Association between Antithrombotic Treatment and Outcomes at 1-year Follow-Up in Patients with Atrial Fibrillation: The EORP-AF General Long-Term Registry

Giuseppe Boriani[1]* MD, PhD, Marco Proietti[2,3]* MD, Cécile Laroche[4] MSc, Laurent Fauchier[5] MD PhD, Francisco Marin[6] MD PhD, Michael Nabauer[7] MD, Tatjana Potpara[8,9] MD PhD, Gheorghe-Andrei Dan[10] MD, Zbigniew Kalarus[11] MD, Luigi Tavazzi[12] MD, PhD, Aldo P Maggioni[4,13] MD, Gregory Y H Lip[2,14,15] MD on behalf of the EORP-AF Long-Term General Registry Investigators[16]

[1]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [2]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom; [3]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy; [4]EURObservational Research Programme Department, European Society of Cardiology, Sophia Antipolis, France; [5]Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, Tours, France; [6]Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, IMIB-Arrixaca, University of Murcia, CIBER-CV, Murcia, Spain; [7]Department of Cardiology, Ludwig-Maximilians-University, Munich, Germany; [8]School of Medicine, Belgrade University, Belgrade, Serbia; [9]Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia; [10]University of Medicine, 'Carol Davila', Colentina University Hospital, Bucharest, Romania; [11]Department of Cardiology, Medical University of Silesia, Katowice, Poland; [12]Maria Cecilia Hospital, GVM Care & Research, Ettore Sansavini Health Science Foundation, Cotignola, Italy; [13]ANMCO Research Center, Firenze, Italy; [14]Liverpool Centre for

Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; [15]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; Listed in Appendix 1[16].

*Both authors equally contributed to the manuscript

Correspondence to:

Prof. Giuseppe Boriani, MD, PhD, FESC.

Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences,

University of Modena and Reggio Emilia, Policlinico di Modena,

Via del Pozzo, 71, 41124 Modena, Italy

Phone +39-059-4225836

Fax: +39-059-4224498

E-mail: giuseppe.boriani@unimore.it

ABSTRACT

Aims: In recent years, stroke prevention in patients with atrial fibrillation (AF) has radically changed, with increasing use of non-vitamin K antagonist oral anticoagulants (NOACs). Contemporary European data on AF thromboprophylaxis are needed.

Methods: We report 1-year follow-up data from the EURObservational Research Programme in Atrial Fibrillation (EORP-AF) General Long-Term Registry. Outcomes were assessed according to antithrombotic therapy.

Results: At 1-year follow-up, 9663 (88.0%) patients had available data for analysis: 586 (6.1%) were not treated with any antithrombotic; 681 (7.0%) with antiplatelets only; 4066 (42.1%) with vitamin K antagonist (VKA) only; 3167 (32.8%) with NOACs only; and 1163 (12.0%) with antiplatelet and oral anticoagulant (OAC). At 1-year follow-up, there was a low rate of stroke (0.7%) and any thromboembolic event [TE] (1.2%), while haemorrhagic events occurred in 222 patients (2.3%). Cardiovascular (CV) death and all-cause death occurred in 3.9% and 5.2% of patients respectively. Cumulative survival for all the three main outcomes considered was highest amongst patients treated only with NOACs ($p<0.0001$). Multivariable-adjusted Cox regression analysis found that VKA or NOACs use was independently associated with a lower risk for any TE/ACS/CV death, while all treatments were independently associated with a lower risk for CV death and all-cause death.

Conclusions: The 1-year follow-up of EORP-AF General Long-Term Registry reported a low occurrence of thromboembolic and hemorrhagic events, although mortality was high. Both VKA and NOACs were associated with a lower risk of all main adverse outcomes. All treatments were associated with a lower risk for CV death and all-cause death.

Keywords: atrial fibrillation; antithrombotic therapy; observational registries; outcomes; Europe.

CONDENSED ABSTRACT

In a contemporary cohort of patients with atrial fibrillation, both VKA and NOACs were similarly associated with a lower risk of adverse outcomes as compared to no treatment. Furthermore, antiplatelet drugs are associated to a lower risk of death (despite with a lower magnitude) in patients with prominent cardiac disease.

INTRODUCTION

Atrial fibrillation (AF) prevalence and incidence have been projected to substantially increase in the future, with more than 15 million Europeans to be affected by 2030 and up to 215.000 new AF patients diagnosed each year[1]. Epidemiology of AF has changed in the last 15 years, with patients found to be older and more affected by cardiovascular (CV) and non-CV comorbidities[2].

AF is associated with an increased risk of stroke, with up to 30% of reported strokes being associated with AF; moreover, an increased risk of CV events, CV related death and all-cause death with AF has clearly been established[3–6]. The introduction of the non-vitamin K antagonist oral anticoagulants (NOACs) as an effective and safer alternative to vitamin K antagonist (VKA) has changed the landscape of clinical management for these patients[7], although there are clear regional differences in prescription of these drugs[8,9].

In order to improve knowledge about AF natural history, association with risk factors and comorbidities and role of antithrombotic therapy in real-life, several observational registries have been conducted worldwide[10–12]. In 2012, the European Society of Cardiology (ESC) initiated the EURObservational Research Programme in AF (EORP-AF) General Pilot Registry, which was the first contemporary independent observational registry to provide a picture of the changing landscape of AF epidemiology and treatment in Europe, taking a snapshot of current practice amongst European cardiologists' on the edge of the 'NOAC era'[3,13,14]. In 2013, the EORP-AF General Long-Term Registry was launched with the aim to provide more

evidence about European AF patient characteristics, clinical practices and use of antithrombotic drugs after NOAC use was largely established in most of Europe[8]. In this paper we report the 1-year follow-up data of the EORP-AF General Long-Term Registry, focusing on the relationship between baseline antithrombotic therapy use and the occurrence of major clinical adverse events.

