moreover, good quality anticoagulation (with high TTR) is essential, to ensure best protection from adverse outcomes in warfarin-treated patients. Recent data show that European guideline-adherent treatment is associated with improved outcomes, suggesting that the recommendation of treating atrial fibrillation patients with one additional stroke risk factor confers a significant clinical advantage[20].

Limitations

The main limitation is the post-hoc nature of the present study, and the SPORTIF trials included atrial fibrillation patients with ≥1 risk factors, the limited number of patients and events (in particular for the age risk factor) limit the generalizability of our results. Furthermore, SPORTIF trials were highly controlled randomized controlled trials the event rates may not resemble those

in real world populations, given the strict control of various risk factors for the entire trial follow-up period.

In conclusion, this post-hoc analysis of a clinical trial cohort of non-valvular atrial fibrillation with only one additional stroke risk factor (*i.e.* CHA_2DS_2-VASc= 1 in males or 2 in females) shows that rates of major adverse events (stroke/systemic thromboembolic event, mortality) were high, despite being anticoagulated. TTR in warfarin-treated patients was inversely associated with the occurrence of both stroke/systemic thromboembolic event and all-cause death.

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REFERENCES

1. Lip GYH, Lane DA. Stroke Prevention in Atrial Fibrillation. *JAMA*. 2015;313:1950–1962.

2. January CT, Wann FLS, Joseph F, Alpert S, Calkins FH, C FJ, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J. Am. Coll. Cardiol*. 2014;64:e1-76.

3. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur. Heart J.* 2012;33:2719–2747.

4. Olesen JB, Torp-Pedersen C. Stroke risk in atrial fibrillation: Do we anticoagulate CHADS2 or CHA2DS2-VASc ≥1, or higher? *Thromb. Haemost.* 2015;113:1165–1169.

5. Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, et al. Oral anticoagulation and the risk of stroke or death in patients with atrial fibrillation and one additional stroke risk factor: the Loire Valley Atrial Fibrillation Project. *Chest*. 2015; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26425935 [Accessed online 20th December 2015].

6. Chao T-F, Liu C-J, Wang K-L, Lin Y-J, Chang S-L, Lo L-W, et al. Should Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA2DS2-VASc Score (Beyond Sex) Receive Oral Anticoagulation? *J. Am. Coll. Cardiol.* 2015;65:635–642.

7. Lip GYH, Skjøth F, Rasmussen LH, Larsen TB. Oral Anticoagulation, Aspirin, or No Therapy in Patients With Nonvalvular AF With 0 or 1 Stroke Risk Factor Based on the CHA2DS2-VASc Score. *J. Am. Coll. Cardiol.* 2015;65:1385–1394.

8. Lip GYH, Skjøth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or

one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb. Haemost.* 2015;114:826–834.

9.   Lip GYH, Skjøth F, Rasmussen LH, Nielsen PB, Larsen TB. Net Clinical Benefit for Oral Anticoagulation, Aspirin, or No Therapy in Nonvalvular Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA2DS2-VASc Score (Beyond Sex). *J. Am. Coll. Cardiol.* 2015;66:488–490.

10.   Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. *J. Am. Coll. Cardiol.* 2015;65:225–232.

11.   Singer DE, Ezekowitz MD. Adding rigor to stroke risk prediction in atrial fibrillation. *J. Am. Coll. Cardiol.* 2015;65:233–235.

12.   Halperin JL. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am. Heart J.* 2003;146:431–438.

13.   Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362:1691–1698.

14.   Albers GW, Diener H-C, Frison L, Grind M, Nevinson M, Partridge S, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293:690–698.

15.   Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. 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.

16.   Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal

intensity of oral anticoagulant therapy. *Thromb. Haemost.* 1993;69:236–239.

17. Lip GYH, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L, Petrescu L, et al. Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur. Heart J.* 2014;35:3365–3376.

18. Steinberg BA, Kim S, Piccini JP, Fonarow GC, Lopes RD, Thomas L, et al. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry. *Circulation*. 2013;128:721–728.

19. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann. Intern. Med*. 2007;146:857–867.

20. Lip GYH, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan G-A, et al. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *Europace*. 2015;17:1777-1786.

