Journal of Nephrology

Effect of oral anticoagulant therapy on mortality in end stage renal disease patients with atrial fibrillation: a prospective study

--Manuscript Draft--

Manuscript Number:	JNEP-D-16-00364R1
Full Title:	Effect of oral anticoagulant therapy on mortality in end stage renal disease patients with atrial fibrillation: a prospective study
Article Type:	Original Article
Funding Information:	Italian Ministry of Education, University and Research. (SIR RBSI14LOVD) — Dr Paola Rebora
Abstract:	Background: Aim of this study was to evaluate, in a cohort of haemodialysis patients with atrial fibrillation (AF), the relationship between oral anticoagulant therapy (OAT) and mortality, thromboembolic and haemorrhagic risk. Methods: 290 patients with AF were prospectively followed-up for four years. Warfarin and antiplatelet intake, age, dialytic age, comorbidities, CHA2DS2-VASc and HASBLED scores were considered as predictors of hazard of death, thromboembolic and bleeding events. In patients taking OAT, the International Normalized Ratio (INR) was assessed and the percentage time in the Target Therapeutic Range (TTR) was calculated. Results: At recruitment, 134/290 patients were taking warfarin. During follow-up there were 170 deaths, 28 thromboembolic events and 95 bleedings. After balancing for treatment propensity, intention-to-treat analysis on OAT assumption at recruitment did not show differences in total mortality, thromboembolic events and bleedings. As-treated analysis, accounting for treatment switch, showed that patients taking OAT at recruitment had a significantly lower mortality than those not taking it (HR 0.53, 95%CI 0.28-0.90, P=0.04), with a slight benefit of OAT on thromboembolic events (HR 0.36, 95%CI 0.13-1.05, P=0.06), and a non-significant increase in bleedings. Among patients taking OAT at recruitment, those continuing warfarin assumption had a significant reduction in the risk of total (HR 0.28, 95%CI 0.14-0.53, P<0.001) and cardiovascular (HR 0.21, 95%CI 0.11-0.40, P<0.001) mortality, compared to patients stopping assumption. Conclusions: In haemodialysis patients with AF, continuously taking warfarin is associated with a reduction of the risk of total and cardiovascular mortality, and with a slight decrease of thromboembolic events.
Corresponding Author:	Simonetta Genovesi Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy and Nephrology Unit S Gerardo Hospital, Monza , Italy ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy and Nephrology Unit S Gerardo Hospital, Monza , Italy
Corresponding Author's Secondary Institution:	
First Author:	Simonetta Genovesi
First Author Secondary Information:	
Order of Authors:	Simonetta Genovesi Paola Rebora Maurizio Gallieni Andrea Stella

	Fabio Badiali
	Ferruccio Conte
	Sonia Pasquali
	Silvio Bertoli
	Patrizia Ondei
	Giuseppe Bonforte
	Claudio Pozzi
	Emanuela Rossi
	MariaGrazia Valsecchi
	Antonio Santoro
Order of Authors Secondary Information:	
Author Comments:	Dear prof. Gambaro, Editor in chief of Journal of Nephrology, we are submitting you the revised version of the manuscript "Effect of oral anticoagulant therapy on mortality in end stage renal disease patients with atrial fibrillation: a prospective study". We think that the comments of the reviewers allowed us to make modifications to the manuscript that have definitely improved it.We included a copy of the manuscript with revisions highlighted and a copy clean, to allow the Editor and the Reviewers to see the changes made to the manuscript. We hope that you may consider this new version of the manuscript acceptable for publication in your journal. My co-authors have all contributed to this manuscript and approve of this new submission. The results presented in this paper have not been published previously in whole or part, except in abstract form. I have communicated with all of my co-authors and obtained their full disclosures. A disclosure statement is also included. My co-authors and I declare no conflicts of interest. Sincerely, Dr. Simonetta Genovesi School of Medicine and Surgery, University of Milano-Bicocca Via Cadore 48, 20900, Monza (MB), Italy tel: +39 039 2332426 Fax: +390392332376 Email: simonetta.genovesi@unimib.it Best regards Simonetta Genovesi
Response to Reviewers:	We thank the Reviewers for their comments that allowed us to make modifications to the manuscript that have definitely improved it.We included a copy of the manuscript with revisions highlighted and a copy clean, to allow the Editor and the Reviewers to see the changes made to the manuscript. Reviewer #1: Thank you for your submission. This is a relatively small study for this topic, as previous studies usually have in excess of 1000 patients. The results are in keeping with some other reports, and as such the data is not novel. We agree with the reviewer that in the literature there are other studies on the same topic that have recruited a larger number of patients. However, those studies were all retrospective and / or registry studies, while ours is a prospective study, with a long follow-up (four years) and including ad hoc information, especially on the exact time of warfarin withdrawal and on INR values.We also think that our results(in particular as regards data on mortality), are not completely in keeping with what reported by other studies.

	Please kindly provide more details as to how patients were recruited into this study, by providing a consort flow diagram We added the patient selection flow chart as supplementary figure and we included also the prevalence of AF in each participating center. The cohort included all prevalent patients with AF of ten centers at 31-10-2010. There are some major confounders which need to be addressed. Firstly the two groups have some major differences, and ideally should be propensity matched, including classic risk factors for stroke, residual renal function and recent echocardiographic findings. We agree that the two groups have some major differences, indeed we did an analysis on the propensity to be under OAT at recruitment. In fact, we adjusted for major confounders by the use of weights on the propensity to be under treatment. These weights, called (stabilized) Inverse Probability of Treatment Weights (IPTW), were computed by a multivariable logistic model on the propensity to be under OAT at recruitment. In the new version of the manuscript we added to this model echocardiographic findings (left ventricular ejection fraction and presence of left ventricular hypertrophy, as suggested by reviewer 1) and peripheral artery disease (as suggested by reviewer 2). Classical risk factors for stroke were already present (comorbidities and CHA2DS2-VASCs score).We don't have data about residual renal function, but a median dialytic age of around 4 years is generally associated to a very limited presence of patients with preserved residual renal function.As,after the addition of new confounders, some variables remained partially unbalanced between groups (standardized difference >10%),we also adjusted for these variables the final model. All new information and results have been added to the Results section and tables. Please explain how patients were censored, and whether there was a difference in transplantation rates between the 2 groups The study design was set up with a follow-up of 4 years. Only 13 patients (4.4%) were lost to follow-up before the 4 years, 9 because they moved, 3 for transplantation and 1 with other (unspecified) reason. As far as transplant, the rate was similar in the two groups: no OAT at recruitment 2/156 (1.3%), OAT at recruitment 1/134(0.8%). Please provide a recognized co-morbidity score for patients The median/mean Charlston Comorbidity Index adapted for end stage renal disease (Hemmelgarn,2003, AJDK;42:125-132) was calculated for the two groups and added in Table 1. No difference was found between the two groups In terms of risks for gastro-intestinal hemorrhage.Please provide details of prescription of H2 blockers, proton pump inhibitors, antacidsetc, and also NSAID use, and do the authors have carriage rates for H.Pylori. We have this information only in a subset of patients (n= 94 patients): 26 (28%) had a prescription of H2 blockers, 63(67%) of proton pump inhibitors and no one of antiacid. We do not have information in NSAID use and carriage rates for H.Pylori. How many patients were prescribed dual anti-platelet therapy for cardiac disease Height patients were taking dual anti-platelet therapy (only one was an OAT-yes patient). Please provide details whether episodes of hemorrhage were the direct cause of acute hospital admission, or occurred during hops ital admission Unfortunately, we did not collect information on hospital admission caused by

hemorrhage, but only on hospital admission for cardiovascular events.

Reviewer #2: The authors describe a prospective analysis of oral anticoagulant effects in HD patients with atrial fibrillation.

METHODS:
- the paper lacks definitions. For example, how were clinical events and history such as peripheral vascular disease or ischemic heart disease defined?

All definitions have been added to the manuscript (see Methods section)

- Which types of OAT were administered? Most of the time, "OAT" seems to be synonymous with "warfarin". Please clarify.

All patients defined as OAT-yes were taking warfarin.

- I am not a statistics expert. However, simple logic would suggest that the frail patient with a tendency for falls etc is less likely to receive oral anticoagulants in particular on a permanent basis. Frailty in turn is one of the major mortality risk factors in HD patients and indeed a surprising 17% of the patients is stated to have died from cachexia. How did this major confounder enter the analyses?

We agree we the reviewer that frail patients might be less likely to receive OAT. For this reason, at baseline of our study, we administrated to nephrologists a questionnaire asking the reason why they did not prescribe warfarin, even if the patient had an indication for taking it (i.e. CHA2DS2-VASc>=2). Only 1.3% of nephrologists responded that “The patient had an unstable equilibrium and risked fallingeasily/had already fallen once” and only 5.1% that “The patient was not reliable and compliant in taking the therapy” (Genovesi S, et al. 2014, J Nephrol 27:187-192). Moreover, we looked at the distribution of death from cachexia by OAT at baseline.No difference was found between groups: 27/156 (17.3%) patients OAT-no and 22/134 (16%)patients OAT-yes died from cachexia (12 were still taking the therapy at the time of death). In addition, when a sensitivity analysis excluding patients who died within 6 months from OAT withdrawal was done, mortality results remained similar. Finally, the median/mean Charlston Comorbidity Index adapted for end stage renal disease (Hemmelgarn,2003, AJDK;42:125-132) was not different between the two groups at recruitment (see revised Table 1).

RESULTS:
- a plethora of numbers renders the results section rather difficult to reduce. Please try to limit the numbers to those that are not shown in the tables

We agree with the reviewer. All numeric data already present in the tables have been removed from the Results section.

DISCUSSION:
- So how does OAT protect HD patients if there is no detectable effect on thromboembolic events and at least a trend for more bleeding episodes (table 2)?

After the modifications suggested by the referees to the manuscript, the as-treated analysis showed a borderline reduction of thromboembolic events in patients taking warfarin. This can partly explain the mortality reduction observed in our population. Moreover, in coronary artery disease patients with and without concomitant AF, oral anticoagulation has been shown to protect against myocardial infarction and to be safe and effective [ref 23, 24]. A recent study demonstrated in older adults (> 75 years) with AF a benefit from OAT in terms of lower mortality, regardless of poor health and functional condition [ref 25]. It’s possible that, also in HD patients, OAT might have a positive effect not only through a reduction of thromboembolic risk. These concepts and related references are present in the Discussion section.

