



# Chronic Kidney Disease, Time in Therapeutic Range and Adverse Clinical Outcomes in Anticoagulated Patients with Non-valvular Atrial Fibrillation: Observations from the SPORTIF Trials



Marco Proietti<sup>a</sup>, Deirdre A. Lane<sup>a</sup>, Gregory Y.H. Lip<sup>a,b,\*</sup>

<sup>a</sup> University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom

<sup>b</sup> Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

## ARTICLE INFO

### Article history:

Received 24 February 2016

Received in revised form 2 April 2016

Accepted 12 April 2016

Available online 19 April 2016

### Keywords:

Non-valvular atrial fibrillation

Chronic kidney disease

Stroke

Major bleeding

Clinical outcomes

## ABSTRACT

**Background:** Chronic kidney disease (CKD) is highly prevalent in atrial fibrillation (AF) patients and associated with an increased risk of adverse outcomes. Our objectives were to study clinical features associated with CKD in AF patients and the impact of CKD on anticoagulation control, as reflected by time in therapeutic range (TTR). We also determined the impact of CKD and TTR in predicting adverse outcomes.

**Methods and Results:** We analysed pooled datasets from SPORTIF III and V trials, including 3646 patients assigned to warfarin with data on renal function. CKD (creatinine clearance <60 ml/min) was present in 952 (26%) patients. TTR was higher in patients with normal renal function compared to those with CKD ( $p < 0.001$ ).

On logistic analysis, chronic AF and male sex were associated with TTR > 70%, whilst diabetes mellitus, aspirin use and CKD were inversely associated with TTR > 70%. On Cox regression analysis, CKD was an independent predictor for stroke ( $p = 0.006$ ) and death ( $p < 0.001$ ). TTR > 70% was independently associated with a lower risk of stroke ( $p = 0.024$ ), death ( $p = 0.001$ ) and major bleeding ( $p = 0.001$ ).

**Conclusions:** CKD is highly prevalent amongst AF patients and a risk factor for stroke and death. Adjusting for CKD, good quality anticoagulation control (TTR > 70%) was an independent predictor for lower risks of stroke, death and major bleeding.

© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Chronic kidney disease (CKD) is highly prevalent in non-valvular AF patients, ranging from 26% to 32%, especially in the elderly (Apostolakis et al., 2013; Banerjee et al., 2013). The presence of CKD in AF patients is associated with a greater risk of adverse clinical outcomes, including stroke, thromboembolism and bleeding. In the Danish nationwide cohort study, for example, the presence of CKD amongst patients with AF was significantly associated with an increased risk for stroke/systemic embolism (by 1.49-fold), all-cause mortality (by 2.37-fold), myocardial infarction (by 2-fold) and major bleeding (by 1.33-fold) (Olesen et al., 2012). Warfarin use amongst such patients has been associated with a substantial risk reduction in overall event rates, with a positive net clinical benefit (Bonde et al., 2014). Similarly, the Loire Valley Atrial Fibrillation Project confirmed the high risk associated with CKD in patients with AF (Banerjee et al., 2014, 2013). In clinical trial populations, CKD also confers a much higher relative risk for both stroke and bleeding (Apostolakis et al., 2013; Piccini et al., 2013).

When Vitamin K Antagonists (VKAs, e.g. warfarin) are used for thromboprophylaxis, good quality anticoagulation control, as reflected by time in therapeutic range (TTR) >70% is recommended (De Caterina et al., 2013). Limited information been reported on the relationship between CKD and TTR in AF patients, but good TTR has been associated with lower risks of thromboembolism and bleeding (Connolly et al., 2008; Friberg et al., 2014; Pokorney et al., 2015).

In this study, our objectives were to study clinical features associated with CKD in AF patients; second, we studied the impact of CKD on anticoagulation control, as reflected by the time in therapeutic range (TTR). Third, we determined the impact of CKD as a risk factor for stroke, myocardial infarction, major bleeding and death amongst warfarin-treated AF patients, after adjustment for TTR as measure of anticoagulation control.

## 2. Methods

For the present analysis, we used the pooled study populations of the Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) III and V trials. The original protocol and principal results have been previously described (Albers et al., 2005; Halperin, 2003; Olsson, 2003). In brief, the SPORTIF trials were

\* Corresponding author at: University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Dudley Road, B18 7QH Birmingham, United Kingdom.  
E-mail address: [g.y.h.lip@bham.ac.uk](mailto:g.y.h.lip@bham.ac.uk) (G.Y.H. Lip).

two multicentre phase III clinical trials comparing the efficacy and safety of the direct thrombin inhibitor, ximelagatran, against warfarin in patients with non-valvular AF. SPORTIF III was an open label trial, while SPORTIF V was a double blind study (Halperin, 2003). Signed, informed consent was required from each participant in accordance with protocol regulations approved by the local review boards governing research involving human subjects, and the Declaration of Helsinki. In both SPORTIF trials, ximelagatran was non-inferior in efficacy and safety as warfarin for stroke prevention in non-valvular AF patients (Lip, 2005) but due to hepatotoxicity, ximelagatran was withdrawn. For the purpose of this study, we studied only SPORTIF patients assigned to warfarin treatment where complete information on renal function was available.

### 2.1. Thromboembolic Risk and Anticoagulation Control

Thromboembolic risk was categorised according to both CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (Gage et al., 2004; Lip et al., 2010). Based on CHADS<sub>2</sub>, patients were categorised as “low risk” when with CHADS<sub>2</sub> = 0, “moderate risk” with CHADS<sub>2</sub> = 1 and “high risk” when CHADS<sub>2</sub> ≥ 2 (Gage et al., 2004). Based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, “low risk” was defined as a CHA<sub>2</sub>DS<sub>2</sub>-VASc 0 in males or 1 in females; “moderate risk” as male patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc = 1; and “high risk” with CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥ 2 (Camm et al., 2012; Lip et al., 2015).

Anticoagulation control, as reflected by the TTR was calculated using the standardized Rosendaal interpolation method (Rosendaal et al., 1993), by assigning an INR value to each day between two successive observed INR values. The percentage of time that the interpolated INR remained between 2.0 and 3.0 was used to establish TTR value, and the cut-off value for defining optimal anticoagulation was a mean individual TTR of ≥70% (De Caterina et al., 2013).