Table 1: Cohort Characteristics

		Overall Population n=1,097
Age *years*		
	Median [IQR]	61 [56-64]
Age 65-74 years		196 (17.9%)
Gender		
	Male	885 (80.7%)
	Female	212 (19.3%)
BMI *kg/cm^2 1,093*		
	Median [IQR]	30.1 [26.8-34.5]
Treatment Arm		
	Ximelagatran	519 (47.3%)
	Warfarin	578 (52.7%)
Chronic Atrial Fibrillation*		925 (84.3%)
Hypertension		719 (65.5%)
Diabetes Mellitus		231 (21.1%)
Creatinine Clearance *ml/min 1,091*		
	Median [IQR]	110.68 [85.29-138.58]
Vascular Disease		397 (36.2%)
Chronic Heart Failure		182 (16.6%)
Clinically Relevant Bleeding		41 (3.7%)
Prior Aspirin Use		204 (18.6%)
Prior Vitamin K-Antagonist Use		854 (77.8%)
TTR *%* 575*		
	Median [IQR]	67.1 [55.0-78.6]
TTR>70%* *575*		255 (44.1%)

Legend: BMI= body mass index; IQR= interquartile range; TTR= time in therapeutic range; *data available only for patients on warfarin.

Table 2: Study Outcomes in Relation to Individual Risk Factors

(per 100 patient-years)	Stroke/Systemic Thromboembolic Event	All-Cause Death	Composite Outcome
Hypertension	0.9	1.4	2.1
Diabetes Mellitus	1.4	0	1.4
Vascular Disease	0.5	1.6	2.0
Chronic Heart Failure	1.1	3.7	4.4
Age 65-74 years	0	0	0

Table 3: Univariate and Multivariable Cox Regression Analysis for Study Outcomes in the Warfarin Treated Patients

	Univariate Analysis			Multivariable Analysis		
	HR	*95% CI*	*p*	*HR*	*95% CI*	*p*
a) Stroke/Systemic Thromboembolic Event						
Congestive Heart Failure	0.73	0.09-5.95	0.771	-	-	-
Hypertension	3.72	0.46-30.27	0.219	-	-	-
Age 65-74 years	0.04	0.00-81.64	0.400	-	-	-
Diabetes Mellitus	0.53	0.07-4.34	0.557	-	-	-
Vascular Disease	0.57	0.14-2.27	0.425	-	-	-
Female Sex *(vs. Male)*	1.57	0.32-7.78	0.581	-	-	-
TTR *(per point)*	0.97	0.94-1.00	0.034	0.97	0.94-1.00	0.034
b) All-Cause Death						
Congestive Heart Failure	3.04	1.19-7.72	0.020	3.11	1.20-8.04	0.019
Hypertension	0.96	0.38-2.45	0.936	-	-	-
Age 65-74 years	0.04	0.00-4.51	0.176	-	-	-
Diabetes Mellitus	1.30	0.47-3.62	0.612	-	-	-
Vascular Disease	1.97	0.80-4.86	0.139	-	-	-
Female Sex *(vs. Male)*	0.55	0.13-2.38	0.423	-	-	-
TTR *(per point)*	0.97	0.95-0.99	0.010	0.97	0.95-0.99	0.015
c) Composite Outcome						
Congestive Heart Failure	2.58	1.11-6.04	0.028	2.74	1.16-6.48	0.021
Hypertension	1.11	0.48-2.61	0.803	-	-	-
Age 65-74 years	0.04	0.00-2.73	0.131	-	-	-
Diabetes Mellitus	0.96	0.36-2.58	0.938	-	-	-
Vascular Disease	1.78	0.80-3.96	0.159	-	-	-
Female Sex *(vs. Male)*	0.94	0.32-2.75	0.908	-	-	-
TTR *(per point)*	0.98	0.96-1.00	0.042	-	-	-

Legend: CI= confidence interval; HR= hazard ratio; TTR= time in therapeutic rate.

