ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
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" ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΣΘΕΝΕΙΣ ΤΕΛΙΚΟΥ ΣΤΑΔΙΟΥ ΝΕΦΡΙΚΗΣ ΑΝΕΠΑΡΚΕΙΑΣ ΥΠΟ ΘΕΡΑΠΕΙΑ ΕΞΩΝΕΦΡΙΚΗΣ ΚΑΘΑΡΣΗΣ – ΜΙΑ ΑΝΑΔΡΟΜΙΚΗ ΜΕΛΕΤΗ ΠΑΡΑΤΗΡΗΣΗΣ ΤΟΥ ΙΠΠΟΚΡΑΤΕΙΟΥ ΝΟΣΟΚΟΜΕΙΟΥ ΘΕΣΣΑΛΟΝΙΚΗΣ "

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'' Atrial Fibrillation in End-Stage Renal Disease Patients Undergoing Renal Replacement Therapy – A Retrospective Observational Study of a Tertiary Greek Hospital ''

Abstract

Introduction: Atrial fibrillation (AF) is a common arrhythmia among end-stage renal disease (ESRD) patients. Optimal antithrombotic management of this complex population remains controversial as data are scarce and insufficient to make firm suggestions. This study aims to provide insight into the management of ESRD patients with AF from a tertiary Greek Hospital.

Methods: During the 2013 to 2019 period records from104 ESRD patients were identified and reviewed. The study population was divided into two groups depending on the presence of AF. Differences between the two groups, events during renal replacement therapy (RRT), antithrombotic and antiarrhythmic trends were reported.

Results: From the 104 patients; 24 (23%) had developed AF during this period. Patients with AF were older (75.3±9.3 vs. 56.9±16.6 years, p<0.0001), displayed more frequently heart failure with preserved ejection fraction (HFpEF; 50% vs. 12.5%, p<0.0001), peripheral artery disease (PAD; 50% vs. 25%, p=0.025) and demonstrated higher mean $CHAD_2DS_2$-VASc and HASBLED scores (p<0.0001). Moreover, they demonstrated a more impaired global cardiac performance as reflected by their lower mean ejection fraction (EF; 52.7±12.1% vs. 60.3±7.5%, p=0.015), larger mean left atrial diameter (LAd; 44.9±4.8mm vs. 36.2±5.1mm, p<0.0001) higher mean right ventricular systolic pressure (RVSP; 42.2±11.4mmHg vs. 33.1±8.8mmHg, p=0.017) and more advanced stages of mitral regurgitation and diastolic dysfunction (p<0.0001). A larger LAd was independently associated with AF. 34 paroxysmal AF episodes were detected during RRT and most received pharmacological cardioversion with amiodarone without any short-term complications. Almost 25% of these episodes were not cardioverted. Bradyarrhythmia episodes during RRT occurred more frequently in patients with AF (p=0.019). From 2013 to 2019 the anticoagulation (AC) rate of AF patients was raised and novel-oral anticoagulants (NOACs) were largely prescribed from 2017 onwards.

Conclusions: There are significant differences in ESRD patients with and without history of AF. Paroxysmal AF episodes during RRT is an emerging problem that was commonly left untreated and a consensus about its appropriate management is necessitated. In the absence of robust data to guide anticoagulation therapies; the decision to anticoagulate patients with AF was not based on conventional risk scores and antithrombotic drugs were arbitrarily offered. Penetration of NOACs is seen in this Greek cohort a few years after their introduction.

Key words: Antiarrhythmic strategies; Anticoagulation; Atrial fibrillation; End-stage renal disease; Novel-oral anticoagulants

Table of Contents

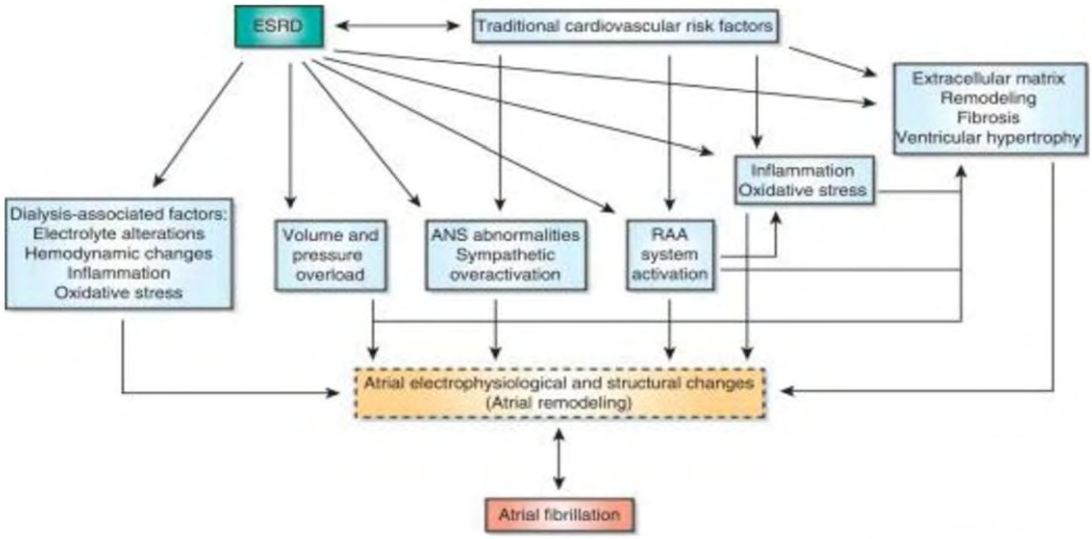
1. Introduction

1.1 Defining atrial fibrillation

Atrial fibrillation (AF) is a common supraventricular tachyarrhythmia that is characterized by uncoordinated atrial activation and loss of atrial contraction. AF is diagnosed by electrocardiographic (ECG) findings of irregular R-R intervals, in the presence of atrioventricular conduction, absence of distinct repeating P waves and irregular atrial activity [1]. In 2016 the European Society of Cardiology (ESC) suggested classifying AF into five different patterns based on presentation, duration, and spontaneous termination. AF is characterized as 1) first diagnosed, 2) paroxysmal if self-terminating or cardioverted within 7 days, 3) persistent when it lasts longer than 7 days, 4) long-standing persistent when it lasts at least 1 year but a rhythm control strategy is adopted and 5) permanent when rhythm control interventions are not pursued [2].