### 2.2. Renal Function

Renal function was based on the estimated creatinine clearance (CrCl), using the 4-item Cockcroft-Gault formula [(140 – age) \* (weight in kg) \* (0.85 if female) / (72 \* creatinine)]. Accordingly, an estimated CrCl level of <60 ml/min was used to define CKD, based on established guidelines (“K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification,” 2002).

### 2.3. Study Outcomes

Principal clinical outcomes were based on the original study protocol, and were centrally adjudicated (Halperin, 2003). Stroke was defined as the acute onset of a focal neurological deficit in any of the carotid, vertebral or cerebral artery distribution territories lasting >24 h. As per the SPORTIF trials protocol, myocardial infarction (MI) diagnosis required 2 out of 3 of the following criteria: (i) typical chest pain lasting at least 20 min; (ii) electrocardiographic changes clearly indicating an acute MI; (iii) significant, i.e. >2 × upper limit, elevation of cardiac biomarkers (creatinine kinase-MB, troponin). Based on the International Society of Thrombosis and Haemostasis (ISTH) criteria (Schulman and Kearon, 2005), major bleeding was defined by one of the following: clinically overt bleeding with a concomitant fall in haemoglobin levels >2 g/dl or requiring blood transfusion of at least 2 units of whole blood or erythrocytes; bleeding episode involving a critical site.

### 2.4. Statistical Analysis

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as means and standard deviations (SD), and tested for differences using a *t*-test. Non-parametric variables were expressed as median and interquartile range (IQR) and differences tested using the Mann-Whitney *U* test. Categorical variables, expressed as counts and percentages, were analysed by chi-squared test. A linear regression analysis between

CrCl and TTR was performed, adjusted for type of AF and thromboembolic risk.

Regression analysis was performed in order to establish clinical factors significantly associated with the presence of CKD. All variables different between the two groups at the baseline with a level of significance of at least  $p < 0.10$  underwent a univariate analysis, and those predictors with a level significance of  $p < 0.10$  were inserted into a forward multivariate logistic model. To determine the factors associated with a TTR > 70%, both for general population and CKD-only population, all baseline clinical variables underwent univariate analyses and those predictors with a level significance of  $p < 0.10$  were inserted into a forward multivariate logistic model. In order to explore the incremental value of TTR in determining events occurrence, a correlation analysis between TTR and hazard risk for study outcomes was performed using Pearson product-moment correlation test, both for the overall cohort and stratified according to CKD presence. Correlation coefficients were then compared using the *z* test, after being processed with Fisher transformation.

Survival analysis, assessed by an intention-to-treat approach, was performed according to the presence of CKD and differences in survival distributors between subgroups were analysed using the Log-Rank test. Evaluation of the clinical characteristics significantly associated with outcomes was performed using a Cox proportional hazards analysis, corrected according to thromboembolic risk, performed with CKD both as a categorical variable and CrCl as a continuous variable. All demographic variables, comorbidities and risk factors analysed at baseline underwent a univariate analysis. All variables with a *p*-value < 0.10 for the association with clinical outcome at the univariate analysis, were inserted into the forward stepwise multivariate model. A backward model was then performed to verify the results of the forward one. A two-sided *p* value < 0.05 was considered statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA) and R v. 3.2.1 (The R Foundation).

## 3. Results

The pooled study population constituted 7329 patients, of which 3665 were assigned to the warfarin treatment arm. Complete data on renal function were available for 3646 (99.5%) [Fig. 1]. Of the selected cohort, 30.5% ( $n = 1113$ ) were female, median age was 72 [IQR 66–77] years, and median CrCl was 78.60 [59.1–102.1] ml/min. Of the entire cohort, 10.8% ( $n = 393$ ) had paroxysmal AF.

### 3.1. Prevalence of CKD and Associated Clinical Characteristics

CKD (defined as CrCl < 60 ml/min) was present in 952 (26.1%) patients. Clinical characteristics of patients with and without CKD are shown in Table 1. Patients with CKD were significantly older ( $p < 0.001$ ), more commonly female ( $p < 0.001$ ) or paroxysmal AF ( $p = 0.009$ ) and a lower median weight ( $p < 0.001$ ). CKD patients had more prevalent coronary heart disease (CHD) ( $p = 0.042$ ) and previous stroke or transient ischemic attack (TIA) ( $p < 0.001$ ). Thromboembolic risk was higher in patients with CKD compared to those with normal renal function, whether based on CHADS<sub>2</sub> (median [IQR] 2 [2–2] vs. 2 [1–2] respectively,  $p < 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc (median [IQR] 4 [3–5] vs. 3 [2–3],  $p < 0.001$ ).

On multivariable logistic regression analysis, clinical characteristics significantly associated with the presence of CKD were age (Odds Ratio (OR) 1.16 per year, 95% confidence interval (CI) 1.15–1.18,  $p < 0.001$ ), weight (OR for any kg 0.92, 95% CI 0.91–0.92,  $p < 0.001$ ), paroxysmal AF (OR 1.67, 95% CI 1.23–2.27,  $p = 0.001$ ), diabetes mellitus (OR 1.47, 95% CI 1.16–1.86,  $p = 0.001$ ), chronic heart failure (CHF) (OR 1.61, 95% CI 1.32–1.96,  $p < 0.001$ ), and previous stroke/TIA (OR 1.41, 95% CI 1.13–1.75,  $p = 0.002$ ).

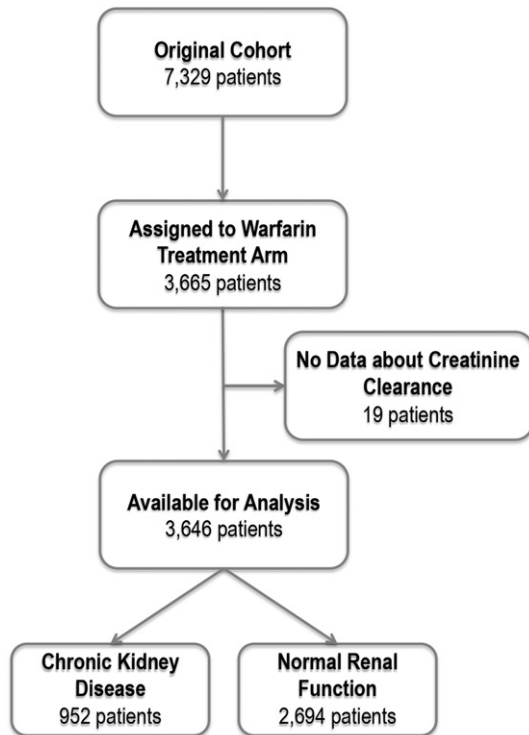


Fig. 1. Patients included in this analysis.