Citing the Danish study on page 11 (ref. #3) may be misleading, as that study lumped together HD, PD and transplant patients into a group called "renal replacement". I suggest to disregard reference #3 here

	We agree with the reviewer.The study by Olesen included also peritoneal and transplant patients and this makes it difficult to compare the results with those of other studies. A sentence has been added to the Discussion section to clarify it. - Limitations need to be discussed in more detail: First, only documented AF episodes entered the analyses We chose to include only cases of AF with a clear electrocardiographic documentation, to be sure of the real presence of the arrhythmia.Furthermore, we have separated different types of AF (paroxismal, persistent, permanent) and, to do this, it was necessary an accurate documentation.We cannot exclude that some centers were more careful in the diagnosis of AF compared to other, especially for paroxysmal forms that are often unrecognized.By note, the prevalence of AF in our population, compared to that reported in the literature (Zimmerman Nephrol Dial Transplant 2012; 27: 3816–3822), suggests that we are close to the true prevalence of the arrhythmia.We added this point in the limitation section. Second, at a median dialytic age of around 4 years, it may be important to point out that this is a cohort of dialysis "survivors" In Italy the survival of dialysis patients is higher than that observed in other countries. Our mortality data (which still show a rate of about 60% of deaths in four years of follow up), are in line with those of the Italian Registry of Dialysis and Transplantation, RIDT (http://ridt.sinitaly.org/web/eventi/RIDT/index.cfm). If the referee considers it necessary, we can include a sentence on this point in the manuscript. Third, the issue of frailty (seeabove) As reported in the limitation section we recognize that as-treated analysis might be subject to selection bias due to adverse events causing warfarin withdrawal. Those patients who succeeded in continuing to take the therapy could be the ones who were less frail and had a better compliance. However, to assess this assumption, we performed a sensitivity analysis in which we censored patients who died within six months of warfarin withdrawal and we obtained similar results (see Results section and limitations).

TITLE PAGE

Effect of oral anticoagulant therapy on mortality in end stage renal disease patients with atrial fibrillation: a prospective study

*Simonetta Genovesi MD [1,3], Paola Rebora PhD [2], Maurizio Gallieni MD [4], Andrea Stella MD [1,3], Fabio Badiali MD [5], Ferruccio Conte MD [6], Sonia Pasquali MD [7], Silvio Bertoli MD [8], Patrizia Ondei MD [9], Giuseppe Bonforte MD [10], Claudio Pozzi MD [11], Emanuela Rossi PhD [2], Maria Grazia Valsecchi PhD [2], Antonio Santoro MD [12]

Author Affiliations

1 Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

2 Center of Biostatistics for Clinical Epidemiology, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

3 Nephrology Unit, San Gerardo Hospital, Monza, Italy

4 Nephrology Unit, San Carlo Borromeo Hospital, Milano, Italy

5 Nephrology Unit, Infermi Hospital, Rimini, Italy

6 Nephrology Unit, S. Uboldo Hospital, Cernusco sul Naviglio, Italy

7 Nephrology Unit, S. Maria Nuova Hospital, Reggio Emilia, Italy

8 Nephrology Unit, IRCCS Multimedica, Sesto S. Giovanni, Italy

9 Nephrology Unit, Ospedali Riuniti, Bergamo, Italy

10 Nephrology Unit, S. Anna Hospital, Como, Italy

11 Nephrology Unit, Bassini Hospital, Cinisello, Milano, Italy

12 Nephrology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy

SHORT TITLE: Warfarin and mortality in haemodialysis patients

Informed consent and Research involving Human Participants :

Procedures were performed according to the Helsinki declaration for ethical treatment of human subjects and approved by the local ethical committee. Informed consent was obtained from the enrolled subjects.

Conflict of interest:

The authors declare that they have no conflict of interest

Acknowledgments:

PR was supported by the grant SIR RBSI14LOVD of the Italian Ministry of Education, University and Research.

***Corresponding author:**

Università di Milano-Bicocca-University of Milano-Bicocca

Dipartimento di Medicina e Chirurgia-School of Medicine and Surgery

Via Cadore 48, 20900, Monza (MB), Italy

tel: +39 039 2332426

Fax: +390392332376

Email: simonetta.genovesi@unimib.it

Effect of oral anticoagulant therapy on mortality in end stage renal disease patients with atrial fibrillation: a prospective study

ABSTRACT

Background: Aim of this study was to evaluate, in a cohort of haemodialysis patients with atrial fibrillation (AF), the relationship between oral anticoagulant therapy (OAT) and mortality, thromboembolic and haemorrhagic risk.

Methods: 290 patients with AF were prospectively followed-up for four years. Warfarin and antiplatelet intake, age, dialytic age, comorbidities, CHA_2DS_2-VAS_c and HASBLED scores were considered as predictors of hazard of death, thromboembolic and bleeding events. In patients taking OAT, the International Normalized Ratio (INR) was assessed and the percentage time in the Target Therapeutic Range (TTR) was calculated.

Results: At recruitment, 134/290 patients were taking warfarin. During follow-up there were 170 deaths, 28 thromboembolic events and 95 bleedings. After balancing for treatment propensity, intention-to-treat analysis on OAT assumption at recruitment did not show differences in total mortality, thromboembolic events and bleedings. , ~~while~~ As~~s~~-treated analysis, accounting for treatment switch, showed that patients taking OAT at recruitment had a significantly lower mortality than those not taking it (HR 0.531, 95%CI 0.289-0.9089, P=0.042), with a~~-~~ slight ~~No~~ benefit of OAT ~~was evident~~ on thromboembolic events (HR 0.36, 95%CI 0.132-1.05, P=0.06)~~–~~, ~~while~~ and a non-significant increase in bleedings ~~was observed~~ . Among patients taking OAT at recruitment, those continuing warfarin assumption had a significant reduction in the risk of total (HR 0.28, 95%CI 0.14-0.53, P<0.001) and cardiovascular (HR 0.21, 95%CI 0.11-0.40, P<0.001) mortality, compared to patients stopping assumption.

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Conclusions: In haemodialysis patients with AF, continuously taking warfarin is associated with a reduction of the risk of total and cardiovascular mortality, and with a slight ~~while it is not associated with a~~ decrease of thromboembolic events.

KEYWORDS: warfarin, haemodialysis, atrial fibrillation, mortality, stroke, bleeding

INTRODUCTION

Data on the risk/benefit ratio of warfarin in patients with atrial fibrillation (AF) and end stage renal disease (ESRD) continue to be inconclusive, despite the high prevalence of the arrhythmia in this population. Some authors report an increased risk of complications derived from the use of oral anticoagulant therapy (OAT) in haemodialysis (HD) patients with AF, without any benefit in terms of thromboembolic risk protection [1, 2]. Other studies are less negative [3, 4] but a big uncertainty remains on how to approach these patients [5]. One major problem is the lack of prospective and randomized data. In fact almost all published studies are based on retrospective analyses of registry data. Recently a large retrospective study showed that warfarin was associated with a reduced mortality in a cohort of HD patients with newly diagnosed AF [6]. This study accounted for confounding by indication with propensity score, but being a register study not all potential confounders were available, in particular International Normalized Ratio (INR) was missing and OAT assumption was based on the prescription. We set a prospective study in a population of HD patients with AF, where information on the exact time of the possible withdrawal of warfarin and on the INR values in subjects taking OAT were collected, over the baseline characteristics of patients. Preliminary results on two years of follow-up indicated that warfarin significantly increased the incidence of bleeding without reducing thromboembolic events. Furthermore, the study suggested the presence of a trend towards a better survival in patients receiving OAT [7]. However, those early results needed to be completed with a long-term efficacy and safety evaluation of warfarin assumption.

The main purpose of the present study was to evaluate prospectively, in a cohort of patients with ESRD and AF followed-up for four years, the relationship between OAT and mortality, thromboembolic and haemorrhagic risk .We evaluated long-term efficacy and safety of OAT using a causal method approach to limit the confounding by indication and to account for the

updated value of confounders/variables over the follow-up. Secondary aim was to test the predictive value of the CHA_2DS_2-VAS_c and HASBLED scores on mortality, thromboembolic and haemorrhagic events, given that these scores are indicated by the Cardiology Guidelines to identify patients at increased thromboembolic and haemorrhagic risk [8], but were developed in cohorts of patients in which HD was an exclusion criterion.

SUBJECTS AND METHODS

All patients alive and under observation in 10 Italian dialysis centers on 31/10/2010 were considered (n=1529) and their clinical charts revised for eligibility to the study. Peritoneal dialysis patients were not included. All subjects with at least one documented paroxysmal (self-terminating) or persistent (required termination by pharmacological or electrical cardioversion) AF episode, or with permanent AF (when there has been a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm) were recruited, for a total of 290 patients (see Supplementary figure 1).

At recruitment data were collected on the presence of hypertension (systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg before the beginning of the HD session or anti-hypertensive drugs administration), diabetes mellitus, peripheral artery disease (clinical presence of claudication and/or evidence of significant stenosis of main arterial trunks by doppler examination), ischemic heart disease (previous myocardial infarction or coronary revascularization procedures and/or previous hospitalization due to acute coronary syndrome), heart failure (presence of left-ventricular dysfunction- ~~(~~left-ventricular ejection fraction<50%~~)~~- and/or previous hospitalization due to acute or chronic heart failure), previous strokes (ischemic or haemorrhagic defined by computed tomographic scan or nuclear magnetic resonance), and major bleeding episodes (haemorrhagic episode requiring

hospitalization or blood transfusion, or causing a haemoglobin plasma level reduction > 2g/dl) and on administration of antiplatelets and anticoagulants [7].

Cardiac ultrasound examination was performed in all the patients during the mid-week dialysis interval. Collected echocardiography data were: left ventricular ejection fraction (LVEF, %) and the presence of left ventricular hypertrophy (LVH), which was defined as left-ventricular mass normalized for body surface area >125 g/m^2 according to the Penn-cube formula, or when its presence was described in the report.