FIGURE LEGENDS

Figure 1: Kaplan-Meier Curves for **(i)** Stroke/Systemic Thromboembolic Event in relation to A) sex;

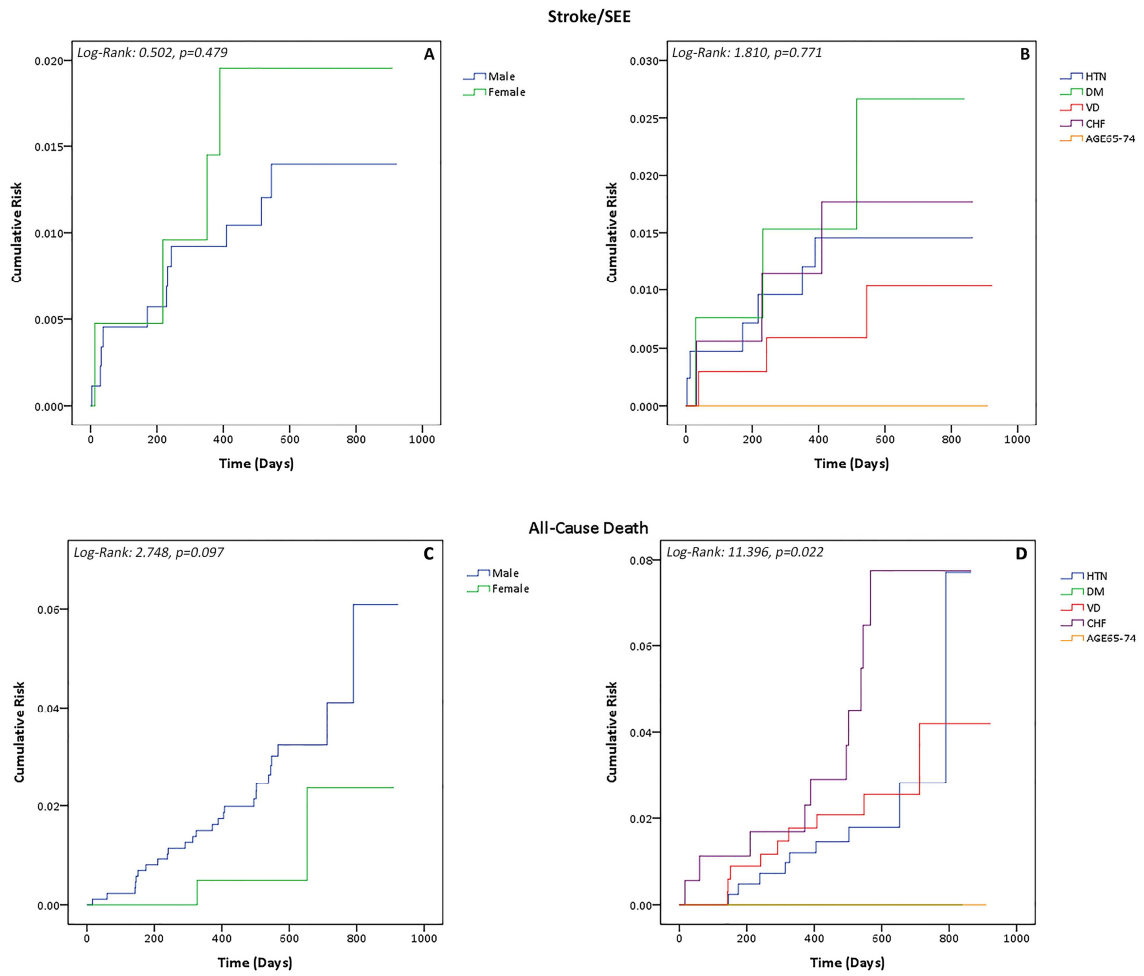B) risk factors; **(ii)** All-Cause Death in relation to C) sex; D) risk factors.

Legend: CHF: chronic heart failure; DM: diabetes mellitus; HTN: hypertension; VD: vascular

disease.