### 3.2. Relationship between CKD and TTR

Median TTR in the whole cohort was 68.6% [IQR 56.5–80.6%], being significantly higher in patients with normal renal function when compared with CKD patients ( $p < 0.001$ ). Also, the proportion with TTR > 70% was more prevalent in patients with normal renal function ( $p < 0.001$ ).

After adjustment for type of AF and thromboembolic risk, a linear relationship was found between CrCl and TTR (standardized beta: 0.054,  $p = 0.003$ ) [Fig. 2]. On multivariable logistic analysis, the presence of chronic AF (OR 1.56, 95% CI 1.25–1.94,  $p < 0.001$ ) and male sex (OR 1.18, 95% CI 1.01–1.35,  $p = 0.033$ ) were positively associated with a TTR > 70%. Conversely, a previous diagnosis of diabetes mellitus (OR 0.82, 95% CI 0.70–0.96,  $p = 0.011$ ), concomitant use of aspirin (OR 0.75, 95% CI 0.63–0.88,  $p < 0.001$ ) and the presence of CKD (OR 0.75, 95% CI 0.67–0.92,  $p = 0.002$ ) were negatively associated with achieving a TTR > 70%.

In the CKD subgroup ( $n = 952$ ), the weight (OR per kg 1.01, 95% CI 1.00–1.02,  $p = 0.041$ ), the presence of CHF (OR 1.38, 95% CI 1.05–1.81,  $p = 0.022$ ) and chronic AF (OR 1.85, 95% CI 1.22–2.81,  $p = 0.004$ ) were significantly associated with TTR > 70%.

### 3.3. Impact of CKD in Predicting Adverse Clinical Outcomes

After a median [IQR] follow-up time of 1.6 [1.3–1.8] years, 504 events (13.8% of patients) were recorded, as follows: 90 strokes (17.9% of total events), 52 myocardial infarctions (10.3%), 198 deaths (39.3%) and 164 major bleeding events (32.5%).

#### 3.3.1. Stroke

Stroke was more common in CKD patients than in patients with normal renal function (2.6% patient-years vs. 1.3% patient-years, respectively), with the unadjusted hazard ratio (HR) for stroke being 1.99 (95% CI: 1.30–3.03,  $p = 0.001$ ). With CrCl as a continuous variable,

every decrease of 10 ml/min was associated with a higher risk of stroke (HR 1.07, 95% CI 1.00–1.14,  $p = 0.048$ ).

On Kaplan-Meier analysis, CKD patients had a higher risk of stroke compared to patients with normal renal function (Log-Rank test: 10.56;  $p = 0.001$ ) [Fig. 3, Panel A]. On multivariable Cox regression analysis, a clinical history of CHD ( $p = 0.045$ ), a previous stroke/TIA ( $p < 0.001$ ) and the presence of CKD ( $p = 0.006$ ) were independent risk factors associated with the occurrence of stroke, while TTR > 70% ( $p = 0.004$ ) was inversely associated with the risk of stroke (Table 2). Cox regression analysis performed using CrCl as a continuous variable (Table 2) shows that its influence in determining stroke risk became non-significant, after adjusting for other clinical risk factors ( $p = 0.337$ ). A backward selection model also confirmed these results. TTR and HR for occurrence of stroke were inversely correlated ( $r = -0.772$ ,  $p < 0.001$ ). Similarly, there was a significant correlation between TTRs and stroke HRs according to renal function subgroups [Fig. 4, Panel A] ( $r = -0.569$ ,  $p < 0.001$ ). A significant difference when comparing the two correlation coefficients for the overall cohort and stratified according to CKD presence, respectively ( $z = 8.61$ ,  $p < 0.001$ ).

#### 3.3.2. Myocardial Infarction

The crude incidence rate of MI was similar between those with CKD and normal renal function (1.1% and 0.9% patient-years, respectively). No significant association was found between CKD and MI (unadjusted HR 1.19, 95% CI 0.66–2.18,  $p = 0.563$ ).

#### 3.3.3. Major Bleeding

Major bleeding was more common in patients with CKD than in those with normal renal function (4.6% patient-years, vs. 2.8% patient-years, respectively). Similar to stroke, patients with CKD had a significantly higher risk of a major bleeding event, compared to those with normal renal function (Log-Rank: 10.03;  $p = 0.002$ ) [Fig. 3, Panel B].

CKD conferred a higher risk of major bleeding (unadjusted HR 1.67, 95% CI 1.21–2.31,  $p = 0.002$ ). This risk was non-significant when CrCl was considered as a continuous variable (per decrease of 10 ml/min, HR 1.04, 95% CI 0.99–1.09,  $p = 0.093$ ). On multivariable analysis (see Table 2), increasing age ( $p = 0.009$ ) and clinical history of CHF ( $p = 0.036$ ) were risk factors for major bleeding; conversely, TTR > 70% ( $p = 0.007$ ) was independently associated with less major bleeding. Entering CrCl in the analysis as a continuous variable did not affect the multivariable model (Table 2). Similar data were obtained when performing a backward selection model.

When correlating TTR and HR for major bleeding, a significant inverse relationship was found in the overall cohort ( $r = -0.527$ ,  $p < 0.001$ ). When performed with HR according to renal function subgroups [Fig. 4, Panel B], there was a numerical reduction in correlation coefficient ( $r = -0.490$ ,  $p < 0.001$ ), but this was non-significant ( $z = 1.57$ ,  $p = 0.116$ ).

#### 3.3.4. All-cause Death

A higher rate of death was found in patients with CKD compared to those with normal renal function (crude incidence rate 6.4% patient-years vs. 2.5% patient-years; unadjusted HR 2.54 (95% CI 1.92–3.36,  $p < 0.001$ )). As for stroke, a decrease of 10 ml/min in CrCl was found associated with a higher risk of death (HR 1.14, 95% CI 1.08–1.20,  $p < 0.001$ ).