Patients were prospectively followed-up for four years (until 31/10/2014 or death) and their clinical charts were updated at each dialysis session. The new onset of permanent AF, stroke ~~(ischemic or haemorrhagic defined by computed tomographic scan or nuclear magnetic resonance)~~, bleeding ~~(haemorrhagic episode requiring hospitalization or blood transfusion, or causing a haemoglobin plasma level reduction > 2g/dl)~~, cardiovascular events (ischemic and heart failure episodes that required hospitalization), and antiplatelet and anticoagulant treatment modifications were recorded.

In patients taking OAT, the INR values were assessed at least once a month and the percentage time in the target INR range (Target Therapeutic Range, TTR) was calculated [9]. Only one center referred patients to a Thrombosis Clinic, while in the others the nephrologist took care of warfarin dosage (the policy was to keep INR between 2 and 3).

Thromboembolic and haemorrhagic risk was calculated using the CHA_2DS_2-VAS_c and HASBLED score, respectively [8].

Procedures were performed according to the Helsinki declaration for ethical treatment of human subjects and approved by the local ethical committee. Informed consent was obtained from the enrolled subjects.

Statistical methods

All data were centrally revised. Patients were considered under OAT at recruitment if taking OAT at 31/10/2010. Rates of mortality, thromboembolic and haemorrhagic events were computed for patients on and not on OAT at recruitment and compared by the Poisson model.

Marginal structural models

In order to evaluate the effect of OAT on mortality, thromboembolic and haemorrhagic risk, we created a pseudo-population (that mimics a randomized trial) which mitigates the selection bias in OAT treatment assignment at recruitment [10]. This pseudo-population, created by the use of (stabilized) Inverse Probability of Treatment (and censoring) Weights (IPTW), is called the "IPTW cohort". IPTW were computed by a multivariable logistic model on the propensity to be under OAT at recruitment that included age, diabetes mellitus, ischemic and bleeding/haemorrhagic strokes, ischemic heart disease, CHA_2DS_2-VAS_c and HASBLED score, type of AF, left ventricular ejection fraction <50% and left ventricular hypertrophy (and their first degree interactions), gender, dialytic age, hypertension, heart failure, peripheral artery disease and antiplatelet therapy. ~~gender, age, dialytic age, hypertension, diabetes mellitus, ischemic and bleeding/haemorrhagic strokes, heart failure, CHA_2DS_2-VAS_c and HASBLED score, antiplatelet therapy and type of AF.~~ In order to evaluate the balance induced by these weights, the confounders among patients under OAT and not in this pseudo-population were compared by standardized differences [11]. Furthermore, an inverse probability of censoring weight was also applied to account for loss to follow-up and informative censoring due to death when analysing thromboembolic and haemorrhagic outcomes. Final weights were computed as the product of the stabilized weights [10] for treatment and censoring (trimming was not necessary as weights ranged between 0.5 to 9.5). The weighted Cox regression model with robust standard error was applied to the IPTW cohort to assess the effect of OAT administration at recruitment on different relevant endpoints. The model was adjusted for each covariate which after balancing (IPTW cohort)

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still showed a standardized difference greater than 10% between the two groups (i. e. bleeding/haemorrhagic stroke and permanent AF). ~~We did not add any covariate in this model, since all observed confounders were balanced in the IPTW cohort by the weighting procedure.~~ Results of the Cox models are expressed in terms of estimated hazard ratios (HR), 95% confidence intervals (95%CI) and P-values.

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In analogy to a randomized trial, two analyses were performed: intention-to-treat (ITT) and as-treated (AT) analyses. In the first one, the treatment (OAT) classification at recruitment was retained for the whole follow-up, while in the AT analysis patients who switched treatment were artificially censored (this artificial censoring was also considered in the inverse probability of censoring weights).

Sequential Cox

In order to better evaluate the effect of the time dependent variables, including OAT assumption, on the risk of mortality, thromboembolic and haemorrhagic events, we evaluated the effect of stopping OAT by the sequential Cox approach [12]. This method mimics several randomized controlled trials, based on individuals stopping OAT in time intervals (of one month), and obtains an overall treatment effect estimate. We adjusted for gender and the updated values (at the beginning of each month) of age, percentage of TTR ,CHA_2DS_2-VAS_c and HASBLED scores, presence of permanent AF and use of antiplatelets.

The effect of suspending OAT was also estimated stratifying according to TTR $\geq$ or <60% [13]. As it was possible that some patients had discontinued therapy because in terminal conditions, a sensitivity analysis was performed, in which we censored patients died within six months of warfarin withdrawal.

Score analysis

The Kaplan-Meier estimator was used to describe survival in subgroups defined according to CHA_2DS_2-VAS_c and HASBLED scores at recruitment. We also computed rates of mortality, thromboembolic and haemorrhagic events by the updated value of the scores during follow-up.

Analyses were carried out by means of the statistical software SAS v.9.4 (SAS Institute Inc, Cary, NC), and R statistical software v.3.1 (http://www.r-project.org).

RESULTS

The study was carried out in a cohort of 290 HD patients, with mean age at recruitment of 74 years (standard deviation 9.7). At recruitment, 134 patients (46.2%) were taking OAT (OAT-yes). The median follow-up time was 4 years. During follow-up, 65/134 (48.5%) patients stopped taking warfarin, while 33/156 (21.1%) subjects without OAT at recruitment (OAT-no) started to take it. During the 4-year follow-up there were 170 deaths (95 in OAT-no versus 75 in OAT-yes at recruitment; 25 and 22 per 100 patient years, respectively; P=0.4), 28 thromboembolic events (17 in OAT-no versus 11 in OAT-yes at recruitment; 4.5 and 3.2 per 100 patient years, respectively; P=0.4) and 95 haemorrhagic events (36 in OAT-no versus 59 in OAT-yes at recruitment; 9.5 and 17 per 100 patient years, respectively; P=0.005).

The main causes of death were: cachexia (n=49, 16.9%), sepsis (n=34, 11.7%), sudden death (n=18, 6.3%), cardiogenic shock and tumor (n=15, 5.2%). One patient died due to ischemic stroke and three for hemorrhagic stroke (0.6 and 1.0%, respectively).

Table 1 shows the clinical characteristics of the OAT-no and OAT-yes patients at recruitment, before and after balancing for treatment propensity.

A plain unadjusted Cox model did not show any difference between patients under OAT-no and OAT-yes at recruitment: HR=0.87 (95%CI: 0.64-1.18, P=0.37) for mortality, HR=0.60 (95%CI: 0.26-1.36, P=0.22) for thromboembolic events and HR=1.57 (95%CI: 0.91-2.72,

P=0.11) for bleeding. Similar results were observed with the ITT analysis of the IPTW cohort that did not show a difference regarding total mortality, cardiovascular mortality, thromboembolic and hemorrhagic events (Table 2). The AT analysis, censoring patients when they switch treatment, showed that patients taking OAT at recruitment had a significantly lower mortality rate than those not taking it (HR 0.51, 95%CI 0.29-0.89, P=0.02), with a non-significant protective effect effect on cardiovascular mortality (HR 0.50, 95%CI 0.22-1.16, P=0.1). A non-significant No benefit of OAT was evident on thromboembolic events, while a non-significant increase in bleedings was observed (HR 1.80, 95%CI 0.91-3.58, P=0.09) (Table 2).

The results from the sequential Cox regression model showed that among patients taking OAT at recruitment (n=134), those continuing OAT assumption (n=69) had a significant reduction in the risk of total (HR 0.28, 95%CI 0.14-0.53, P<0.001) and cardiovascular (HR 0.21, 95%CI 0.11-0.40, P<0.001) mortality, compared to patients stopping the assumption during follow-up. There was a slight increase of mortality in patients with higher HASBLED score for cardiovascular mortality (HR 1.71, 95%CI 1.00-2.93, P=0.05). A higher TTR seemed to have a modest protective effect against thromboembolic events (HR 0.13, 95%CI 0.013-1.37, P=0.09). Warfarin slightly increased the risk of bleeding (HR 5.20, 95%CI 0.63-42.70, P=0.12). In order to evaluate whether the beneficial effect of warfarin on mortality was due to the fact that patients who do not interrupt warfarin have a better INR, we stratified the analysis for TTR lower and higher than 60%: also in patients with a labile INR (TTR<60%) continuous warfarin intake had a beneficial effect. (HR 0.37, 95%CI 0.18-0.77, P=0.007). A more marked effect was seen in patients with TTR≥60% (HR 0.07, 95%CI 0.02-0.19 P<0.001) (Table 3).The results were similar when patients who died within six months after warfarin withdrawal (n=15) were censored: OAT was still associated with a reduction of total (HR 0.44, 95%CI 0.23-0.84, P=0.013) and cardiovascular mortality (HR 0.36, 95%CI 0.19-

0.66, P=0.001). Mortality results were confirmed also stratifying for TTR lower and higher than 60% (HR 0.49, 95%CI 0.24-0.99, P=0.048 and HR 0.24, 95%CI 0.07-0.82, P=0.023, respectively).

At recruitment, 12 (4.1%) patients had a CHA_2DS_2-VAS_c score between 0-1, 149 (51.4%) between 2-4 and 129 (44.5%) between 5-9, while patients with a HASBLED score between 0-1 were 3 (1%), between 2-3 were 137 (47.2%) and between 4-9 were 149 (51.4%). Total mortality was significantly related to both CHA_2DS_2-VAS_c (log-rank test $P<0.001$, Figure 1A) and HASBLED score (log-rank test P=0.003, Figure 1B). Coherently we found higher rates of mortality with higher scores, when the scores were updated during follow-up: 8.4, 18.4, 31.2 per 100 person years for CHA_2DS_2-VAS_c between 0-1, 2-4 and 5-9, respectively, and 0, 17.5, 26.8 per 100 patient years for HASBLED between 0-1, 2-3 and 4-9, respectively. Thromboembolic events (3.9 per 100 patient years) also increased with higher CHA_2DS_2-VAS_c score during follow-up (0, 2.1 and 6.1 per 100 patient years for CHA_2DS_2-VAS_c between 0-1, 2-4 and 5-9, respectively) (Figure 2A), and similarly bleeding events (13.1 per 100 patient years) increased with higher HASBLED score as updated during follow-up (0, 8.5 and 15.6 per 100 patient years HASBLED between 0-1, 2-3 and 4-9, respectively) (Figure 2B).