1.2 Pathophysiology of atrial fibrillation in end-stage renal disease

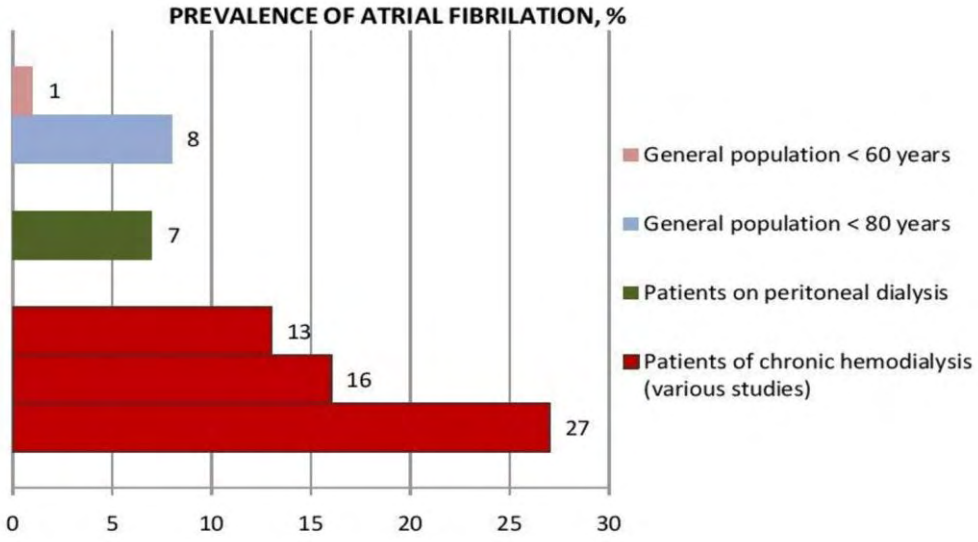
In latter stages of chronic kidney disease (CKD) patients frequently develop structural myocardial changes. The most important are left ventricular hypertrophy, diffuse interstitial fibrosis, focal scarring, systolic and diastolic dysfunction; in the absence of significant coronary artery disease [3]. Those phenotypical changes commonly defined as uraemic cardiomyopaphy, develop throughout the course of CKD and resemble the dilated phase of hypertrophic cardiomyopathy in the end-stages of renal disease (ESRD) [4]. Beyond structural changes there are also significant functional changes affecting myocardial tissue. Among them; the increased volume and pressure overload of the left atria attributed to volume overload, the increased sympathetic and renin-angiotensin-aldosterone system (RAAS) activation, the increased oxidative stress along with acid-base and electrolyte disorders favor structural and electrical remodeling of the atria that predisposes to AF [5] (Figure 1). Thus, as glomerular filtration rate (GFR) declines the risk of developing new onset AF increases linearly [6]. In dialysis-dependent patients the hemodialysis (HD) process has been suggested to be an AF trigger as well [7].



(Figure 1) A simplified depiction of the complex pathophysiology of atrial fibrillation in end-stage renal disease. ANS = autonomic nervous system; ESRD = end-stage renal disease; RAA = renin–angiotensin–aldosterone. Reprinted from Korantzopoulos, P.G. and J.A. Goudevenos, *Atrial fibrillation in end-stage renal disease: an emerging problem.* Kidney Int, 2009. 76(3): p. 247-9

1.3 Prevalence of atrial fibrillation in end-stage renal disease

A dramatic increase in AF diagnosis among the ESRD population has been reported over time [8]. Nonetheless, the exact prevalence of AF in dialysis-dependent populations in Greece has not been yet investigated. In the Dialysis Outcomes and Practice Patterns Study (DOPPS); the prevalence of preexisting AF in HD patients was 12.5% (2,188 out of 17,513) [9], but the reported prevalence varies in several smaller studies [10-13]. In patients undergoing peritoneal dialysis (PD) the US Renal Data System (USRDS) reported a 7% prevalence of AF [14]. Compared to the general population's prevalence, which is estimated to range from 0.4% to 1% and increases with age, AF prevalence is higher in ESRD patients [15](Figure 2).



(Figure 2) Prevalence of atrial fibrillation stratified by age in the general population and type of dialysis in end-stage renal disease patients. Modified from Reinecke, H., et al., *Dilemmas in the management of atrial fibrillation in chronic kidney disease.* J Am Soc Nephrol, 2009. 20(4): p. 705-11

It should be mentioned that assessing the prevalence of paroxysmal AF episodes is challenging as it is mainly based on patients' history, given that routine methods such as 12-lead ECG recordings, 24-h Holter recordings and regular follow-up visits could only partially assist in detecting AF episodes; as those means of assessment have a low yield of AF detection [5].

1.4 Association with stroke

Dialysis patients are at a markedly elevated risk of stroke [16], which has been reported to be five to ten-fold higher compared to patients without CKD [17]. Data from a large US registry revealed that AF was strongly associated with ischemic stroke in dialysis patients and the risk was highest soon after the AF diagnosis [18]. The DOPPS study as well published elevated risk of stroke in HD patients with AF compared with naïve HD patients [9]. Contrary to those data; Shih, C.J., et al. suggested that risk of stroke was not higher in AF patients undergoing HD compared to their matched naïve HD cohort; after adjustment for the competing risk of in-hospital death [19]. In accordance with this finding, AF was not among risk factors for stroke in another study of dialysis patients [20]. The USRDS indicated that more than 60% of dialysis patients with new-onset AF died before stroke occurrence [21], which denotes that the risk of death of this high risk group overwhelms the overall stroke risk. There is no doubt that AF is strongly associated with increased mortality in ESRD patients [14]. However, data remain contradictory as to whether AF enhances the overall stroke risk in this complex population.

1.5 Stroke Prevention

1.5.1 The official recommendations

Simple and clinically-applicable thromboembolic and bleeding risk-stratification schemes have been suggested to guide anticoagulation (AC) treatment in AF. CHA_2DS_2-VASc score was first incorporated in the ESC guidelines in 2010 and is recommended in the 2016 ESC guidelines as a stroke risk predictor to guide AC treatment initiation in AF patients. Several bleeding scores have been suggested by the 2016 ESC guidelines to identify modifiable risk factors for major bleeding rather than guide AC treatment decisions in AF patients [2]. HASBLED score, that was initially addressed to assess 1-year risk of major bleeding in patients with AF [22], is included among those.

For the general population, overwhelming evidence from large scale randomized controlled trials support oral anticoagulation in the setting of AF for stroke thromboprophylaxis, and this has been universally adopted in clinical practice guidelines [2]. However, this does not apply to dialysis-dependent populations with AF. The ESC did not make a direct recommendation in their newest 2016 Guidelines but rather suggested further controlled studies on warfarin and novel-oral anticoagulants (NOACs) are required [2]. However, the 2018 European Heart Rhythm Association (EHRA) Practical Guide on the use of NOACs in patients with AF made firm suggestions. The use of dabigatran in patients with eGRF <30mL/min and the use of apixaban, rivaroxaban and edoxaban in patients with

eGFR<15mL/min was officially contraindicated [23]. Based on pharmacokinetic data alone, the US Food and Drug Administration (FDA) approved the use of apixaban for patients with eGFR < 15 mL/min [24]. American College of Cardiology and American Heart Association in 2016 recommended warfarin use with acceptable risks of hemorrhage in HD patients [25] and added the use of apixaban as an alternative to warfarin with a class IIB recommendation in their newest focused update [26]. KDIGO Controversies Conference concluded in 2018 that there are insufficient high-quality data to recommend warfarin for stroke prevention in dialysis-dependent ESRD patients with AF [27].

1.5.2 Vitamin K Antagonists

Data remain conflicting as for warfarin administration. Prospective randomized control trials assessing efficacy and safety of warfarin excluded patients with eGRF<30mL/min [28]. A large scale of observational studies have investigated the efficacy-safety profile of vitamin-K antagonists (VKA) in ESRD populations. The majority of the meta-analysis and systematic reviews conclude that warfarin did not significantly minimize the ischemic stroke risk but, on the contrary, increased the risk of bleeding including the risk of hemorrhagic stroke [29-36]. That is reasonable taking into account the extremely high bleeding risk that ESRD patients exhibit. However, given the observational nature of these studies it should be emphasized that the increased bleeding complications of warfarin users do not necessarily imply causality of the drug.

Additional considerations have come to the fore regarding VKA use in ESRD. Anticoagulation with VKA leads to acceleration of vascular calcification [37-39], which is a strong prognostic marker of all-cause and cardiovascular mortality [40]. Additionally, warfarin use has been associated with calciphylaxis that is a rare but potentially disastrous complication characterized by calcific occlusion of the microvasculate [41].

1.5.3 Novel-Oral Anticoagulants

NOACs have been proven non-inferior to VKA for stroke prevention of AF in non-ESRD populations [42]. Nonetheless, this is not applicable to ESRD patients, as they were not included in large randomized trials leaving behind a huge gap of evidence.