Survival analysis confirmed a higher mortality of patients with CKD compared to patients with normal renal function (Log-Rank test: 45.62;  $p < 0.001$ ) [Fig. 3, Panel C]. Multivariable Cox regression analysis (Table 2) shows that female sex ( $p = 0.013$ ) and TTR > 70% ( $p = 0.002$ ) were independently associated with a lower risk of death; conversely, a clinical history of CHF ( $p = 0.004$ ), CHD ( $p < 0.001$ ), smoking habit ( $p = 0.049$ ) and the presence of CKD ( $p < 0.001$ ) were risk factors associated with an increased risk of death. When the Cox multivariable analysis was performed using CrCl as a continuous variable, a decrease

**Table 1**  
Patient characteristics in relation to baseline renal function.

N (%)	Normal renal function ( $\geq 60$ ml/min) N = 2694	Chronic kidney disease ( $< 60$ ml/min) N = 952	p
Age, years (median [IQR])	70 [64–75]	78 [74–82]	<0.001
Weight, kg (median [IQR])	89 [78–100]	70 [61–79]	<0.001
Female	656 (24.4)	457 (48.0)	<0.001
Creatinine clearance, ml/min	88.86 [74.02–111.57]	49.77 [43.01–55.25]	<0.001
Type of atrial fibrillation (n = 3644)			0.009
Paroxysmal	269 (10.0)	124 (13.0)	
Chronic	2424 (90.0)	827 (87.0)	
Heart rate (n = 3510), per min	76 [67–87]	73 [64–86]	<0.001
Hypertension	2082 (77.3)	717 (75.3)	0.216
Diabetes mellitus	652 (24.2)	205 (21.5)	0.095
Current smoker	272 (10.1)	58 (6.1)	<0.001
Coronary heart disease	1162 (43.2)	447 (46.9)	0.042
Chronic heart failure	988 (36.7)	378 (39.7)	0.097
Previous stroke/TIA	485 (18.0)	263 (27.6)	<0.001
Previous bleeding	154 (5.7)	54 (5.7)	0.958
Aspirin use	518 (19.2)	205 (21.6)	0.119
TTR (n = 3606), % (median [IQR])	69.6 [56.7–80.2]	66.6 [51.9–76.8]	<0.001
TTR > 70% (n = 3606)	1307 (48.9)	390 (41.8)	<0.001
Median [IQR] CHADS <sub>2</sub>	2 [1–2]	2 [2–2]	<0.001
CHADS <sub>2</sub> score			
0	99 (3.7)	13 (1.4)	
1	1233 (45.8)	196 (20.6)	<0.001
$\geq 2$	1362 (50.6)	743 (78.0)	
Median [IQR] CHA <sub>2</sub> DS <sub>2</sub> -VASC	3 [2–3]	4 [3–5]	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASC risk class			<0.001
Low risk	8 (0.3)	1 (0.1)	
Intermediate risk	457 (17.0)	19 (2.0)	
High risk	2229 (82.7)	932 (97.9)	

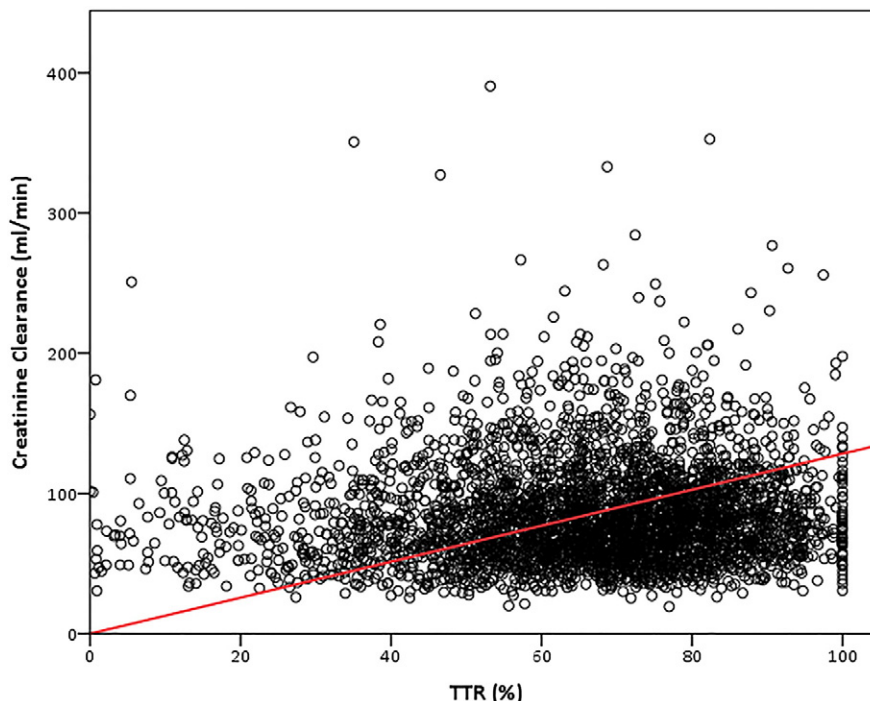
**Legend:** BPM = beats per minute; IQR = interquartile range; TIA = transient ischemic attack; TTR = time in therapeutic range. Low risk = male patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC 0 or female patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC 1; intermediate risk = male patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC 1; high risk = all patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC  $\geq 2$ .

of 10 ml/min was associated with a higher risk of death (Table 2). No difference was found when backward selection model was performed.

Similar to stroke, there was significant inverse correlation between unadjusted HR for death and TTR ( $r = -0.676$ ,  $p < 0.001$ ), but the correlation coefficient was reduced ( $r = -0.478$ ,  $p < 0.001$ ) when stratifying according to CKD presence [Fig. 4, Panel C]. The difference between correlation coefficients was significant ( $z = 8.40$ ,  $p < 0.001$ ).