DISCUSSION

In HD patients with AF, during a follow-up of four years, warfarin assumption at recruitment was associated with a non-significant risk reduction in total mortality when an intention-to-treat approach was taken, while the continued warfarin assumption was associated with a risk reduction in total mortality of about 50 percent with an as-treated approach. When subjects who continue to take OAT from recruitment onwards as compared to those who discontinue the treatment are considered, the benefit is also evident for cardiovascular mortality. Taking

warfarin was not associated with a significant decrease of thromboembolic events with both approaches, even if a trend towards a reduction of thromboembolism and an ~~while there was a trend of~~ increase of~~d~~ bleeding in patients receiving OAT was observed~~-~~ with as-treated analysis. ~~-~~The scores of thromboembolic and bleeding risk were effective in predicting both events and increased risk of mortality.

Data on the relationship between OAT and risk of death in ESRD patients with AF are not conclusive. Two retrospective studies, evaluating the effect of warfarin on mortality without taking into account the reason for the prescription, showed reduced survival in subjects receiving OAT [14, 15]. More recently, evidence suggesting a protective effect of OAT on the risk of mortality emerged [4, 16]. To understand the relationship between warfarin and risk of death in HD patients with AF is a very complex problem for several reasons. The percentage of people taking OAT is often a minority compared to the number of patients who would have an indication in accordance with the current guidelines. In two recent studies, the prevalence of ESRD subjects with AF receiving warfarin was 8.4% [6] and 15% [17]. The underutilization of OAT in presence of ESRD makes it difficult to compare its effect in HD population versus patients with AF, but with preserved renal function. Moreover, a high percentage of HD patients taking OAT suspend it after severe bleeding [6, 7]. For these reasons the results of intention-to-treat analysis are difficult to interpret. To overcome the problem, Shen JI, in a cohort of HD patients from a registry of newly diagnosed AF, performed an as-treated analysis, after applying a propensity score approach to treatment. The author's conclusion was that patients under OAT had a better survival than those who were not anticoagulated [6]. Applying a similar statistical approach, our study, which has the advantage of being a prospective study where the INR values and the exact date of OAT suspension are known, comes to similar conclusions. Moreover the Cox model evaluating the effect of stopping OAT during follow-up reveals that a drug withdrawal in patients taking

OAT at recruitment is accompanied by an increase in mortality from both all and cardiovascular causes. Our preliminary results had suggested the presence of a slight non significant trend towards a better survival in HD patients with AF taking warfarin, compared with those not anticoagulated [7]. The present study indicates that, in order that the protective effect of the drug becomes evident, it is necessary that only the actual time of warfarin assumption is considered. Although patients who benefit most from taking warfarin are those who have a higher TTR, the survival of patients with labile INR is still better than that of those who suspend the drug.

In our population, OAT warfarin appears to have a modest protective effect ~~does not seem to protect~~ against the risk of stroke. This finding is in line with recent retrospective studies based on registry data [2, 17, 18], while only a large Danish study described a clear reduction in the risk of stroke associated with taking warfarin [3]. In the latter study, however, peritoneal dialysis patients and transplant patients are lumped into a group called "renal replacement", and this makes it difficult to compare the results with those of other studies. In most ~~of~~ ~~None~~ of these studies it is not taken into account ~~took into account~~ that many patients probably discontinued treatment during follow-up and this weakens their conclusions~~. Also in the only study in which an as-treated analysis was performed [6], warfarin did not emerge as a protective factor of thromboembolic events. In all of these studies however~~ Moreover, patients taking OAT at recruitment were a minority compared to those who did not take it (from 6% to 25%), except for the Canadian study (46% of OAT patients) [2]. A recent study [17] shows that ESRD patients with AF have, as previously highlighted [19], an increased risk of total and cardiovascular mortality, but not an increased risk of stroke. Authors suggest that the net clinical benefit of stroke prevention for patients on dialysis with AF has to be rethought. In our cohort the rate of thromboembolic events was relatively low (3.9 per 100 patient years) compared to what expected, given the elevated CHA_2DS_2-VAS_c scores. A

similar relatively low rate of stroke was described before in ESRD patients with AF by others authors [20]. Despite ESRD is associated with an increased of overall stroke (i.e. thromboembolic and thrombotic cerebrovascular events) [21], in HD patients with AF the incidence of thromboembolic stroke could be lower than expected because of a protective effect of possible platelets disorders present in uremia [22] and the chronic administration, three times a week, of heparin during each HD session. Therefore, we cannot exclude that the protective effect of warfarin against thromboembolic risk can be blunted by the fact that HD patients are already partially anticoagulated. Oral a~~A~~nticoagulation has been shown to protect against myocardial infarction and to be safe and effective in coronary artery disease patients with and without concomitant AF [2~~1~~, 24~~2~~]. Moreover a recent study demonstrated in older adults with AF a benefit from OAT in terms of lower mortality, regardless of poor health and functional condition [25~~3~~4]. It's possible that, also in HD patients, OAT might have a positive effect ~~in HD patients~~ not only ~~necessarily~~ through a reduction of thromboembolic risk. ~~Despite ESRD is associated with an increased of overall stroke (i.e. thromboembolic and thrombotic cerebrovascular events) [243], in HD patients with AF the incidence of thromboembolic stroke could be lower than expected because of a protective effect of possible platelets disorders present in uremia [254] and the chronic administration, three times a week, of heparin during each HD session. At the same time, these two factors may be responsible for a higher risk of bleeding.~~ The rate of bleeding events of our population was extremely high (13.1 per 100 patient years) and significantly exceeded that of thromboembolic events. The haemorrhagic risk tends to increase in patients taking OAT, according to what has already been reported in the literature [2, 8] and stresses the importance of a careful assessment of the bleeding risk when deciding whether to start OAT in an ESRD patient. In HD patients with AF and particularly high haemorrhagic risk, alternatives to OAT as percutaneous ~~closure~~ occlusion of the left atrial appendage may be considered [26~~5~~].

In our population, both CHA_2DS_2-VAS_c and HASBLED values were very high and both scores were associated with an increase of total mortality and thromboembolic and haemorrhagic events, respectively. Also if the two scores were developed in populations which excluded ESRD subjects, this result confirms that they have some utility in identifying frail patients who need particular attention in warfarin prescription also among HD patients, even if the small percentage of subjects with low scores, may reduce the possibility to stratified appropriately patients at lower thromboembolic and bleeding risk.

Our study has some limitations and strengths. We cannot be sure that all AF episodes have been included in our study, especially for paroxysmal forms that are often unrecognized. However we decided to include only cases with a clear electrocardiographic documentation to be sure of the real presence of the arrhythmia. By note, the prevalence of AF in our population was similar to that reported in the literature [27].Our study, compared to the majority of those available, has the advantage of being prospective and of considering many factors that are useful in guiding clinical practice. However, it has the limitation of not being a randomized trial, even if we carefully considered in our analysis all statistical corrections that allow to limit the bias due to lack of randomization. In our opinion, however, a randomized study has a low feasibility in this context. Our patients often have high haemorrhagic scores and the risk of experiencing bleeding increases with increasing HASBLED. Warfarin is associated with the possibility of suffering bleeding episodes during follow-up. We would be reluctant to randomize a patient with very high HASBLED to take OAT and even if we did, there would be a high chance for this patient to drop out for bleeding. In addition, our data suggest a protective effect of warfarin in terms of mortality, so we would possibly deprive a HD patient able to take OAT of the opportunity to do so. We acknowledge that the intention-to-treat analysis is hampered by treatment crossover, while as-treated analysis might be subject to selection bias due to adverse events occurring in the follow-up, causing warfarin withdrawal.

Those patients who succeeded in continuing to take the therapy could be the ones who were less frail and had a better compliance. However, to assess this assumption, we performed a sensitivity analysis in which we censored patients who died within six months of warfarin withdrawal and we obtained similar results.

In conclusion, our data suggest that in a HD population presenting both a high thromboembolic and bleeding risk, a protective effect of warfarin on total and cardiovascular mortality is present in patients taking OAT without discontinuations and with INR kept within the therapeutic range, with a slight decrease of thromboembolic events.

The study also shows that CHA_2DS_2-VAS_c and HASBLED scores can be useful also in HD patients to identify those at highest risk of mortality and thromboembolic and bleeding events.

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TABLES HEADINGS

Table 1: Patient characteristics by OAT at recruitment before and after balancing for treatment propensity

Table 2: Results from intention-to-treat (ITT) and as-treated (AS) Cox regression model on warfarin administration (Yes vs No) effect

Table 3: Sequential Cox regression model on mortality, cardiovascular mortality, bleeding and thromboembolic events in cohort of patients who always took OAT (n=69) vs those who took OAT at recruitment, but suspended it during follow-up (n=65)

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LEGENDS TO FIGURES

Figure 1: Kaplan-Meier mortality curves by A) CHA_2DS_2-$VASC_S$ and B) HASBLED scores

Figure 2: A) Thromboembolic event rate by CHA_2DS_2-$VASC_S$ and B) Bleeding event rate by HASBLED score

Effect of oral anticoagulant therapy on mortality in end stage renal disease patients with atrial fibrillation: a prospective study

ABSTRACT

Background: Aim of this study was to evaluate, in a cohort of haemodialysis patients with atrial fibrillation (AF), the relationship between oral anticoagulant therapy (OAT) and mortality, thromboembolic and haemorrhagic risk.

Methods: 290 patients with AF were prospectively followed-up for four years. Warfarin and antiplatelet intake, age, dialytic age, comorbidities, CHA_2DS_2-VAS_c and HASBLED scores were considered as predictors of hazard of death, thromboembolic and bleeding events. In patients taking OAT, the International Normalized Ratio (INR) was assessed and the percentage time in the Target Therapeutic Range (TTR) was calculated.