Based on pharmacokinetic studies alone the FDA approved apixaban 5mg dose for stroke prevention in ESRD patients and the 2,5mg dose only in patients 80 years of age or older and those who weigh 60kg or below. Data from registries and meta-analysis of observational studies suggest that apixaban had no difference in stroke outcomes with reduction in major bleeding compared with warfarin [43]. According to Siontis, K.C., et al. the dose of 5mg twice daily was associated with reduction in thromboembolic and mortality risk compared with both warfarin and the reduced apixaban dose [44].

Rivaroxaban and dabigatran have a more predominant renal elimination, compared with apixaban. When rivaroxaban and dabigatran were evaluated from real life data by registries and observational studies, they were associated with a higher risk of hospitalization and death from bleeding compared with warfarin and that trend was even larger for dabigatran [45]. This was further highlighted by a systematic review which indicated that rivaroxaban

and dabigatran had an elevated major bleeding risk compared with warfarin, whereas that was not observed with apixaban [46].

Randomized trials are ultimately necessitated to validate pharmacokinetically-driven outcomes and to overcome biases from observational data.

1.6 Aim of the study

National registries and observational studies with regard to ESRD groups are scarce and data on prevalence of AF among dialysis patients in Greece are lacking. Additionally, strategies of antithrombotic management of these patients in Greece have not been reported since the advent of NOACs. A complete paucity of data exists on the optimal antiarrhythmic approach of AF in the setting of ESRD and paroxysmal AF during renal replacement therapy (RRT). This study aims to fill those gaps by reporting prevalence of AF in this complex population and demonstrating the preferable therapeutic management of AF in this group in a tertiary Greek Hospital.

2. Methods

2.1 Design and data collection

For the current study; during the 2013 to 2019 period records of 104 ESRD patients undergoing either HD or PD from a tertiary Greek Hospital were identified and reviewed. The study population was divided into two groups depending on the presence of AF. Patterns of AF were characterized as paroxysmal, persistent or permanent as classified by the 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS [47].

The demographics, comorbidities, transthoracic echocardiographic (TTE) features, baseline biochemical indices, main medications of the two groups were collected and compared. Episodes of paroxysmal AF, bradyarrhythmia, hypotension and angina during RRT were recorded.

Main demographic characteristics including age, gender, months on RRT, type of RRT and type of vascular access of the HD subgroup were gathered. Regarding comorbidities of the study population; cause of renal disease, presence and type of AF, coronary artery disease, heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), permanent pacemaker, hypertension, ischemic stroke, hemorrhagic stroke, history of gastrointestinal (GI) bleeding, diabetes mellitus type 2 (DMT2), diabetes mellitus type 1 (DMT1), chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), dislipidemia, hyperthyroidism, hypothyroidism were included.

The CHA_2DS_2-VASc, HASBLED and HAVOC scores of the two groups were identified and reported. It is important to stress that CHA_2DS_2-VASc and HASBLED scores have not been

validated in AF populations with severe renal impairment and they possibly underestimate the actual risk [48]. Thus, these scores should cautiously be applied to this complex cohort. HAVOC score was used to identify patients who will develop future AF episodes and it was initially addressed to identify patients who will be diagnosed with AF after cryptogenic stroke/ transient ischemic attacks [49].

The TTE features that have been collected comprise left ventricular end diastolic diameter (LVEDd), left atrial end systolic diameter (LAd), intraventricular septum end diastolic diameter (IVSd), left ventricular posterior wall end diastolic diameter (LVPWd), aortic root diameter (AOd). All measurements were obtained from a 2-dimentional TTE parasternal long axis view. Ejection fraction (EF) was calculated with Simpson's modified biplane method and right ventricular systolic pressure (RVSP) was measured using the simplified Bernuli equation. Presence/degree of mitral regurgitation (MR), presence/degree of aortic stenosis (AS) and presence/degree of aortic regurgitation (AR) were also obtained according to the existent guidelines. Presence/stage of diastolic dysfunction was acquired in all patients in sinus rhythm.

Baseline biochemical indices including last measured serum creatinine (Cr), blood urea nitrogen (BUN), serum parathyroid hormone (iPTH), serum sodium (Na), serum potassium (K), serum calcium (Ca), serum phosphorus (P) and dialyzer clearance of urea x dialysis time/volume of distribution of urea (Kt/V) were collected. Main medications including AC therapy, antiplatelet (APT) drugs, aspirin (ASA), clopidogrel (CL), loop diuretics, b-blockers, antiarrhythmic therapy, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), mineralocorticoid receptor antagonists (MRA), statins, erythropoietin (EPO), other erythropoiesis-stimulating proteins (ES p) were as well gathered. The antiarrhythmic management of paroxysmal AF episodes during RRT was reported.

2.2 Statistical analysis

The statistical analysis was conducted via IBM SPSS Statistics version 26 in order to compare the above-mentioned characteristics of the AF with the non-AF group. The continuous variables were compared with Independent-Samples T-test while for the categorical variables Chi-Square test was employed. Continuous variables are presented with mean values ± Standard Deviation and categorical data as numbers and percentages of patients. Univariate and multivariate logistic regression analysis was performed to identify the factors that correlate with the presence of AF.

3. Results

3.1 Characteristics and differences of the groups

Baseline demographics and comorbidities of the two groups are summarized in Table 1. Of the 104 ESRD patients; 59 (56.3%) were undergoing HD and 45 (43.4%) PD. For 29.8% of the study population the cause of renal disease was undiagnosed. For the rest the commonest cause was hypertention (14.4%), followed by glomerulonephritis (13.5%), polycystic kidney disease (11.5%), diabetes (8.6%), vesicoureteral reflux (3.8%) and cardiorenal syndrome (2.9%).

The overall prevalence rate of AF was 23% (Paroxysmal AF; n=16, Persistent AF; n=2, Permanent AF; n=6). Patients with AF had a longer duration on RRT compared with the non-AF group but that difference did not reach statistical significance (82.6±84.8 vs. 60.5±58.9 months, p=0.158). Patients with AF were older and presented more frequently HFpEF and PAD compared with non-AF patients. The AF cohort displayed higher mean CDA_2DS_2-VASc and HASBLED scores ($p<0.0001$); which denotes their higher thromboembolic and hemorrhagic risk.