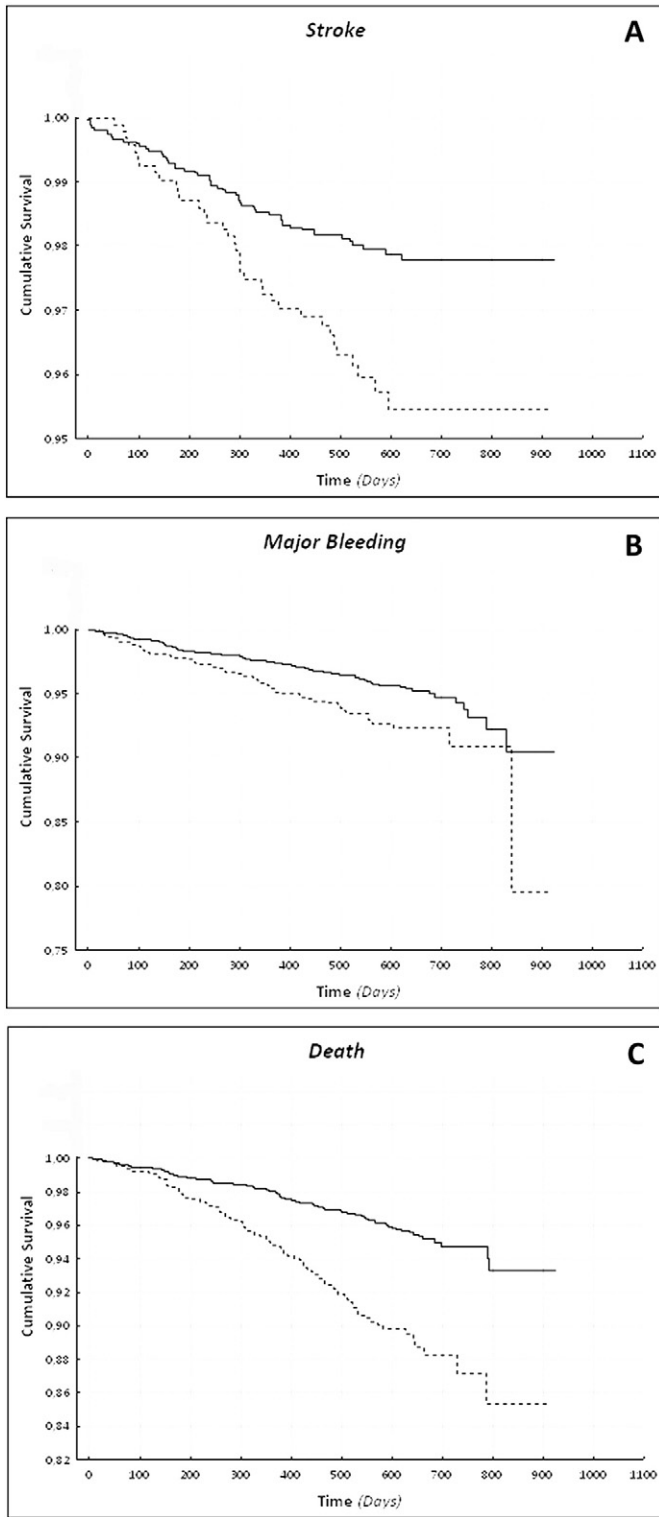
#### 4. Discussion

In this study, we demonstrate that more than a quarter of AF patients have CKD, and that age, female sex, CHF, previous stroke/TIA and the occurrence of paroxysmal AF were significantly associated with CKD in AF patients. Second, we found a linear association between CrCl and TTR in AF, and those patients with CKD had poorer anticoagulation control, as



**Fig. 2.** Scatterplot and regression line between creatinine clearance and TTR Legend = TTR: time in therapeutic range.





**Fig. 3.** Cumulative event-free survival in patients according to the presence of chronic kidney disease. Panel A) Stroke  $p = 0.001$ ; Panel B) Major bleeding  $p = 0.002$ ; Panel C) Death  $p < 0.001$ . Legend = Solid line: normal renal function; dashed line: CKD.

shown by a lower TTR when compared to patients with normal renal function. Importantly, the presence of CKD was negatively associated with achieving a TTR > 70%. Third, CKD was an independent risk factor for the occurrence of stroke and death, independently from TTR; however, no significant association was found between CKD and

**Table 2**

Multivariable Cox regression analysis for clinical outcomes performed with chronic kidney disease as a categorical variable or creatinine clearance as a continuous variable.

	Multivariable analysis		
	Hazard ratio	95% CI	<i>p</i>
<i>Categorical variable</i>			
<i>Stroke</i>			
TTR > 70%	0.63	0.41–0.98	0.040
Coronary heart disease	1.54	1.01–2.34	0.042
Chronic kidney disease <sup>a</sup>	1.82	1.19–2.80	0.006
Previous stroke/TIA	2.23	1.44–3.44	<0.001
<i>Major bleeding</i>			
TTR > 70%	0.58	0.42–0.80	0.001
Age (per year)	1.03	1.01–1.05	0.009
Chronic heart failure	1.40	1.02–1.92	0.036
<i>Death</i>			
TTR > 70%	0.63	0.47–0.84	0.002
Female	0.66	0.47–0.92	0.013
Chronic heart failure	1.53	1.14–2.04	0.003
Current smoker	1.54	1.00–2.38	0.049
Coronary heart disease	1.77	1.32–2.37	<0.001
Chronic kidney disease <sup>a</sup>	2.58	1.92–3.46	<0.001
<i>Continuous variable</i>			
<i>Stroke</i>			
TTR > 70%	0.60	0.39–0.93	0.024
Coronary heart disease	1.54	1.01–2.34	0.045
Previous stroke/TIA	2.18	1.40–3.38	0.001
<i>Major bleeding</i>			
TTR > 70%	0.58	0.42–0.80	0.001
Age (per year)	1.03	1.01–1.05	0.009
Chronic heart failure	1.40	1.02–1.92	0.036
<i>Death</i>			
TTR > 70%	0.61	0.46–0.82	0.001
Female	0.69	0.49–0.96	0.029
Current smoker	1.55	1.00–2.38	0.047
Chronic heart failure	1.58	1.19–2.12	0.002
Coronary heart disease	1.75	1.30–2.35	<0.001
Creatinine clearance (per 10 ml/min decrease)	1.13	1.07–1.19	<0.001