Results: At recruitment, 134/290 patients were taking warfarin. During follow-up there were 170 deaths, 28 thromboembolic events and 95 bleedings. After balancing for treatment propensity, intention-to-treat analysis on OAT assumption at recruitment did not show differences in total mortality, thromboembolic events and bleedings. As-treated analysis, accounting for treatment switch, showed that patients taking OAT at recruitment had a significantly lower mortality than those not taking it (HR 0.53, 95%CI 0.28-0.90, P=0.04), with a slight benefit of OAT on thromboembolic events (HR 0.36, 95%CI 0.13-1.05, P=0.06), and a non-significant increase in bleedings. Among patients taking OAT at recruitment, those continuing warfarin assumption had a significant reduction in the risk of total (HR 0.28, 95%CI 0.14-0.53, P<0.001) and cardiovascular (HR 0.21, 95%CI 0.11-0.40, P<0.001) mortality, compared to patients stopping assumption.

Conclusions: In haemodialysis patients with AF, continuously taking warfarin is associated with a reduction of the risk of total and cardiovascular mortality, and with a slight decrease of thromboembolic events.

KEYWORDS: warfarin, haemodialysis, atrial fibrillation, mortality, stroke, bleeding

INTRODUCTION

Data on the risk/benefit ratio of warfarin in patients with atrial fibrillation (AF) and end stage renal disease (ESRD) continue to be inconclusive, despite the high prevalence of the arrhythmia in this population. Some authors report an increased risk of complications derived from the use of oral anticoagulant therapy (OAT) in haemodialysis (HD) patients with AF, without any benefit in terms of thromboembolic risk protection [1, 2]. Other studies are less negative [3, 4] but a big uncertainty remains on how to approach these patients [5]. One major problem is the lack of prospective and randomized data. In fact almost all published studies are based on retrospective analyses of registry data. Recently a large retrospective study showed that warfarin was associated with a reduced mortality in a cohort of HD patients with newly diagnosed AF [6]. This study accounted for confounding by indication with propensity score, but being a register study not all potential confounders were available, in particular International Normalized Ratio (INR) was missing and OAT assumption was based on the prescription. We set a prospective study in a population of HD patients with AF, where information on the exact time of the possible withdrawal of warfarin and on the INR values in subjects taking OAT were collected, over the baseline characteristics of patients. Preliminary results on two years of follow-up indicated that warfarin significantly increased the incidence of bleeding without reducing thromboembolic events. Furthermore, the study suggested the presence of a trend towards a better survival in patients receiving OAT [7]. However, those early results needed to be completed with a long-term efficacy and safety evaluation of warfarin assumption.

The main purpose of the present study was to evaluate prospectively, in a cohort of patients with ESRD and AF followed-up for four years, the relationship between OAT and mortality, thromboembolic and haemorrhagic risk .We evaluated long-term efficacy and safety of OAT using a causal method approach to limit the confounding by indication and to account for the

updated value of confounders/variables over the follow-up. Secondary aim was to test the predictive value of the CHA_2DS_2-VAS_c and HASBLED scores on mortality, thromboembolic and haemorrhagic events, given that these scores are indicated by the Cardiology Guidelines to identify patients at increased thromboembolic and haemorrhagic risk [8], but were developed in cohorts of patients in which HD was an exclusion criterion.

SUBJECTS AND METHODS

All patients alive and under observation in 10 Italian dialysis centers on 31/10/2010 were considered (n=1529) and their clinical charts revised for eligibility to the study. Peritoneal dialysis patients were not included. All subjects with at least one documented paroxysmal (self-terminating) or persistent (required termination by pharmacological or electrical cardioversion) AF episode, or with permanent AF (when there has been a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm) were recruited, for a total of 290 patients (see Supplementary figure 1).

At recruitment data were collected on the presence of hypertension (systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg before the beginning of the HD session or anti-hypertensive drugs administration), diabetes mellitus, peripheral artery disease (clinical presence of claudication and/or evidence of significant stenosis of main arterial trunks by doppler examination), ischemic heart disease (previous myocardial infarction or coronary revascularization procedures and/or previous hospitalization due to acute coronary syndrome), heart failure (presence of left-ventricular dysfunction- left-ventricular ejection fraction<50%- and/or previous hospitalization due to acute or chronic heart failure), previous strokes (ischemic or haemorrhagic defined by computed tomographic scan or nuclear magnetic resonance), and major bleeding episodes (haemorrhagic episode requiring

hospitalization or blood transfusion, or causing a haemoglobin plasma level reduction > 2g/dl) and on administration of antiplatelets and anticoagulants [7].

Cardiac ultrasound examination was performed in all the patients during the mid-week dialysis interval. Collected echocardiography data were: left ventricular ejection fraction (LVEF, %) and the presence of left ventricular hypertrophy (LVH), which was defined as left-ventricular mass normalized for body surface area >125 g/m^2 according to the Penn-cube formula, or when its presence was described in the report.

Patients were prospectively followed-up for four years (until 31/10/2014 or death) and their clinical charts were updated at each dialysis session. The new onset of permanent AF, stroke, bleeding, cardiovascular events (ischemic and heart failure episodes that required hospitalization), and antiplatelet and anticoagulant treatment modifications were recorded.

In patients taking OAT, the INR values were assessed at least once a month and the percentage time in the target INR range (Target Therapeutic Range, TTR) was calculated [9]. Only one center referred patients to a Thrombosis Clinic, while in the others the nephrologist took care of warfarin dosage (the policy was to keep INR between 2 and 3).
Thromboembolic and haemorrhagic risk was calculated using the CHA_2DS_2-VAS_c and HASBLED score, respectively [8].
Procedures were performed according to the Helsinki declaration for ethical treatment of human subjects and approved by the local ethical committee. Informed consent was obtained from the enrolled subjects.

Statistical methods

All data were centrally revised. Patients were considered under OAT at recruitment if taking OAT at 31/10/2010. Rates of mortality, thromboembolic and haemorrhagic events were computed for patients on and not on OAT at recruitment and compared by the Poisson model.

Marginal structural models

In order to evaluate the effect of OAT on mortality, thromboembolic and haemorrhagic risk, we created a pseudo-population (that mimics a randomized trial) which mitigates the selection bias in OAT treatment assignment at recruitment [10]. This pseudo-population, created by the use of (stabilized) Inverse Probability of Treatment (and censoring) Weights (IPTW), is called the "IPTW cohort". IPTW were computed by a multivariable logistic model on the propensity to be under OAT at recruitment that included age, diabetes mellitus, ischemic and bleeding/haemorrhagic strokes, ischemic heart disease, CHA_2DS_2-VAS_c and HASBLED score, type of AF, left ventricular ejection fraction <50% and left ventricular hypertrophy (and their first degree interactions), gender, dialytic age, hypertension, heart failure, peripheral artery disease and antiplatelet therapy. In order to evaluate the balance induced by these weights, the confounders among patients under OAT and not in this pseudo-population were compared by standardized differences [11]. Furthermore, an inverse probability of censoring weight was also applied to account for loss to follow-up and informative censoring due to death when analysing thromboembolic and haemorrhagic outcomes. Final weights were computed as the product of the stabilized weights [10] for treatment and censoring (trimming was not necessary as weights ranged between 0.5 to 9.5).

The weighted Cox regression model with robust standard error was applied to the IPTW cohort to assess the effect of OAT administration at recruitment on different relevant endpoints. The model was adjusted for each covariate which after balancing (IPTW cohort) still showed a standardized difference greater than 10% between the two groups (i. e. bleeding/haemorrhagic stroke and permanent AF). Results of the Cox models are expressed in terms of estimated hazard ratios (HR), 95% confidence intervals (95%CI) and P-values.

In analogy to a randomized trial, two analyses were performed: intention-to-treat (ITT) and as-treated (AT) analyses. In the first one, the treatment (OAT) classification at recruitment

was retained for the whole follow-up, while in the AT analysis patients who switched treatment were artificially censored (this artificial censoring was also considered in the inverse probability of censoring weights).

Sequential Cox

In order to better evaluate the effect of the time dependent variables, including OAT assumption, on the risk of mortality, thromboembolic and haemorrhagic events, we evaluated the effect of stopping OAT by the sequential Cox approach [12]. This method mimics several randomized controlled trials, based on individuals stopping OAT in time intervals (of one month), and obtains an overall treatment effect estimate. We adjusted for gender and the updated values (at the beginning of each month) of age, percentage of TTR ,CHA_2DS_2-VAS_c and HASBLED scores, presence of permanent AF and use of antiplatelets.

The effect of suspending OAT was also estimated stratifying according to TTR $\geq$ or <60% [13]. As it was possible that some patients had discontinued therapy because in terminal conditions, a sensitivity analysis was performed, in which we censored patients died within six months of warfarin withdrawal.

Score analysis

The Kaplan-Meier estimator was used to describe survival in subgroups defined according to CHA_2DS_2-VAS_c and HASBLED scores at recruitment. We also computed rates of mortality, thromboembolic and haemorrhagic events by the updated value of the scores during follow-up.

Analyses were carried out by means of the statistical software SAS v.9.4 (SAS Institute Inc, Cary, NC), and R statistical software v.3.1 (http://www.r-project.org).

RESULTS

The study was carried out in a cohort of 290 HD patients, with mean age at recruitment of 74 years (standard deviation 9.7). At recruitment, 134 patients (46.2%) were taking OAT (OAT-yes). The median follow-up time was 4 years. During follow-up, 65/134 (48.5%) patients stopped taking warfarin, while 33/156 (21.1%) subjects without OAT at recruitment (OAT-no) started to take it. During the 4-year follow-up there were 170 deaths (95 in OAT-no versus 75 in OAT-yes at recruitment; 25 and 22 per 100 patient years, respectively; P=0.4), 28 thromboembolic events (17 in OAT-no versus 11 in OAT-yes at recruitment; 4.5 and 3.2 per 100 patient years, respectively; P=0.4) and 95 haemorrhagic events (36 in OAT-no versus 59 in OAT-yes at recruitment; 9.5 and 17 per 100 patient years, respectively; P=0.005).

The main causes of death were: cachexia (n=49, 16.9%), sepsis (n=34, 11.7%), sudden death (n=18, 6.3%), cardiogenic shock and tumor (n=15, 5.2%). One patient died due to ischemic stroke and three for hemorrhagic stroke (0.6 and 1.0%, respectively).