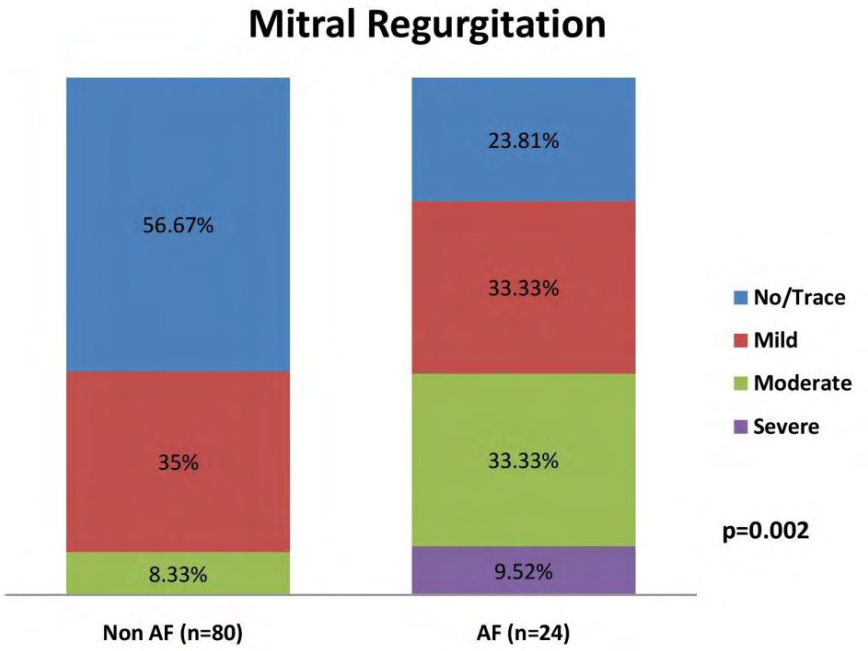
Demographics-Comorbidities		All patients (n=104)	Non-AF (n=80)	AF (n=24)	P-value
Age (years, mean ± SD)		61.2(17)	56.9(16.6)	75.3(9.3)	**<0.0001**
Gender (%)	Male	58(55.7)	44(55)	14(58.3)	0.818
	Female	46(44.2)	36(45)	10(41.7)	
Type of RRT	Hemodialysis	59(56.3)	48(60)	11(45.8)	0.247
	Peritoneal Dialysis	45(43.3)	32(40)	13(54.2)	
Type of vascular access in HD patients	Native AVF	33(31.7)	28(35)	5(20.8)	0.548
	CVC	18(17.3)	14(17.5)	4(16.7)	
	PTFE Graft	8(7.7)	6(7.5)	2(8.3)	
Months on RRT		65.6(66)	60.5(58.9)	82.6(84.8)	0.158
Bradyarrythmia episodes during RRT		6(5.8)	2(2.5)	4(16.7)	**0.019**
Episodes of angina during RRT		12(11.5)	11(13.75)	1(4.2)	0.287
Hypotention episodes on RRT		34(32.7)	24(30)	10(41.7)	0.325
CHA_2DS_2-VASc		3(1.7)	2.59(1.6)	4.38(1.4)	**<0.0001**
HASBLED		3.45(1.2)	3.18(1.1)	4.38(1.1)	**<0.0001**
HAVOC		5.39(3.1)	4.58(2.7)	8.13(2.9)	**<0.0001**
Coronary artery disease		20(19.2)	15(18.75)	5(20.8)	0.822
HFrEF		7(6.7)	4(5)	3(12.5)	0.229
HFpEF		22(21.1)	10(12.5)	12(50)	**<0.0001**
Permanent Pacemaker		5(4.8)	2(2.5)	3(12.5)	0.069
Hypertension		89(85.6)	67(83.6)	22(91.6)	0.308
Ischemic Stroke		10(9.6)	6(7.5)	4(16.7)	0.207
Hemmorhagic Stroke		2(1.9)	1(1.25)	1(4.2)	0.402
GI bleed history		12(11.5)	7(8.75)	5(20.8)	0.125
DMT2		19(18.2)	13(16.3)	6(25)	0.344
COPD		16(15.4)	13(16.3)	3(12.5)	0.649
PAD		32(30.8)	20(25)	12(50)	**0.025**
Dislipidemia		56(53.8)	41(51.3)	15(62.5)	0.361
Hypothyroidism		11(10.6)	8(10)	3(12.5)	0.731
Hyperthyroidism		3(2.9)	2(2.4)	1(4.2)	0.682

(Table 1) Demographics and comorbidities of the study population. AF = atrial fibrillation; AVF = arterio-venous fistulae; COPD = chronic obstructive pulmonary disease; CVC = central venous catheter; DMT2 = diabetes mellitus type 2; GI = gastrointestinal; HD = hemodialysis; HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction; PAD = peripheral artery disease; PTEF = poly-tetrafluoroethylene; RRT = renal replacement therapy; SD = standard deviation

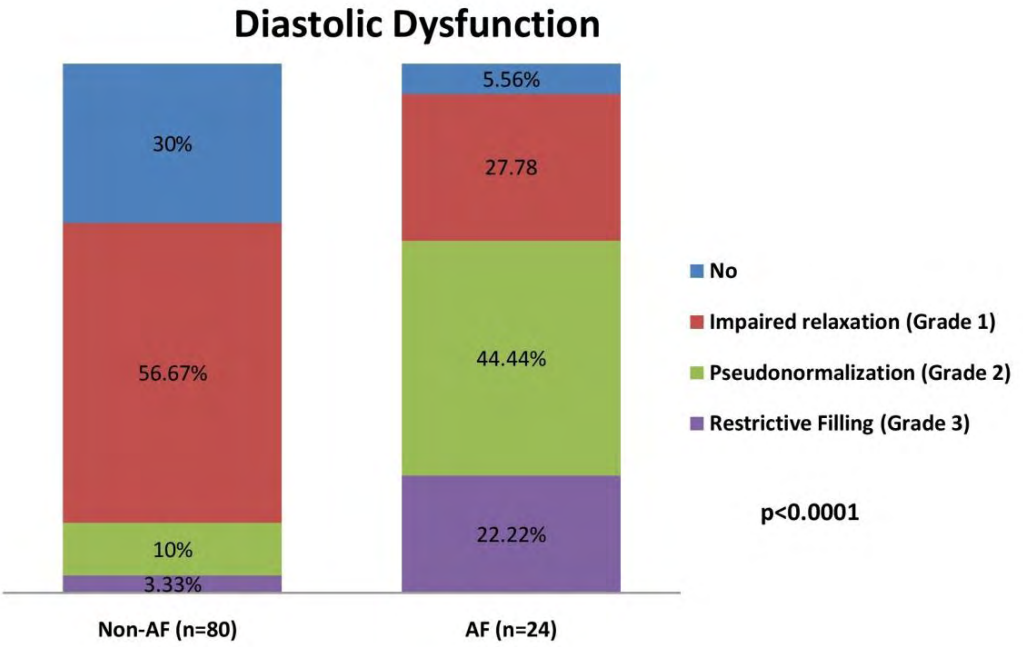
The baseline echocardiographic features of the study population are summarized in Table 2. Patients with AF had a lower mean EF, a larger mean LAd diameter, a larger mean aortic root diameter and a higher mean RVSP. A tendency towards more advanced stages of mitral regurgitation and diastolic dysfunction was observed in the AF group and this is presented in Figures 3 and 4. The overall echocardiographic profile of the AF group denotes a more impaired global cardiac performance compared with the non-AF group.

TTE features		All patients (n=104)	Non-AF (n=80)	AF (n=24)	P-value
EF (%, mean ± SD)		58.9(9.1)	60.3(7.5)	54.7(12.1)	**0.015**
LAd (mm)		38.5(6.3)	36.2(5.1)	44.9(4.8)	**<0.0001**
LVEDd (mm)		50.9(5.8)	50.3(4.9)	52.6(7.8)	0.111
IVSd (mm)		11.1(2.5)	11(2.4)	11.5(2.8)	0.392
LVPWd (mm)		10.6(2.3)	10.4(2.3)	11.3(2.3)	0.108
Aortic root diameter (mm)		31.9(4.8)	31(4.6)	34.4(4.6)	**0.004**
RVSP (mmHg)		37.7(11)	33.1(8.8)	42.2(11.4)	**0.017**
Diastolic dysfunction (%)	No	19(18.3)	18(22.5)	1(4.2)	**<0.0001**
	Impaired relaxation (Grade 1)	39(37.5)	34(42.5)	5(20.8)	
	Pseudonormalization (Grade 2)	14(13.5)	6(7.5)	8(33.3)	
	Restrictive Filling (Grade 3)	6(5.7)	2(2.5)	4(16.7)	
Mitral Regurgitation	None/Trace	39(37.5)	34(42.5)	5(20.8)	**0.002**
	Mild	28(26.9)	21(26.3)	7(29.2)	
	Moderate	12(11.5)	5(6.3)	7(29.2)	
	Severe	2(1.9)	0(0)	2(8.3)	
Aortic Stenosis	None	73(70.2)	57(71.3)	16(66.7)	**0.01**
	Mild	4(3.8)	1(1.3)	3(12.5)	
	Moderate	2(1.9)	0(0)	2(8.3)	
	Severe	2(1.9)	2(2.5)	0(0)	
Aortic Regurgitation	None/Trace	60(57.7)	48(58.5)	12(50)	0.125
	Mild	15(14.4)	9(11.3)	6(25)	
	Moderate	6(5.7)	3(3.8)	3(12.5)	
	Severe	0(0)	0(0)	0(0)	