**Legend:** CI = confidence interval; TIA = transient ischemic attack; TTR = time in therapeutic range.

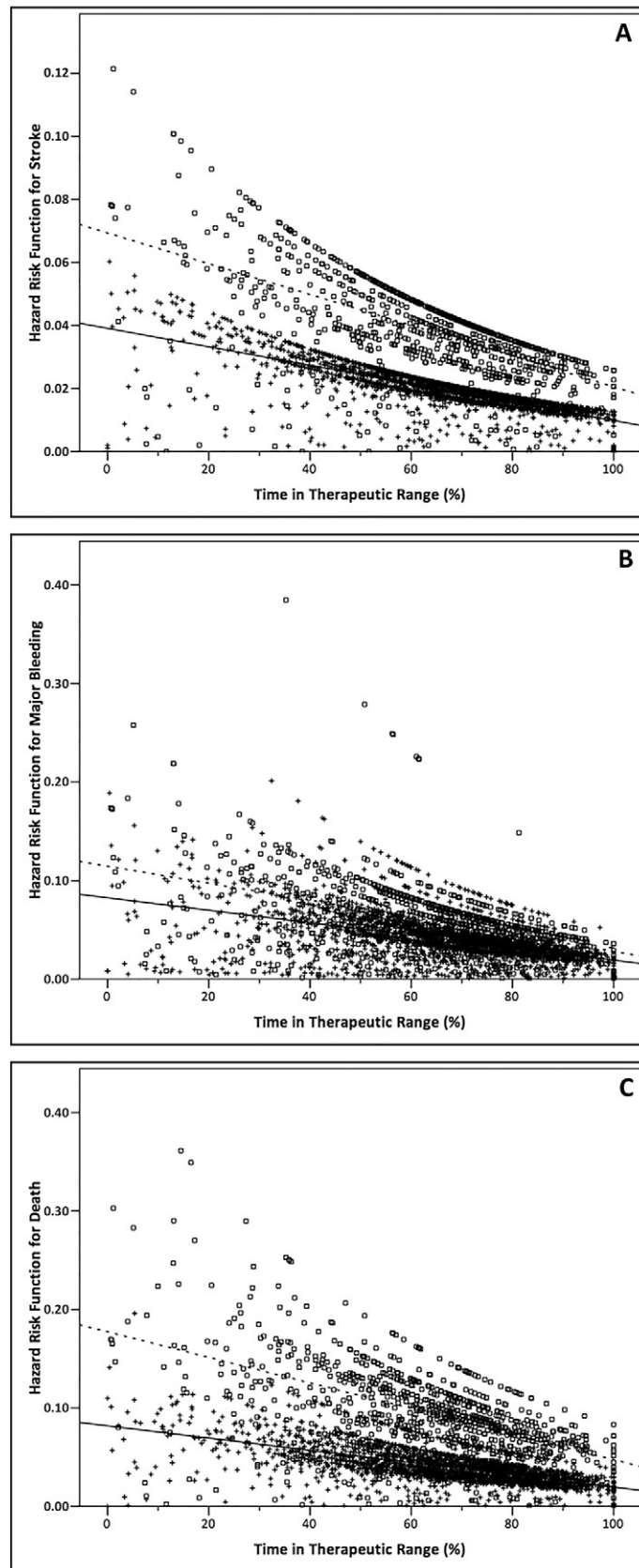
<sup>a</sup> Creatinine clearance <60 ml/min.

both myocardial infarction or major bleeding after adjusting for TTR. Conversely, adequate anticoagulation control as expressed by TTR > 70% was inversely associated with major bleeding.

Clinical factors associated with CKD have been previously reported in a smaller real-world’ populations of AF patients and our data are broadly confirmatory of the role of age, diabetes mellitus and CHF in predicting the presence of CKD in AF patients (Roldán et al., 2013). Indeed, both increasing age and diabetes mellitus are major predictors of CKD in the general population (Fox, 2004). Conversely, hypertension (an important risk factor for CKD in general population (Fox, 2004)) had no significant influence on CKD amongst AF patients in our trial cohort.

CKD is predictive of stroke in AF patients, whilst oral anticoagulation with VKA lowers stroke risk albeit at a higher risk of bleeding (Hart et al., 2011). The Loire Valley Atrial Fibrillation Project showed that CKD, defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m<sup>2</sup>, was associated with a higher incidence of ischemic stroke/thromboembolism events, but multivariable Cox regression analysis did not demonstrate an independent effect of renal impairment on predicting major adverse events, after adjusting for CHA<sub>2</sub>DS<sub>2</sub>-VASc score risk factors (Banerjee et al., 2014, 2013).

Our results demonstrate that even in AF patients treated with warfarin, CKD was still associated with a higher incidence of stroke, independent of other concomitant risk factors. These data support previous findings from another prospective randomised trial, where the presence of a CrCl < 60 ml/min was associated with two-fold higher risk of stroke compared with those with CrCl ≥ 60 ml/min (Apostolakis et al., 2013). Importantly, we show that the predictive ability of CKD in identifying



**Fig. 4.** Correlation between TTR and hazard risk according to presence of chronic kidney disease. Panel A) Stroke  $p < 0.001$ ; Panel B) Major bleeding  $p < 0.001$ ; Panel C) Death  $p < 0.001$ . Legend = Cross and solid line: normal renal function; square and dashed line: CKD.

patients with a greater risk of stroke was independent of anticoagulation control, as reflected by the TTR, notwithstanding the latter being a strong predictor of adverse outcomes in patients with AF (White et al., 2007).

The lack of significant association between CrCl when analysed as a continuous variable, and the risk of stroke could be attributed to more complex and multifactorial physiological alterations present in patients with established CKD that statistical adjustments would not be able to fully adjust for. Indeed, the risk of cardiovascular disease is non-linear in the transition from one functional CKD class to another, but increases exponentially with greater impairment of renal function (Schiffirin et al., 2007).

Our study also supports previous evidence showing that CKD is associated with a higher risk for major bleeding (Apostolakis et al., 2013; Banerjee et al., 2014), even when stratified according to VKA treatment (Banerjee et al., 2014). Nonetheless, major bleeding is strongly related to the quality of anticoagulation control, and supra-therapeutic INR values amongst CKD patients are associated with a higher risk of developing a major bleed especially with progressive renal impairment (Limdi et al., 2015). In contrast to other previous studies (Olesen et al., 2012), we failed to show a significant association with MI risk, but given the low number of MIs recorded, this lack of association could partially be due to an inadequate sample size, and being unpowered. Finally, we found that CKD was an independent predictor for a higher risk of all cause death, consistent with prior studies (Apostolakis et al., 2013; Banerjee et al., 2014; Olesen et al., 2012). Importantly, the high risk for death in our study was independently related to CKD and inversely to effective anticoagulation (TTR > 70%).