Table 1 shows the clinical characteristics of the OAT-no and OAT-yes patients at recruitment, before and after balancing for treatment propensity.

A plain unadjusted Cox model did not show any difference between patients under OAT-no and OAT-yes at recruitment: HR=0.87 (95%CI: 0.64-1.18, P=0.37) for mortality, HR=0.60 (95%CI: 0.26-1.36, P=0.22) for thromboembolic events and HR=1.57 (95%CI: 0.91-2.72, P=0.11) for bleeding. Similar results were observed with the ITT analysis of the IPTW cohort that did not show a difference regarding total mortality, cardiovascular mortality, thromboembolic and hemorrhagic events (Table 2). The AT analysis, censoring patients when they switch treatment, showed that patients taking OAT at recruitment had a significantly lower mortality rate than those not taking it, with a non-significant protective effect on thromboembolic events, while a non-significant increase in bleedings was observed (Table 2).

The results from the sequential Cox regression model showed that among patients taking OAT at recruitment (n=134), those continuing OAT assumption (n=69) had a significant

reduction in the risk of total and cardiovascular mortality, compared to patients stopping the assumption during follow-up. Warfarin slightly increased the risk of bleeding. In order to evaluate whether the beneficial effect of warfarin on mortality was due to the fact that patients who do not interrupt warfarin have a better INR, we stratified the analysis for TTR lower and higher than 60%: also in patients with a labile INR (TTR<60%) continuous warfarin intake had a beneficial effect. A more marked effect was seen in patients with TTR≥60% (Table 3).The results were similar when patients who died within six months after warfarin withdrawal (n=15) were censored: OAT was still associated with a reduction of total (HR 0.44, 95%CI 0.23-0.84, P=0.013) and cardiovascular mortality (HR 0.36, 95%CI 0.19-0.66, P=0.001). Mortality results were confirmed also stratifying for TTR lower and higher than 60% (HR 0.49, 95%CI 0.24-0.99, P=0.048 and HR 0.24, 95%CI 0.07-0.82, P=0.023, respectively).

At recruitment, 12 (4.1%) patients had a CHA_2DS_2-VAS_c score between 0-1, 149 (51.4%) between 2-4 and 129 (44.5%) between 5-9, while patients with a HASBLED score between 0-1 were 3 (1%), between 2-3 were 137 (47.2%) and between 4-9 were 149 (51.4%). Total mortality was significantly related to both CHA_2DS_2-VAS_c (log-rank test P<0.001, Figure 1A) and HASBLED score (log-rank test P=0.003, Figure 1B). Coherently we found higher rates of mortality with higher scores, when the scores were updated during follow-up: 8.4, 18.4, 31.2 per 100 person years for CHA_2DS_2-VAS_c between 0-1, 2-4 and 5-9, respectively, and 0, 17.5, 26.8 per 100 patient years for HASBLED between 0-1, 2-3 and 4-9, respectively. Thromboembolic events (3.9 per 100 patient years) also increased with higher CHA_2DS_2-VAS_c score during follow-up (0, 2.1 and 6.1 per 100 patient years for CHA_2DS_2-VAS_c between 0-1, 2-4 and 5-9, respectively) (Figure 2A), and similarly bleeding events (13.1 per 100 patient years) increased with higher HASBLED score as updated during follow-up (0, 8.5

and 15.6 per 100 patient years HASBLED between 0-1, 2-3 and 4-9, respectively) (Figure 2B).

DISCUSSION

In HD patients with AF, during a follow-up of four years, warfarin assumption at recruitment was associated with a non-significant risk reduction in total mortality when an intention-to-treat approach was taken, while the continued warfarin assumption was associated with a risk reduction in total mortality of about 50 percent with an as-treated approach. When subjects who continue to take OAT from recruitment onwards as compared to those who discontinue the treatment are considered, the benefit is also evident for cardiovascular mortality. Taking warfarin was not associated with a significant decrease of thromboembolic events with both approaches, even if a trend towards a reduction of thromboembolism and an increase of bleeding in patients receiving OAT was observed with as-treated analysis. The scores of thromboembolic and bleeding risk were effective in predicting both events and increased risk of mortality.

Data on the relationship between OAT and risk of death in ESRD patients with AF are not conclusive. Two retrospective studies, evaluating the effect of warfarin on mortality without taking into account the reason for the prescription, showed reduced survival in subjects receiving OAT [14, 15]. More recently, evidence suggesting a protective effect of OAT on the risk of mortality emerged [4, 16]. To understand the relationship between warfarin and risk of death in HD patients with AF is a very complex problem for several reasons. The percentage of people taking OAT is often a minority compared to the number of patients who would have an indication in accordance with the current guidelines. In two recent studies, the prevalence of ESRD subjects with AF receiving warfarin was 8.4% [6] and 15% [17]. The underutilization of OAT in presence of ESRD makes it difficult to compare its effect in HD

population versus patients with AF, but with preserved renal function. Moreover, a high percentage of HD patients taking OAT suspend it after severe bleeding [6, 7]. For these reasons the results of intention-to-treat analysis are difficult to interpret. To overcome the problem, Shen JI, in a cohort of HD patients from a registry of newly diagnosed AF, performed an as-treated analysis, after applying a propensity score approach to treatment. The author's conclusion was that patients under OAT had a better survival than those who were not anticoagulated [6]. Applying a similar statistical approach, our study, which has the advantage of being a prospective study where the INR values and the exact date of OAT suspension are known, comes to similar conclusions. Moreover the Cox model evaluating the effect of stopping OAT during follow-up reveals that a drug withdrawal in patients taking OAT at recruitment is accompanied by an increase in mortality from both all and cardiovascular causes. Our preliminary results had suggested the presence of a slight non-significant trend towards a better survival in HD patients with AF taking warfarin, compared with those not anticoagulated [7]. The present study indicates that, in order that the protective effect of the drug becomes evident, it is necessary that only the actual time of warfarin assumption is considered. Although patients who benefit most from taking warfarin are those who have a higher TTR, the survival of patients with labile INR is still better than that of those who suspend the drug.

In our population, OAT warfarin appears to have a modest protective effect against the risk of stroke. This finding is in line with recent retrospective studies based on registry data [2, 17, 18], while only a large Danish study described a clear reduction in the risk of stroke associated with taking warfarin [3]. In the latter study, however, peritoneal dialysis patients and transplant patients are lumped into a group called "renal replacement", and this makes it difficult to compare the results with those of other studies. In most of these studies it is not taken into account that many patients probably discontinued treatment during follow-up and

this weakens their conclusions Moreover, patients taking OAT at recruitment were a minority compared to those who did not take it (from 6% to 25%), except for the Canadian study (46% of OAT patients) [2]. A recent study [17] shows that ESRD patients with AF have, as previously highlighted [19], an increased risk of total and cardiovascular mortality, but not an increased risk of stroke. Authors suggest that the net clinical benefit of stroke prevention for patients on dialysis with AF has to be rethought. In our cohort the rate of thromboembolic events was relatively low (3.9 per 100 patient years) compared to what expected, given the elevated CHA_2DS_2-VAS_c scores. A similar relatively low rate of stroke was described before in ESRD patients with AF by others authors [20]. Despite ESRD is associated with an increase of overall stroke (i.e. thromboembolic and thrombotic cerebrovascular events) [21], in HD patients with AF the incidence of thromboembolic stroke could be lower than expected because of a protective effect of possible platelets disorders present in uremia [22] and the chronic administration, three times a week, of heparin during each HD session. Therefore, we cannot exclude that the protective effect of warfarin against thromboembolic risk can be blunted by the fact that HD patients are already partially anticoagulated. Oral anticoagulation has been shown to protect against myocardial infarction and to be safe and effective in coronary artery disease patients with and without concomitant AF [2, 24]. Moreover a recent study demonstrated in older adults with AF a benefit from OAT in terms of lower mortality, regardless of poor health and functional condition [25]. It's possible that, also in HD patients, OAT might have a positive effect not only through a reduction of thromboembolic risk. The rate of bleeding events of our population was extremely high (13.1 per 100 patient years) and significantly exceeded that of thromboembolic events. The haemorrhagic risk tends to increase in patients taking OAT, according to what has already been reported in the literature [2, 8] and stresses the importance of a careful assessment of the bleeding risk when deciding whether to start OAT in an ESRD patient. In HD patients with

AF and particularly high haemorrhagic risk, alternatives to OAT as percutaneous occlusion of the left atrial appendage may be considered [26].

In our population, both CHA_2DS_2-VAS_c and HASBLED values were very high and both scores were associated with an increase of total mortality and thromboembolic and haemorrhagic events, respectively. Also if the two scores were developed in populations which excluded ESRD subjects, this result confirms that they have some utility in identifying frail patients who need particular attention in warfarin prescription also among HD patients, even if the small percentage of subjects with low scores, may reduce the possibility to stratified appropriately patients at lower thromboembolic and bleeding risk.

Our study has some limitations and strengths. We cannot be sure that all AF episodes have been included in our study, especially for paroxysmal forms that are often unrecognized. However we decided to include only cases with a clear electrocardiographic documentation to be sure of the real presence of the arrhythmia. By note, the prevalence of AF in our population was similar to that reported in the literature [27].Our study, compared to the majority of those available, has the advantage of being prospective and of considering many factors that are useful in guiding clinical practice. However, it has the limitation of not being a randomized trial, even if we carefully considered in our analysis all statistical corrections that allow to limit the bias due to lack of randomization. In our opinion, however, a randomized study has a low feasibility in this context. Our patients often have high haemorrhagic scores and the risk of experiencing bleeding increases with increasing HASBLED. Warfarin is associated with the possibility of suffering bleeding episodes during follow-up. We would be reluctant to randomize a patient with very high HASBLED to take OAT and even if we did, there would be a high chance for this patient to drop out for bleeding. In addition, our data suggest a protective effect of warfarin in terms of mortality, so we would possibly deprive a HD patient able to take OAT of the opportunity to do so. We acknowledge that the intention-to-treat

analysis is hampered by treatment crossover, while as-treated analysis might be subject to selection bias due to adverse events occurring in the follow-up, causing warfarin withdrawal. Those patients who succeeded in continuing to take the therapy could be the ones who were less frail and had a better compliance. However, to assess this assumption, we performed a sensitivity analysis in which we censored patients who died within six months of warfarin withdrawal and we obtained similar results.