(Table 2) Transthoracic echocardiographic features of the study population. AF = atrial fibrillation; EF = ejection fraction; IVSd = intraventricular septum diameter; LAd = left atrial diameter; LVEDd = left ventricular end diastolic diameter; LVPWd = left ventricular posterior wall diameter; RVSP = right ventricular systolic pressure; SD = standard deviation

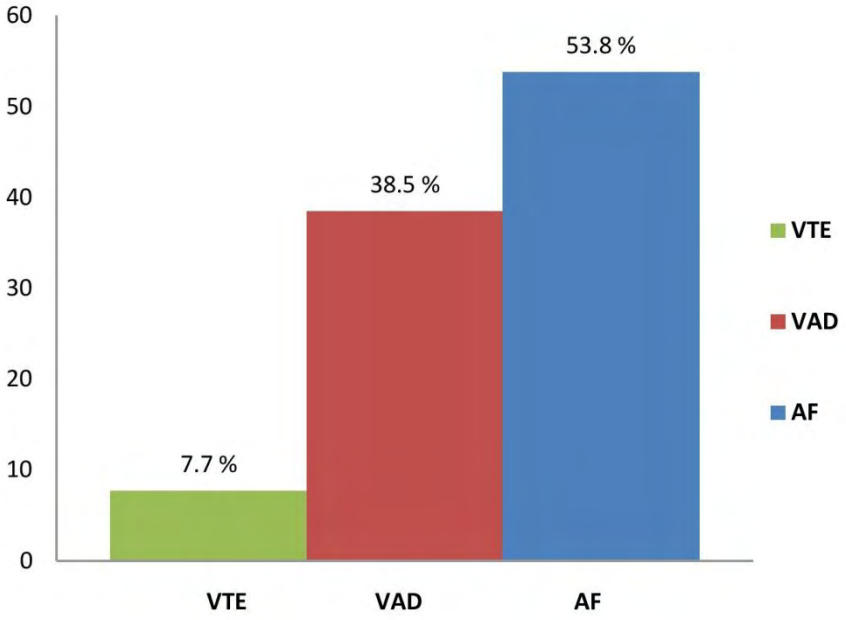


(Figure 3) Stages of mitral regurgitation stratified by the presence of atrial fibrillation. Patients with atrial fibrillation and end-stage renal disease display more severe stages of mitral regurgitation compared with naïve end-stage renal disease patients. AF = atrial fibrillation



(Figure 4) Stages of diastolic dysfunction stratified by the presence of atrial fibrillation. End-stage renal disease patients who delevoped atrial fibrillation demonstrate more advanced stages of diastolic dysfunction compared with naïve end-stage renal disease patients. AF = atrial fibrillation

From a total of 104 ESRD patients; 26 (25%) were using AC therapy. The principal cause for AC therapy was AF (53.8%), followed by either thrombosis or dysfunction of the vascular access (VAD) of HD patients (38.5%) and venous thromboembolism (VTE) (7.7%) (Figure 5).



(Figure 5) Reasons for anticoagulation treatment in the study population (n=26). Atrial fibrillation is the most prevalent reason for anticoagulation. AF = atrial fibrillation; VAD = vascular access dysfunction; VTE= venous tromboembolism

Tables 3 and 4 summarize the main medications and baseline biochemical indices of the study population. Patients with AF were more frequently treated with AC treatment, cardioselective b-blockage and antiarrhythmic therapy. In contradistinction, ASA and ARBs were more commonly used in naïve ESRD patients. Moreover, the AF group had lower levels of serum Cr and P.

Medication use	All patients (n=104)	Non-AF (n=80)	AF (n=24)	P-value
AC therapy (%)	26(25)	11(13.8)	15(62.5)	**<0.0001**
APT	44(42.3)	38(47.5)	6(25)	0.061
ASA	27(26)	25(31.3)	2(8.3)	**0.032**
CL	21(20.2)	17(21.3)	4(16.7)	0.618
B-blocker	74(71.2)	56(70)	18(75)	0.799
Cardioselective b-blocker	34(32.7)	19(23.8)	15(75)	**0.002**
ACEi	5(4.8)	3(3.8)	2(8.3)	0.386
ARB	28(26.9)	26(32.5)	2(8.3)	**0.019**
CCB	39(37.5)	30(37.5)	9(37.5)	1
Loop diuretic	43(41.3)	30(37.5)	13(54.1)	0.163
Statin	50(48.1)	39(48.6)	11(45.8)	0.82
MRA	7(6.7)	6(7.5)	1(4.2)	0.548
Antiarrhythmic therapy	6(5.8)	0(0)	6(25)	**<0.0001**
EPO	46(44.2)	35(43.8)	11(26.4)	0.857
E-S p	29(27.9)	21(26.3)	8(33.3)	0.604
EPO (Units/week, mean ± SD)	3721.2(5481.6)	3425(5201.7)	4708.3(6348.2)	0.317

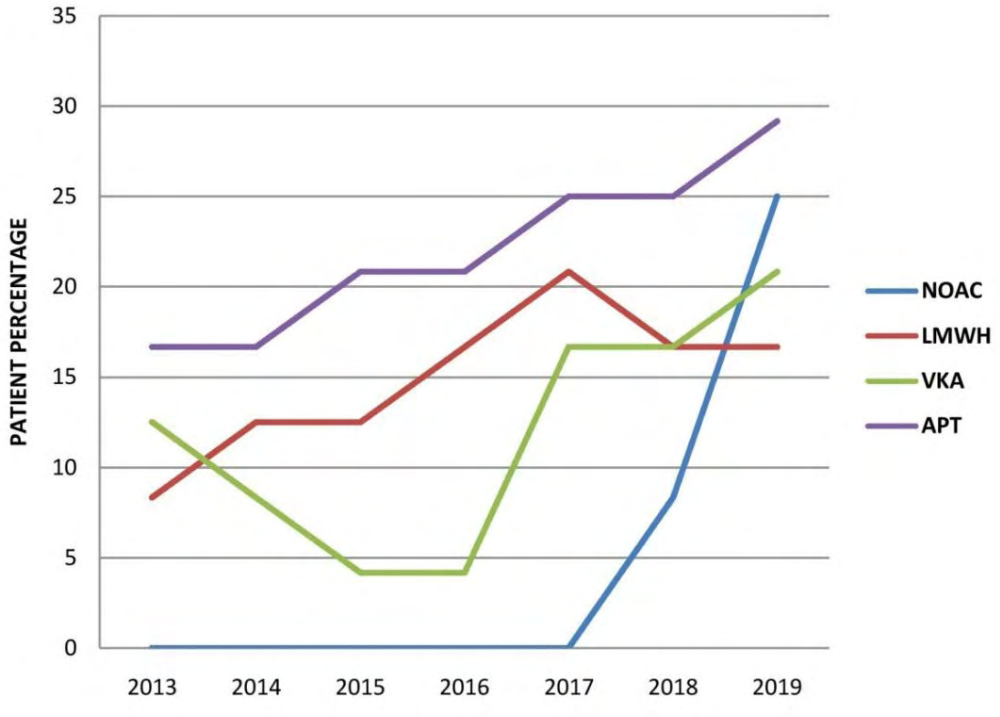
(Table 3) Main medications of the study population. AC = anticoagulation; ACEi = angiotensin - converting enzyme inhibitors; AF = atrial fibrillation; APT = antiplatelet; ASA = aspirin; CCB = calcium channel blockers; CL = clopidogrel; EPO = erythropoietin; E-S p = erythropoiesis stimulating protein; MRA = mineralocorticoid receptor antagonists; SD = standard deviation