Our data strengthen and reinforce the relationship between renal function and TTR (Kleinow et al., 2011; Kooiman et al., 2014). One study derived from a cohort of anticoagulated AF patients found that patients with moderate and severe CKD had higher TTR than patients with normal renal function, although CKD patients spent more time above therapeutic range and INR-variability significantly increased in patients with moderate and severe CKD (Kooiman et al., 2014). Recently, an analysis from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry found that an estimated glomerular filtration rate below 60 ml/min/1.73 m<sup>2</sup> was significantly associated with a reduced TTR ( $\leq 53\%$ ) (Pokorney et al., 2015). Our results strongly reinforce this relationship between renal function and anticoagulation control, and that CKD patients derived benefit from VKA treatment with good TTRs (Bonde et al., 2014).

Good quality anticoagulation control (TTR > 70%) was an independent predictor for a lower risk of stroke, death and major bleeding. There was a significant inverse correlation between TTR and HR risk function for stroke, death and major bleeding overall, but when this analysis was repeated in the CKD subgroup, the degree of correlation was reduced for stroke and death risk, perhaps reflecting how CKD modulates the risk of adverse events.

#### 4.1. Limitations

Renal function data was only available based on the Cockcroft-Gault formula and not by more recent and validated methods of eGFR evaluation (Levey et al., 2015). The original trial protocol excluded patients with a severe CKD, and this may have led to an underestimate in the prevalence of CKD in AF population. Also, the absence of subjects with severe CKD precluded a more detailed analysis of the wider spectrum of renal function and its influence on TTR and clinical outcomes. Moreover, other parameters used to evaluate anticoagulation control (e.g. time spent below or above the target, proportion of INRs in range, etc.) were not available for this analysis. Since the original trials were run between 2000 and 2002, current clinical practice in managing AF patients could have changed, with possible implications for the generalizability of our results. However, VKAs are still very widely used worldwide for thromboprophylaxis, in particular for treating AF patients with CKD (Potpara et al., 2015). Thus, the association between CKD and TTR

remains relevant during the decision-making process to prescribe the right drug for the right patient (Shields and Lip, 2015). Finally, the association of CKD with paroxysmal AF could be spurious, since only a low proportion of these subjects were enrolled in the original trial cohort.

**In conclusion**, CKD is highly prevalent amongst AF patients and associated with several clinical comorbidities. Importantly, CKD in AF patients is an independent risk factor for stroke and death, but not major bleeding after adjustment for TTR. Even after adjusting for CKD, good quality anticoagulation control (TTR > 70%) was an independent predictor for a lower risk of stroke, death and major bleeding.

#### Author Contributions

MP and GYHL conceived the study, analysed data, interpreted results and drafted the manuscript. DAL provided critical revision of the manuscript.

#### Funding

None directly related to this manuscript.

#### Disclosures

**GYHL:** Chairman, Scientific Documents Committee, European Heart Rhythm Association (EHRA). Reviewer for various guidelines and position statements from ESC, EHRA, NICE etc. Steering Committees/trials: Includes steering committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc. Consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.

**DAL:** Investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim. Speaker's bureau for Boehringer Ingelheim, Bristol-Myers-Squibb and Bayer for lectures at educational meetings. Dr Lane is also on the Steering Committee of a Phase IV clinical trial sponsored by Bristol-Myers-Squibb.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ebiom.2016.04.013>.