In conclusion, our data suggest that in a HD population presenting both a high thromboembolic and bleeding risk, a protective effect of warfarin on total and cardiovascular mortality is present in patients taking OAT without discontinuations and with INR kept within the therapeutic range, with a slight decrease of thromboembolic events.

The study also shows that CHA_2DS_2-VAS_c and HASBLED scores can be useful also in HD patients to identify those at highest risk of mortality and thromboembolic and bleeding events.

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TABLES HEADINGS

Table 1: Patient characteristics by OAT at recruitment before and after balancing for treatment propensity

Table 2: Results from intention-to-treat (ITT) and as-treated (AS) Cox regression model on warfarin administration (Yes vs No) effect

Table 3: Sequential Cox regression model on mortality, cardiovascular mortality, bleeding and thromboembolic events in cohort of patients who always took OAT (n=69) vs those who took OAT at recruitment, but suspended it during follow-up (n=65)

Table 1

	FULL COHORT					IPTW COHORT				
	OAT ITT				Standardized difference	OAT ITT				Standardized difference
	NO		YES			NO		YES		
	N	%	N	%		N	%	N	%	
Total	**156**		**134**			**149.9160.3**		**134.0130.0**		
Male gender	88	*56.4*	86	*64.2*	15.9%16%	88.194.3	*58.858.8*	84.684.7	*63.165.2*	8.8%1%
Age ≥75 years	86	*55.1*	69	*51.5*	-7.3% -7%	77.076.8	*51.447.9*	72.770.3	*54.254.1*	5.7%1%
median (1st - 3rd quartile)	*76(67-82)*		*76(68-80)*			*75(64-82)*		*76(68-80)*		*76(64-82)*
Dialytic age ≥3 years	92	*59.0*	80	*59.7*	1.5%1%	89.192.8	*59.557.9*	78.375.4	*58.558.0*	-2.1%0%
median (1st - 3rd quartile)	*4.3(1.8-8.3)*		*3.7(1.6-7.2)*			*4.4(1.4-9.5)*		*3.6(1.5-10.0)*		
Charlson Comorbidity Index *median (1st - 3rd quartile)*	*3(1-6)*		*3(2-5)*			*3(2-6)*				
Presence of:										

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Hypertension	133	*85.3*	102	*76.1*	-23.3%~~23%~~	121.2~~126.1~~	*80.8~~78.7~~*	110.9~~105.9~~	*82.8~~81.5~~*	5.0%~~-1%~~
Diabetes mellitus	52	*33.3*	39	*29.1*	-9.1%~~9%~~	49.3~~55.8~~	*32.9~~34.8~~*	38.4~~42.0~~	*28.7~~32.3~~*	-9.2%~~0%~~
Heart failure	57	*36.5*	58	*43.3*	13.8%~~-14%~~	60.0~~67.7~~	*40.0~~42.2~~*	59.7~~53.0~~	*44.5~~40.8~~*	9.1%~~0%~~
Ischaemic stroke	22	*14.1*	21	*15.7*	4.4%~~-4%~~	24.3~~27.9~~	*16.2~~17.4~~*	20.9~~21.2~~	*15.6~~16.3~~*	-1.7%~~0%~~
Bleeding/Haemorrhagic stroke	41	*26.3*	16	*11.9*	-37.1%~~37%~~	30.5~~30.0~~	*20.4~~18.7~~*	20.8~~24.9~~	*15.5~~19.2~~*	-12.7%~~0%~~
Permanent AF	33	*21.2*	68	*50.7*	64.8%~~-65%~~	49.3~~56.0~~	*32.9~~34.9~~*	51.8~~45.4~~	*38.7~~34.9~~*	12.0%~~0%~~
Ischaemic heart disease	79	*50.6*	61	*45.5*	-10.3%~~-10.3%~~	73.6	*49.1*	67.5	*50.4*	2.5%
Peripheral artery disease	106	67.9	95	70.9	6.4%	103.9	*69.3*	93.2	*69.6*	0.6%
LVEF <=50%	40	25.6	33	24.6	-2.3%	43.8	*29.2*	35.1	*26.2*	-6.8%
LVH	85	54.5	80	59.7	10.6%	85.0	*56.7*	81.5	*60.8*	8.2%
~~**Administration of Antiplatelet therapy**~~	107	*68.6*	32	*23.9*	-100.3%~~100%~~	76.5~~75.2~~	*51.1~~46.9~~*	69.3~~62.3~~	*51.7~~47.9~~*	1.3%~~0%~~
CHA_2DS_2-$VASC_S$										
0-1	9	*5.8*	3	*2.2*	-18.1%~~-18%~~	6.3~~5.8~~	*4.2~~3.6~~*	3.5~~3.2~~	*2.6~~2.5~~*	-8.7%~~-1%~~
2-4	72	*46.1*	77	*57.5*	22.8%~~23%~~	79.2~~85.4~~	*52.8~~53.3~~*	72.4~~74.0~~	*54.0~~56.9~~*	2.4%~~0%~~

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5-9	75	*48.1*	54	*40.3*	-15.7%~~-16%~~	64.3~~69.1~~	*42.9~~43.1~~*	58.1~~52.8~~	*43.3~~40.6~~*	0.8%~~0%~~
HASBLED*										
0-1	1	*0.6*	3	*2.2*	13.4%~~1%~~	1.7~~2.8~~	*1.1~~1.7~~*	1.9~~1.8~~	*1.4~~1.4~~*	2.2%~~0%~~
2-3	43	*27.6*	94	*70.2*	94.2%~~6%~~	68.3~~66.6~~	*45.6~~41.6~~*	61.1~~74.9~~	*45.6~~57.6~~*	0.0%~~2%~~
4-9	112	*71.8*	37	*27.6*	-98.5%~~-6%~~	79.9~~90.9~~	*53.3~~56.7~~*	71.1~~53.3~~	*53.1~~41.0~~*	-0.5%~~-2%~~

*It does not include the score related to labile INR, because unavailable at recruitment.

Note: IPTW COHORT: Inverse Probability of Treatment Weights cohort

AF: atrial fibrillation; LVEF: left ventricular ejection fraction, LVH: left ventricular hypertrophy

Table 1 clean

	FULL COHORT					IPTW COHORT				
	OAT ITT				Standardized difference	OAT ITT				Standardized difference
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	N	%	N	%		N	%	N	%	
Total	**156**		**134**			**149.9**		**134.0**		
Male gender	88	*56.4*	86	*64.2*	15.9%	88.1	*58.8*	84.6	*63.1*	8.8%
Age ≥75 years	86	*55.1*	69	*51.5*	-7.3%	77.0	*51.4*	72.7	*54.2*	5.7%
median (1st - 3rd quartile)	*76(67-82)*		*76(68-80)*			*76(64-82)*		*76(69-80)*		
Dialytic age ≥3 years	92	*59.0*	80	*59.7*	1.5%	89.1	*59.5*	78.3	*58.5*	-2.1%
median (1st - 3rd quartile)	*4.3(1.8-8.3)*		*3.7(1.6-7.2)*			*4.4(1.6-12.2)*		*3.6(2.0-8.8)*		
Charlson Comorbidity Index *median (1st - 3rd quartile)*	*3(1-6)*		*3(2-5)*			*3(2-6)*		*3(2-5)*		
Presence of:										
Hypertension	133	*85.3*	102	*76.1*	-23.3%	121.2	*80.8*	110.9	*82.8*	5.0%

Diabetes mellitus	52	*33.3*	39	*29.1*	-9.1%	49.3	*32.9*	38.4	*28.7*	-9.2%
Heart failure	57	*36.5*	58	*43.3*	13.8%	60.0	*40.0*	59.7	*44.5*	9.1%
Ischaemic stroke	22	*14.1*	21	*15.7*	4.4%	24.3	*16.2*	20.9	*15.6*	-1.7%
Bleeding/Haemorrhagic stroke	41	*26.3*	16	*11.9*	-37.1%	30.5	*20.4*	20.8	*15.5*	-12.7%
Permanent AF	33	*21.2*	68	*50.7*	64.8%	49.3	*32.9*	51.8	*38.7*	12.0%
Ischaemic heart disease	79	*50.6*	61	*45.5*	-10.3%	73.6	*49.1*	67.5	*50.4*	2.5%
Peripheral artery disease	106	67.9	95	70.9	6.4%	103.9	*69.3*	93.2	*69.6*	0.6%
LVEF <=50%	40	25.6	33	24.6	-2.3%	43.8	*29.2*	35.1	*26.2*	-6.8%
LVH	85	54.5	80	59.7	10.6%	85.0	*56.7*	81.5	*60.8*	8.2%
Antiplatelet therapy	107	*68.6*	32	*23.9*	-100.3%	76.5	*51.1*	69.3	*51.7*	1.3%
CHA_2DS_2-$VASC_S$										
0-1	9	*5.8*	3	*2.2*	-18.1%	6.3	*4.2*	3.5	*2.6*	-8.7%
2-4	72	*46.1*	77	*57.5*	22.8%	79.2	*52.8*	72.4	*54.0*	2.4%
5-9	75	*48.1*	54	*40.3*	-15.7%	64.3	*42.9*	58.1	*43.3*	0.8%
HASBLED*										
0-1	1	*0.6*	3	*2.2*	13.4%	1.7	*1.1*	1.9	*1.4*	2.2%

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2-3	43	*27.6*	94	*70.2*	94.2%	68.3	*45.6*	61.1	*45.6*	0.0%
4-9	112	*71.8*	37	*27.6*	-98.5%	79.9	*53.3*	71.1	*53.1*	-0.5%

*It does not include the score related to labile INR, because unavailable at recruitment.