Biochemical indices	All patients (n=104)	Non-AF (n=80)	AF (n=24)	P-value
Kt/V (mean ± SD)	2.3(4.5)	2.4(5)	1.9(0.7)	0.711
Cr (mg/dl)	7.6(2.5)	8(2.6)	6(1.6)	**0.001**
BUN (mg/dl)	126.1(28.4)	129(27.1)	116.3(31.1)	0.054
Na (mmol/L)	138(2.7)	137.9(2.6)	138.1(3.2)	0.764
K (mmol/L)	4.8(0.8)	4.9(0.8)	4.6(0.9)	0.089
Ca (mmol/L)	10.7(0.6)	8.8(0.6)	8.8(0.5)	0.981
P (mmol/L)	4.6(1)	4.7(1)	3.9(1)	**0.001**
iPTH (mg/dl)	303.9(216.7)	313.9(230.8)	270.5(161.6)	0.392

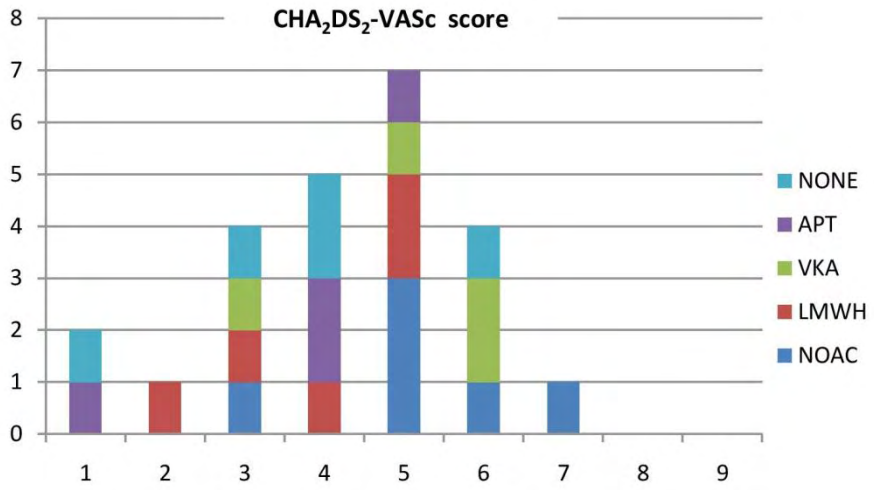
(Table 4) Baseline biochemical indices of the study population. AF = atrial fibrillation; BUN = blood urea nitrogen; Ca = serum calcium; Cr = serum creatinine; iPTH = serum parathyroid hormone; K = serum potassium; Kt/V = dialyzer clearance of urea x dialysis time/volume of distribution of urea; Na = serum sodium; P = serum phosphorus; SD = standard deviation

3.2 Antithrombotic management of the atrial fibrillation group during the study period

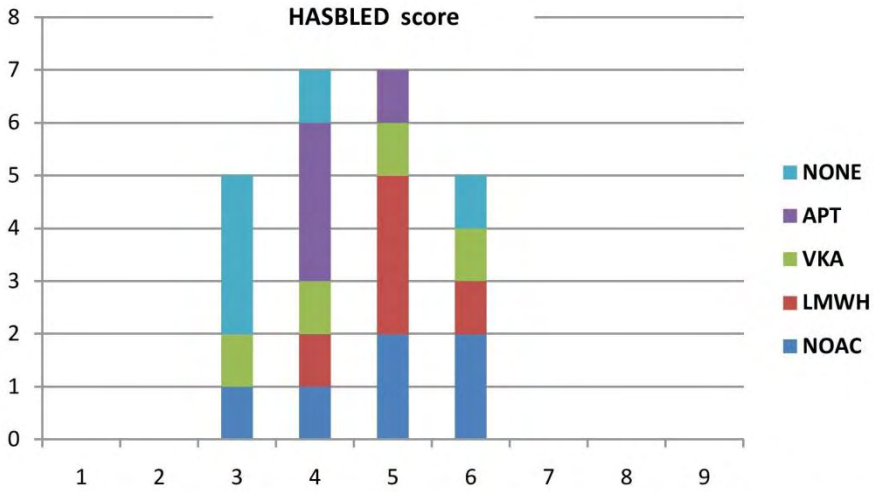
It is evident that the AC rate of the AF cohort was notably raised from 2013 to 2019. Nonetheless, many patients from the AF group were either not receiving AC therapy or receiving off-label APT drugs. Particularly, in 2013 only about 20% of the AF group was anticoagulated, while a remarkably larger AC rate was seen in 2019 (62.5%). Until 2017 none of the AF patients was receiving NOACs. Penetration of NOACs is noted from 2017 onwards and strikingly NOACs were the most prevalent anticoagulant prescribed in 2019, even though it is otherwise suggested by the European official guidelines. A considerable number of AF patients were using APT instead of AC therapy and that trend was not only maintained but enlarged throughout the years (Figure 6). Selection of antithrombotic treatment of the AF group stratified by their CHA_2DS_2-VASc and HASBLED score is illustrated in Figures 7 and 8. Physicians prescribed antithrombotic treatments irrespective of those scores in this cohort.



(Figure 6) Trend of antithrombotic therapy of end-stage renal disease patients with atrial fibrillation from 2013 to 2019 (n=24). APT = atiplatelet drugs; LMWH = low molecular weight heparin; NOAC = novel-oral anticoagulants; VKA = vitamin-K antagonists



(Figure 7) Choice of antithrombotic treatment of end - stage renal disease patients with atrial fibrillation stratified by their CHA_2DS_2-VASc score (n=24). APT = antiplatelet drugs; LMWH = low molecular weight heparin; NOAC = novel oral anticoagulants; VKA = vitamin-K antagonists

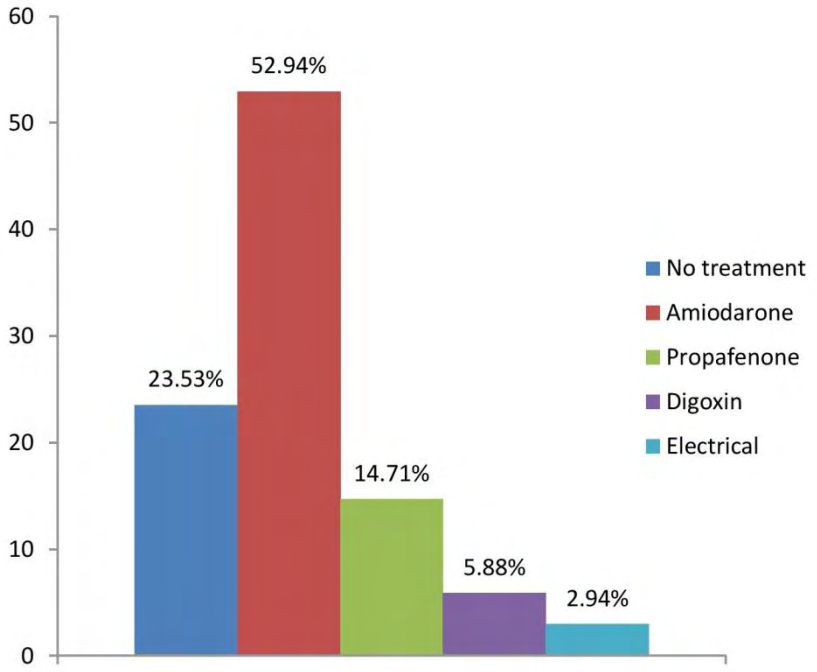


(Figure 8) Choice of antithrombotic treatment of end-stage renal disease patients with atrial fibrillation stratified by their HASBLED score (n=24). APT = antiplatelet drugs; LMWH = low molecular weight heparin; NOAC = novel oral anticoagulants; VKA = vitamin-K antagonists