Figure 2: Forest-Plot for Study Outcomes According to Every Risk Factor
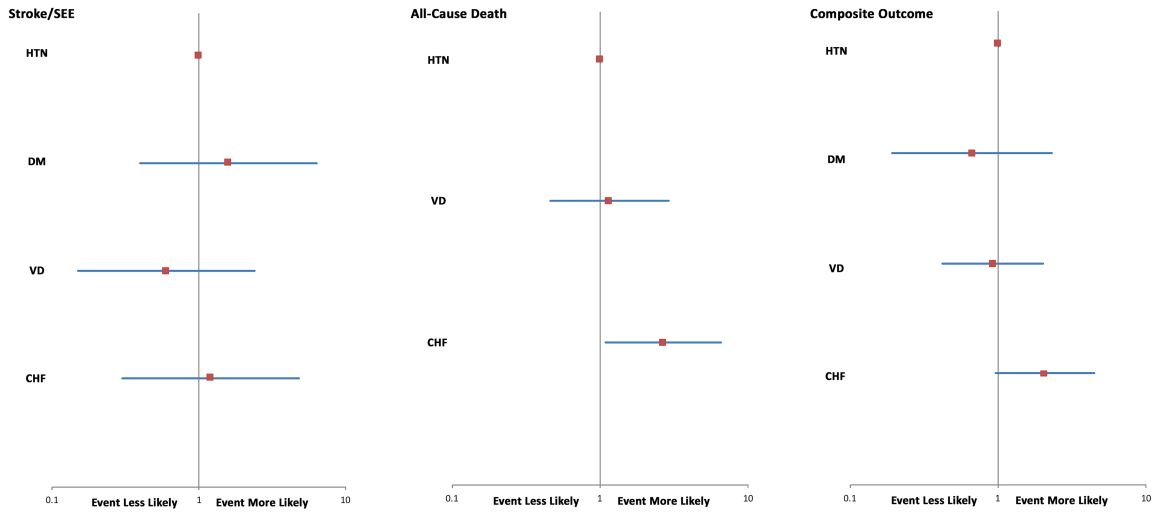
Legend: CHF= chronic heart failure; DM= diabetes mellitus; HTN= hypertension; VD= vascular

disease.

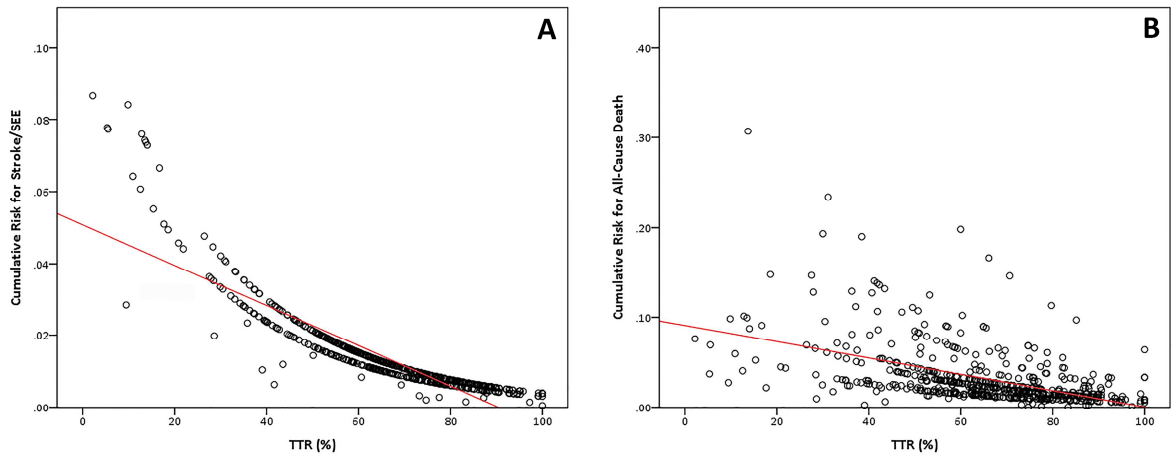**Figure 3:** Scatterplot and Regression Line between TTR and Cumulative Risk

Legend: A) Stroke/Systemic Thromboembolic Event; B) All-Cause Death. TTR= time in therapeutic

range.

Stroke/SEE

All-Cause Death

Stroke/SEE

HTN

DM

VD

CHF

0.1   **Event Less Likely**   1   **Event More Likely**   10

All-Cause Death

HTN

VD

CHF

0.1   **Event Less Likely**   1   **Event More Likely**   10

Composite Outcome

HTN

DM

VD

CHF

0.1   **Event Less Likely**   1   **Event More Likely**   10

Clinical significance

- In patients with atrial fibrillation with only one additional stroke risk factor (*i.e.* CHA_2DS_2-VASc= 1 in males or 2 in females), rates of major adverse events (stroke/systemic thromboembolic event, all-cause death) were high, despite being on oral anticoagulation.

- Quality of anticoagulation control (time in therapeutic range, TTR) in warfarin-treated patients was inversely associated with the occurrence of both stroke/systemic thromboembolic event and all-cause death.