Note: IPTW COHORT: Inverse Probability of Treatment Weights cohort

AF: atrial fibrillation; LVEF: left ventricular ejection fraction, LVH: left ventricular hypertrophy

Table 2

OUTCOME	ANALYSIS	N. events	HR	95%CI	P-value
MORTALITY	**ITT**	170	0.910.82	0.56; 1.480.54; 1.23	0.700.3
	AT	115	0.530.51	0.28; 0.900.29; 0.89	0.040.02
CARDIOVASCULAR MORTALITY	**ITT**	43	1.151.04	0.47; 2.800.51; 2.13	0.80.9
	AT	31	0.490.50	0.14; 1.660.22; 1.16	0.300.1
THROMBOEMBOLIC EVENT	**ITT**	25	0.440.84	0.16; 1.200.32; 2.17	0.100.7
	AT	24	0.360.71	0.13; 1.050.28; 1.95	0.060.5
BLEEDING EVENT	**ITT**	55	1.161.33	0.48; 2.820.70; 2.66	0.700.4
	AT	49	1.791.80	0.72; 4.390.91; 3.58	0.200.09

Note: only first event was evaluate

Table 2 clean

OUTCOME	ANALYSIS	N. events	HR	95%CI	P-value
MORTALITY	**ITT**	170	0.91	0.56; 1.48	0.7
	AT	115	0.53	0.28; 0.90	0.04
CARDIOVASCULAR MORTALITY	**ITT**	43	1.15	0.47; 2.80	0.8
	AT	31	0.49	0.14; 1.66	0.3
THROMBOEMBOLIC EVENT	**ITT**	25	0.44	0.16; 1.20	0.1
	AT	24	0.36	0.13; 1.05	0.06
BLEEDING EVENT	**ITT**	55	1.16	0.48; 2.82	0.7
	AT	49	1.79	0.72; 4.39	0.2

Note: only first event was evaluate

Table 3

	OAT (Yes vs No)		
	HR	**95%CI**	**P-value**
MORTALITY*	0.28	0.14; 0.53	<0.001
*Patients with TTR ≥60%***	*0.07*	*0.02;0.19*	*<0.001*
*Patients with TTR<60%***	*0.37*	*0.18; 0.77*	*0.007*
CARDIOVASCULAR MORTALITY*	0.21	0.11; 0.40	<0.001
THROMBOEMBOLIC EVENTS*	4.41	0.28; 69.02	0.290
BLEEDING EVENTS*	5.20	0.63; 42.70	0.125

Note: TTR: Percentage time in target INR range

*Model adjusted for gender, age (years), TTR, CHA_2DS_2-$VASC_S$, HASBLED, antiplatelet therapy and permanent atrial fibrillation

**Model adjusted for gender, age (years), CHA_2DS_2-$VASC_S$, HASBLED, antiplatelet therapy and permanent atrial fibrillation

Figure 1

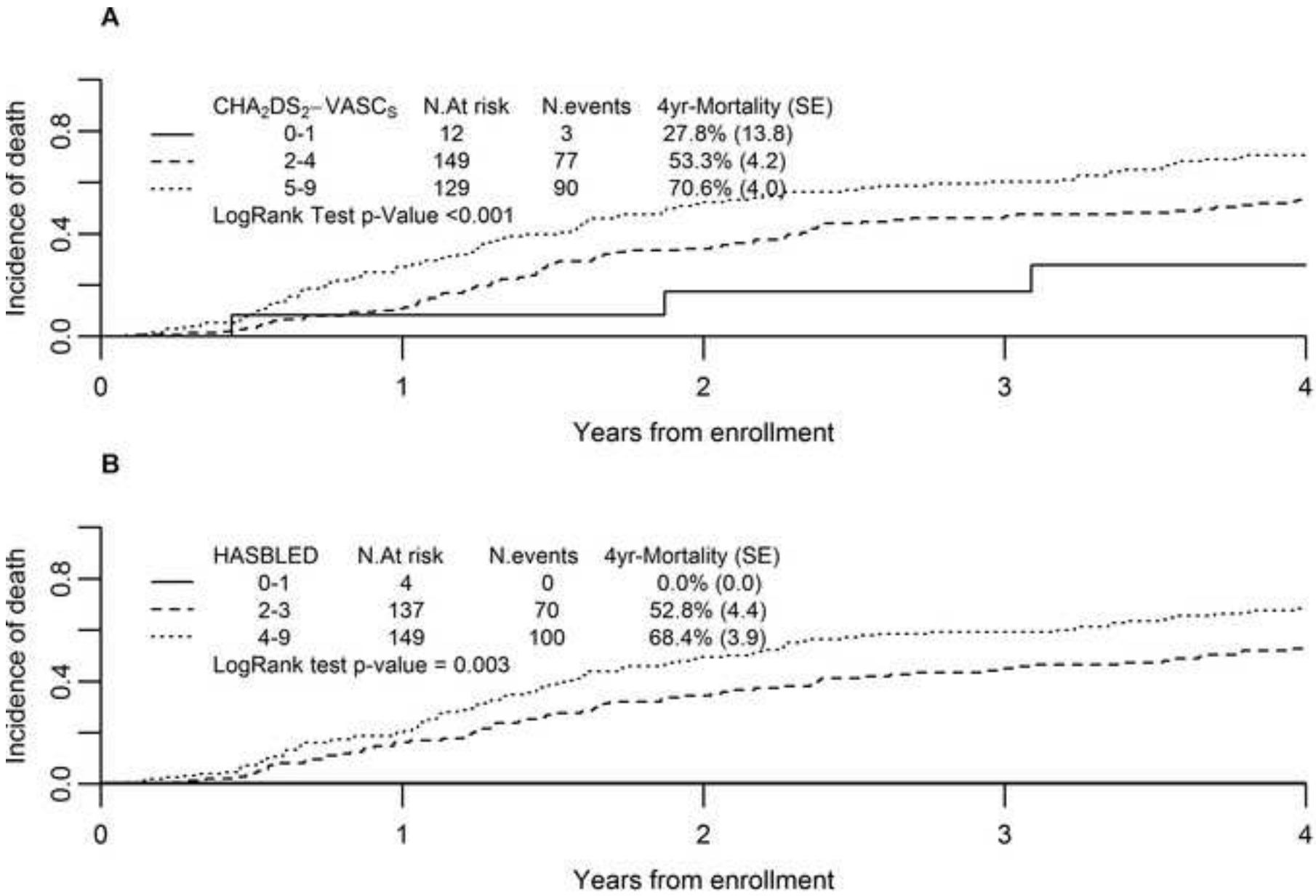

Figure 2

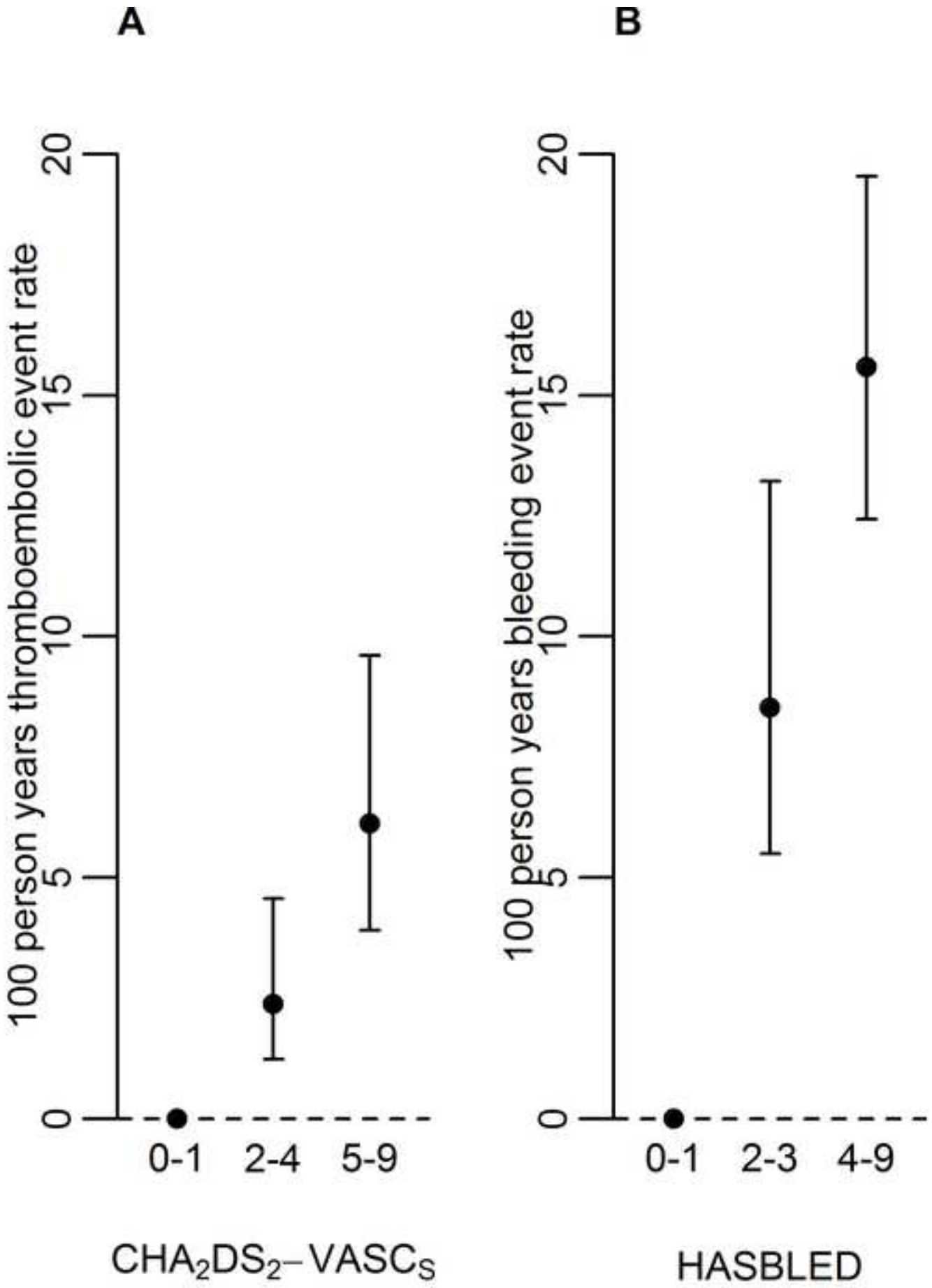

Figure S1: Patient selection flow-chart.