3.3 Events during renal replacement therapy

Bradyarrhythmia episodes during RRT occurred in 6 patients (5.8%) and 4 of them belonged to the AF group. The AF group, which demonstrated a more impaired overall cardiac performance, was more prone to bradyarrhythmia episodes due to electrolyte derangements compared with the non-AF group (16.7% vs. 2.5%, p=0.019) (Table 1). Interestingly, patients from the AF group who developed bradyarrhythmia on RRT had higher mean serum K levels compared with AF patients without such episodes (5 mmol/L vs. 4.5 mmol/L, p=0.297) but that difference was not statistically significant.

During the 2013 to 2019 period the AF group had developed in total 34 episodes of paroxysmal AF on RRT. About half of those (52.94%) were cardioverted pharmacologically with intravenous amiodarone without any short-term complications being reported. Strikingly, almost 25% of those episodes received no cardioversion therapy and the rest were treated either pharmacologically with propafenone (14.71%) and digoxin (5.88%) or electrically (2.94%) due to hemodynamic compromise (Figure 9).



(Figure 9) Cardioversion treatment of recorded paroxysmal atrial fibrillation episodes during renal replacement therapy from 2013 to 2019 (n=34).

3.4 Atrial fibrillation correlates

Univariate and multivariate correlations of AF are summarized in Table 5. Several factors are crudely associated with AF in the univariate analysis. Those include age (OR 1.13, 95% CI 1.06-1.19, p<0.0001), the presence of bradyarrhythmia episodes during RRT (OR 7.8, 95% CI 1.33-45.66, p=0.023), a CHA_2DS_2-VASc score more than 4 (OR 7, 95% CI 2.47-19.78, p<0.0001), a HASBLED score more than 3 (OR 6, 95% CI 2.03-17.74, p=0.001), HFpEF (OR 7, 95% CI 2.47-19.78, p<0.0001), PAD (OR 3, 95% CI 1.16-7.73, p=0.023), a lower EF (OR 0.94, 95% CI 0.89-0.99, p=0.025), a larger LAd (OR 1.41, 95% CI 1.2-1.65, p<0.0001), more than mild mitral regurgitation (OR 8.25, 95% CI 2.34-29.06, p=0.001), presence of grade 2 diastolic dysfunction or more (OR 13, 95% CI 3.8-44.5, p<0.0001), a higher RVSP (OR 1.1, 95% CI 1-1.2, p=0.033), lower serum P levels (OR 0.42, 95% CI 0.24-0.74, p=0.003), AC therapy (OR 10.46, 95% CI 3.68-29.67, p<0.0001), use of cardioselective b-blocker (OR 5.9, 95% CI 2-17.58, p=0.001) and absence of treatment with ARBs (OR 0.19, 95% CI 0.04-0.86, p=0.032). However, when adjusted for age, PAD, bradyarrhythmia episodes during RRT, EF, LAd , RVSP and aortic root diameter; AF maintained independent association only with the presence of a larger LAd (OR 1.76, 95% CI 1.05-2.94, p=0.033) (Table 5).

	Univariate analysis		Multivariate analysis	
Factors	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age	1.13 (1.06-1.19)	**<0.0001**	1.06 (0.85-1.33)	0.603
Bradyarrythmia during RRT	7.8 (1.33-45.66)	**0.023**	0.21 (0.04-12.1)	0.447
CHA_2DS_2-VASc ≥ 5	7 (2.47-19.78)	**<0.0001**		
HASBLED ≥ 4	6 (2.03-17.74)	**0.001**		
HFpEF	7 (2.47-19.78)	**<0.0001**		
PAD	3 (1.16-7.73)	**0.023**		
EF (%)	0.94 (0.89-0.99)	**0.025**	1.01 (0.81-1.27)	0.927
LAd (mm)	1.41 (1.2-1.65)	**<0.0001**	1.76 (1.05-2.94)	**0.033**
LVEDd (mm)	1.08 (0.98-1.16)	0.116		
Mitral regurgitation more than mild	8.25 (2.34-29.06)	**0.001**		
Diastolic dysfunction grade 2 or more	13 (3.8-44.5)	**<0.0001**		
RVSP (mmHg)	1.1 (1.-1.2)	**0.033**	0.9 (0.71-1.13)	0.356
P (mmol/L)	0.42 (0.24-0.74)	**0.003**		
AC therapy	10.46 (3.68-29.67)	**<0.0001**		
Cardioselective b-blocker	5.9 (2-17.58)	**0.001**		
ARBs	0.19 (0.04-0.86)	**0.032**		

(Table 5) Factors related to the presence of atrial fibrillation. AC = anticoagulation; ARBs = angiotensin receptor blockers; CI = confidence interval; EF = ejection fraction; HFpEF = heart failure preserved ejection fraction; LAd = left atrial diameter; LVEDd = left ventricular end diastolic diameter; OR = odds ratio; P = serum phosphorus; PAD = peripheral artery disease; RRT = renal replacement therapy; RVSP = right ventricular systolic pressure

4. Discussion

4.1. Study population's characteristics compared with existent evidence

The prevalence of AF in this dialysis-dependent cohort was 23% which is higher than the relative prevalence reported in most studies [9-12]. The only Greek study identified to examine ESRD patients reported a similar prevalence [13]. As ordinal means of AF detection yield low diagnostic performance; paroxysmal AF episodes in dialysis patients possibly occur more commonly than reported. A study that used implantable loop recorder (ILR) for arrhythmia detection in ESRD patients undergoing HD reported paroxysmal AF episodes in 41% of the study population [51].

Hypertension (85.6%), followed by dislipidemia (53.8%), PAD (30.8%), any type of HF (27.8%) and CAD (19.2%) were the commonest comorbidities of the study population. This profile of comorbidities suggests a high overall cardiovascular and AF risk [52, 53] and is consistent with the profile highlighted by a Greek study which examined a similar population [13]. In this study patients with AF were older, had more frequently a history of HFpEF and a history of PAD, as was previously demonstrated in a similar study [10]. Several studies have concluded that AF patients have a significantly longer duration on renal replacement therapy [54, 55], which was as well pointed out in the DOPPS study [9]. Our study showed similar

results although the difference did not reach statistical significance, due to small study population. Data derived from the USRDS registry from 1989 to 2006 concluded that heart failure was far the strongest associate with AF in more than half a million ESRD patients [8]. The fact that HFpEF is more commonly seen in AF patients indicates that the presence of this arrhythmia begets heart failure in dialysis patients, which is pointed out by changes in their TTE profile.