#### References

- Albers, G.W., Diener, H.-C., Frison, L., Grind, M., Nevinson, M., Partridge, S., Halperin, J.L., Horrow, J., Olsson, S.B., Petersen, P., Vahanian, A., 2005. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 293, 690–698. <http://dx.doi.org/10.1001/jama.293.6.690>.
- K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am. J. Kidney Dis.* 39, S1–266.
- Apostolakis, S., Guo, Y., Lane, D.A., Buller, H., Lip, G.Y.H., 2013. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. *Eur. Heart J.* 34, 3572–3579. <http://dx.doi.org/10.1093/eurheartj/ehz328>.
- Banerjee, A., Fauchier, L., Vourch, P., Andres, C.R., Taillandier, S., Halimi, J.M., Lip, G.Y.H., 2013. Renal impairment and ischemic stroke risk assessment in patients with atrial fibrillation: the Loire Valley atrial fibrillation project. *J. Am. Coll. Cardiol.* 61, 2079–2087. <http://dx.doi.org/10.1016/j.jacc.2013.02.035>.
- Banerjee, A., Fauchier, L., Vourch, P., Andres, C.R., Taillandier, S., Halimi, J.M., Lip, G.Y.H., 2014. A prospective study of estimated glomerular filtration rate and outcomes in patients with atrial fibrillation: the Loire Valley atrial fibrillation project. *Chest* 145, 1370–1382. <http://dx.doi.org/10.1378/chest.13-2103>.
- Bonde, A.N., Lip, G.Y.H., Kamper, A.-L., Hansen, P.R., Lamberts, M., Hommel, K., Hansen, M.L., Gislason, G.H., Torp-Pedersen, C., Olesen, J.B., 2014. Net clinical benefit of anti-thrombotic therapy in patients with atrial fibrillation and chronic kidney disease. *J. Am. Coll. Cardiol.* 64, 2471–2482. <http://dx.doi.org/10.1016/j.jacc.2014.09.051>.
- Camm, A., Lip, G., De Caterina, R., Savelieva, I., Atar, D., Hohnloser, S., Hindricks, G., Kirchhof, P., 2012. 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.* 33, 2719–2747. <http://dx.doi.org/10.1093/eurheartj/ehs253>.
- Connolly, S.J., Pogue, J., Eikelboom, J., Flaker, G., Commerford, P., Franzosi, M.G., Healey, J.S., Yusuf, S., 2008. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 118, 2029–2037. <http://dx.doi.org/10.1161/CIRCULATIONAHA.107.750000>.
- De Caterina, R., Husted, S., Wallentin, L., Andreotti, F., Arnesen, H., Bachmann, F., Baigent, C., Huber, K., Jespersen, J., Kristensen, S.D., Lip, G.Y.H., Morais, J., Rasmussen, L.H., Siegbahn, A., Verheugt, F.W.A., Weitz, J.I., 2013. Vitamin K antagonists in heart disease: current status and perspectives (Section III). *Thromb. Haemost.* 110, 1087–1107. <http://dx.doi.org/10.1160/TH13-06-0443>.
- Fox, C.S., 2004. Predictors of new-onset kidney disease in a community-based population. *JAMA* 291, 844. <http://dx.doi.org/10.1001/jama.291.7.844>.
- Friberg, L., Benson, L., Lip, G.Y.H., 2014. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur. Heart J.* 297–306. <http://dx.doi.org/10.1093/eurheartj/ehu139>.
- Gage, B.F., van Walraven, C., Pearce, L., Hart, R.G., Koudstaal, P.J., Boode, B.S.P., Petersen, P., 2004. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 110, 2287–2292. <http://dx.doi.org/10.1161/01.CIR.0000145172.55640.93>.
- Halperin, J.L., 2003. 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.* 146, 431–438. [http://dx.doi.org/10.1016/S0002-8703\(03\)00325-9](http://dx.doi.org/10.1016/S0002-8703(03)00325-9).
- Hart, R.G., Pearce, L.A., A Singer, R.W., Herzog, C.A., 2011. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* 6, 2599–2604. <http://dx.doi.org/10.2215/CJN.02400311>.
- Kleinow, M.E., Garwood, C.L., Clemente, J.L., Whittaker, P., 2011. Effect of chronic kidney disease on warfarin management in a pharmacist-managed anticoagulation clinic. *J. Manag. Care Pharm.* 17, 523–530.
- Kooiman, J., van Rein, N., Spaans, B., van Beers, K.A.J., Bank, J.R., van de Peppel, W.R., del Sol, A.I., Cannegieter, S.C., Rabelink, T.J., Lip, G.Y.H., Klok, F.A., Huisman, M.V., 2014. Efficacy and safety of vitamin K-antagonists (VKA) for atrial fibrillation in non-dialysis dependent chronic kidney disease. *PLoS One* 9, e94420. <http://dx.doi.org/10.1371/journal.pone.0094420>.
- Levey, A.S., Becker, C., Inker, L.A., 2015. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *JAMA* 313, 837–846. <http://dx.doi.org/10.1001/jama.2015.0602>.
- Limdi, N.A., Nolin, T.D., Booth, S.L., Centi, A., Marques, M.B., Crowley, M.R., Allon, M., Beasley, T.M., 2015. Influence of kidney function on risk of supratherapeutic international normalized ratio-related hemorrhage in warfarin users: a prospective cohort study. *Am. J. Kidney Dis.* 65, 701–709. <http://dx.doi.org/10.1053/j.ajkd.2014.11.004>.
- Lip, G.Y.H., 2005. Preventing stroke in atrial fibrillation: the SPORTIF programme. *Pathophysiol. Haemost. Thromb.* 34 (Suppl. 1), 25–30. <http://dx.doi.org/10.1159/000083081>.
- Lip, G.Y.H., Nieuwlaat, R., Pisters, R., Lane, D.A., Crijns, H.J.G.M., 2010. 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* 137, 263–272. <http://dx.doi.org/10.1378/chest.09-1584>.
- Lip, G.Y.H., Skjøth, F., Rasmussen, L.H., Larsen, T.B., 2015. 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.* 65, 1385–1394. <http://dx.doi.org/10.1016/j.jacc.2015.01.044>.
- Olesen, J.B., Lip, G.Y.H., Kamper, A.-L., Hommel, K., Køber, L., Lane, D.A., Lindhardsen, J., Gislason, G.H., Torp-Pedersen, C., 2012. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N. Engl. J. Med.* 367, 625–635. <http://dx.doi.org/10.1056/NEJMoa1105594>.
- Olsson, S.B., 2003. 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* 362, 1691–1698.
- Piccini, J.P., Stevens, S.R., Chang, Y., Singer, D.E., Lokhnygina, Y., Go, A.S., Patel, M.R., Mahaffey, K.W., Halperin, J.L., Breithardt, G., Hankey, G.J., Hacke, W., Becker, R.C., Nessel, C.C., Fox, K.A.A., Califf, R.M., 2013. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K ant. *Circulation* 127, 224–232. <http://dx.doi.org/10.1161/CIRCULATIONAHA.112.107128>.
- Pokorney, S.D., Simon, D.N., Thomas, L., Fonarow, G.C., Kowey, P.R., Chang, P., Singer, D.E., Ansell, J., Blanco, R.G., Gersh, B., Mahaffey, K.W., Hylek, E.M., Go, A.S., Piccini, J.P., Peterson, E.D., 2015. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am. Heart J.* 170, 141–148. <http://dx.doi.org/10.1016/j.ahj.2015.03.017>.
- Potpara, T.S., Lenarczyk, R., Larsen, T.B., Deharo, J.-C., Chen, J., Dagues, N., Conducted by the Scientific Initiatives Committee, E.H.R.A., Conducted by the Scientific Initiatives Committee European Heart Rhythm Association, 2015. Management of atrial fibrillation in patients with chronic kidney disease in Europe results of the European Heart Rhythm Association survey. *Europace* 17, 1862–1867. <http://dx.doi.org/10.1093/europace/euv416>.
- Roldán, V., Marín, F., Fernández, H., Manzano-Fernández, S., Gallego, P., Valdés, M., Vicente, V., Lip, G.Y.H., 2013. Renal impairment in a “real-life” cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). *Am. J. Cardiol.* 111, 1159–1164. <http://dx.doi.org/10.1016/j.amjcard.2012.12.045>.
- Rosendaal, F.R., Cannegieter, S.C., van der Meer, F.J., Briët, E., 1993. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb. Haemost.* 69, 236–239.
- Schiffrin, E.L., Lipman, M.L., Mann, J.F.E., 2007. Chronic kidney disease: effects on the cardiovascular system. *Circulation* 116, 85–97. <http://dx.doi.org/10.1161/CIRCULATIONAHA.106.678342>.
- Schulman, S., Kearon, C., 2005. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J. Thromb. Haemost.* 3, 692–694. <http://dx.doi.org/10.1111/j.1538-7836.2005.01204.x>.
- Shields, A.M., Lip, G.Y.H., 2015. Choosing the right drug to fit the patient when selecting oral anticoagulation for stroke prevention in atrial fibrillation. *J. Intern. Med.* 278, 1–18. <http://dx.doi.org/10.1111/joim.12360>.
- White, H.D., Gruber, M., Feyzi, J., Kaatz, S., Tse, H.-F., Husted, S., Albers, G.W., 2007. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Arch. Intern. Med.* 167, 239–245. <http://dx.doi.org/10.1001/archinte.167.3.239>.