The lower mean EF, the larger mean LA diameter, the higher mean RVSP, the more severe stages of mitral regurgitation and diastolic dysfunction of the AF group make evident that these patients demonstrate a more impaired global cardiac performance compared with the naïve group. Regarding differences in LAd and EF, those have been noticed in previous studies [54] and the DOPPS study found that valvular heart disease and heart failure among others were more commonly encountered in patients with AF [9]. AF might be a causative factor or a manifestation of this echocardiographic profile which has been described as uraemic cardiomyopathy [3]. In the present study LA diameter was the only factor that was independently associated with AF in the multivariable regression analysis. This finding is consistent with the findings from Hensen, L.C.R., et al., who reported a significantly larger LA volume and larger LVEDd in ESRD patients with AF compared with non-AF patients and indicated that LA volume was among others an independent AF associate [56]. As highlighted in this study; the majority of ESRD patients with and without AF (81.7%) showed signs of left ventricular diastolic dysfunction and a similar percentage of diastolic dysfunction was found in another HD group of patients [57]. The impaired diastolic function of naïve ESRD patients might be an AF precursor. Hence, the stress ought to be put in more premature detection of diastolic dysfunction markers in ESRD patients.

4.2 Bradyarrhythmia episodes during renal replacement therapy

In a population of 66 HD patients with ILR; bradyarrhythmia episodes occurred in 19.7% and asystole episodes in 9.1% of the cohort [51]. Hyperkalaemia induced bradyarrhythmia is common in ESRD patients and bradyarrhythmia episodes have been suggested to be particularly malignant in these populations. This was demonstrated in a study by Wong, M.C.G., et al., where bradyarrhythmia and asystole episodes were present in all 6 sudden cardiac deaths of 50 stable ambulatory dialysis patients with implantable cardiac monitoring [58]. In our study 6 symptomatic bradyarrhythmia episodes occurred during RRT in the 2013 to 2019 period and they were more commonly developed in patients with AF. It is probable that ESRD patients with AF manifest more extensive biochemical disarray and structural myocardial abnormalities compared with non-AF patients. These abnormalities favor myocardial fibrosis, which slows or disrupts normal conduction leading to bradycardia or asystole [59]. Additionally in this study; AF patients who developed bradyarrhythmia had higher mean serum potassium levels compared with the rest of the AF group. As ESRD patients with AF frequently demonstrate impaired left ventricular systolic function; they are often offered RAAS inhibitors and potassium-sparing drugs. Thus, special consideration is needed when prescribing hyperkalaemia-associated drugs in dialysis patients as bradyarrhythmia-induced episodes might be fatal.

4.3 Managing atrial fibrillation in the study population

In the absence of definite guidelines for the antithrombotic management of AF in the ESRD setting; a variety of different drugs are offered in our study. In 2013 only about 20% of the AF population was anticoagulated but the AC rate was notably increased reaching 62.5% in 2019. In a recent study, among 8,410 AF patients with ESRD the oral AC rate was 36.2% [60], which is particularly low compared with the relative AC rate of our cohort in 2019. In this study, about 1 out of 4 AF patients were receiving off-label APT therapy and that trend was maintained throughout the years. AF group had a significantly higher mean CHA_2DS_2-VASc and HASBLED score compared with the non-AF group. It has been suggested that AF patients on RRT suffer a significantly higher risk of stroke compared with patients with normal renal function and that risk is dramatically enhanced with higher CHA_2DS_2-VASc scores [61]. However, the hesitation of the Greek physicians to prescribe AC drugs in this AF group is justified taking into account the delicate balance of both increased bleeding and thrombotic risk which sets this AF population apart from the average AF population. Moreover, the decision of the Greek physicians to anticoagulate or not these AF patients was independent of their CHA_2DS_2-VASc and HASBLED scores and different antithrombotic drugs were arbitrarily offered (Figures 7, 8). The need for novel risk-stratification schemes that will identify ESRD patients who will be benefited from AC treatment is emerging.

Despite the absence of randomized trials, the indirect evidence of augmented bleeding risk without offering significant ischemic stroke reduction [29-35] and the association with accelerated vascular calcification [39] more than 20% of the group was receiving VKA in 2019. Strikingly, despite the contraindication from the EHRA [23] and the absence of direct recommendation from the ESC [2]; NOACs were prescribed in this dialysis cohort from 2017 onwards. NOACs were used more frequently within the next two years and about 25% was receiving NOACs in 2019. It should be mentioned that apixaban was the only NOAC regimen that was used in this tertiary Greek Hospital. Apixaban has been licensed in the US by FDA in ESRD and seems to carry a better efficacy-safety profile compared to warfarin according to observational data [43, 44]. To our knowledge this is the first study to point out NOACs penetration in the dialysis setting in Greece.

4.4 Managing paroxysmal atrial fibrillation episodes during renal replacement therapy

Paroxysmal AF episodes during RRT or post-RRT are very common in ESRD patients [51] and many of these episodes are subclinical. As paroxysmal AF episodes are associated with augmented stroke risk [62, 63] and increased mortality [64, 65]; their detection is of paramount importance and merits enhanced vigilance by the physicians. In our study 34 such episodes have been detected during the 2013 to 2019 period but their prevalence has undoubtedly been underestimated. Surprisingly, almost 25% of those episodes received no cardioversion treatment. More than half of those episodes were pharmacologically cardioverted with intravenous amiodarone without short-term complications. Data on therapeutic management of arrhythmic events in ESRD patients are insufficient. Several studies have demonstrated that HD itself is associated with QTc interval prolongation [66,

67]. Consequently, specific considerations are required regarding the use of drugs inducing QT prolongation in this setting.

4.5 Limitations

The retrospective design which does not provide information on the outcome of these patients, the mix of patients with HD and PD, the absence of official certificate for the presence of arrhythmia in some patients and the small number of patients are some limitations of this study. Furthermore, although a large scale of information is provided the interpretation of some data is not clear. Additionally, due to small number of patients some associations could not be satisfactorily highlighted. Nevertheless, this is the first study to officially report NOAC use in ESRD patients in Greece and to provide information regarding approach of paroxysmal AF episodes during RRT.

5. Conclusions

AF is a very common arrhythmia in the setting of ESRD and is probably far underdiagnosed and underemphasized. It is highlighted that patients with AF and ESRD tend to be older and suffer from HFpEF and PAD more frequently. Additionally, they exhibit a higher thromboembolic and hemorrhagic risk which makes their antithrombotic management challenging.

AF patients demonstrated a more impaired global cardiac performance compared with non-AF patients. Due to this profile they were more prone to bradyarrhthmia episodes during RRT, which is a finding that merits special attention. As AF patients who developed bradyarrhythmia had higher serum potassium levels, concerns are raised regarding safety of hyperkalaemia-associated drugs in this setting. In this study a larger LA predicted AF occurrence, which is a significant finding. This study reinforces the need for detection of more premature echocardiographic signs which will foresee the development of AF in this complex population.

Paroxysmal AF episodes during RRT occurred frequently. However, almost 25% of those were not treated. It is emphasized that diagnosis and treatment of those episodes is crucial as they have been associated with elevated thromboembolic risk. Furthermore, the need for a consensus about the optimal antiarrhythmic management of those is emerging.

In the present study AF patients were commonly not anticoagulated. However, higher AC rates are noticed from 2013 to 2019 and penetration of NOACs in seen from 2017 onwards. The decision to anticoagulate was not based on CHA_2DS_2-VASc and HASBELD scores and different antithrombotic drugs were arbitrarily offered. This study highlights the need to better stratify the thromboembolic risk of those patients in order to identify the ones who will be benefited from AC therapy. It is imprudent to extrapolate AC strategies used in the general population in this high-risk cohort as the differences between them are huge.

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