METHODS

The EORP-AF General Long-Term Registry is a prospective, observational, multicenter registry established by ESC in 27 participating countries. The study enrolled consecutive AF patients presenting in 250 cardiology practices, both in- and outpatient settings. The detailed description of the design and baseline characteristics have been provided previously[8]. Briefly, all AF patients enrolled had AF documented within 12 months before enrollment on the basis of objective electrocardiographic evaluation. All patients were ≥18 years old and provided written informed consent form. Enrollment was undertaken from October 2013 to September 2016, while 1-year follow-up was performed up until to September 2017. Institutional review board approved the study protocol for every institution, and the study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki[8].

Baseline information were collected according to study procedures previously described[8]. Thromboembolic risk was defined according to CHA_2DS_2-VASc score[1]. 'Low risk' was defined as a CHA_2DS_2-VASc 0 in males and 1 in females; 'moderate risk' was defined for a CHA_2DS_2-VASc 1 in males; 'high risk' was defined as CHA_2DS_2-VASc ≥2. Bleeding risk was defined according to HAS-BLED score[1]. 'Low

risk' was defined as HAS-BLED 0-2, while 'high risk' was defined as HAS-BLED ≥3. Symptomatic status was defined according to EHRA (European Heart Rhythm Association) score[1].

For the purpose of this analysis, patients were categorised according to antithrombotic therapy prescribed at discharge/after consultation, following enrolment in the study. Patients were then divided in five groups: 1) no antithrombotic therapy; 2) only antiplatelet drugs; 3) only VKA; 4) only NOACs; and 5) antiplatelet drugs plus any oral anticoagulant (OAC).

Follow-Up Procedures

All follow-up was performed at 1-year after enrollment. During follow-up all incident major adverse clinical events were recorded, with the composite outcome of any thromboembolism (TE) (including stroke, transient ischemic attack and any peripheral embolism)/acute coronary syndrome (ACS)/CV death, CV death, all-cause death as the main outcomes of interest.

We also considered the individual outcomes of stroke, any TE, any hemorrhagic events and intracranial hemorrhage. Hemorrhagic events were not specifically defined, but all significant events which investigators became aware, were reported. All data about hospital admissions (any admission, AF-related and CV-related) were also recorded. Investigators reported all available details about incident major adverse clinical events on the centralized electronic case report form. Events are reported according to the five prespecified groups.

Statistical Analysis

All continuous variables were reported as mean±SD or as median and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal-Wallis test. Categorical variables were reported as counts and percentages. Among-group comparisons were made using a chi-square test or Fisher's exact test (if any expected cell count was less than five). Plots of Kaplan-Meier curves for time to any TE/ACS/CV death, to cardiovascular deaths or to all-cause of death according to antithrombotic pattern were performed. Survival distributions were compared using the log-rank test.

A univariate and stepwise multivariate Cox regression analysis, adjusted for all the main outcomes predictors in AF patients, was performed to establish the relationship between the various antithrombotic therapy patterns and the risk of the composite outcome of any TE/ACS/CV death, CV death or all-cause death. Into the model all the candidate variables (variables with $p<0.10$ in univariate) were included. A univariate significance level of 0.05 was required to allow a variable into the model (SLENTRY=0.05) and a multivariate significance level of 0.05 was required for a variable to stay in the model (SLSTAY=0.05). No interaction was tested. Hosmer and Lemeshow Goodness-of-Fit and Harrell's C statistic tests were used to verify that the models were optimal. A two-sided $p<0.05$ was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Of the original 11096 patients enrolled in the EORP-AF General Long-Term Registry at baseline from October 2013 to November 2017, 121 (1.1%) withdrew their consent for the follow-up phase for their own personal choice, in accordance to good clinical practice. Of the remaining 10975 patients, 9663 (88.0%) had available data about follow-up status. The overall demographic and clinical characteristics of this cohort have been previously reported[8]. Baseline characteristics according to antithrombotic therapy prescribed at discharge are reported in Table 1.

Patients prescribed with only antiplatelet drugs and antiplatelet drugs and OAC were older, with the latter ones were also less females ($p<0.0001$), while those not prescribed with any antithrombotic therapy were the youngest ($p<0.0001$) (Table 1). AF patients not prescribed with any antithrombotic therapy were generally less affected with concomitant cardiac diseases, CV risk factors and other comorbidities, while patients prescribed with both antiplatelet drugs and OAC were more likely diagnosed with most of those conditions. NOAC patients were more likely asymptomatic, compared to other groups ($p<0.0001$) (Table 1). In general, patients not prescribed with any antithrombotic therapy were less prescribed with other cardiovascular and non-cardiovascular drugs (Table S1).

Baseline CHA_2DS_2-VASc score and proportion of patients with high thromboembolic risk (Table S2) were significantly lower in patients not prescribed with any antithrombotic, while it was progressively higher for patients prescribed only with NOACs, VKA, antiplatelet drugs, and with both antiplatelet drugs and OAC (all $p<0.0001$).

Similarly, HAS-BLED score (Table S2) and proportion of patients with high bleeding risk were lower in patients not prescribed with any antithrombotic therapy and progressively higher for patients prescribed only with NOACs, VKA, antiplatelet drugs and with both antiplatelet drugs and OAC (all p<0.0001).

Use of Antithrombotic Therapy at 1-year Follow-up

Antithrombotic therapy at follow-up visit discharge, according to baseline discharge antithrombotic therapy is shown in Figure 1. Almost half of the patients initially not prescribed with any antithrombotic were then prescribed with an antithrombotic drug, mostly NOACs (17.9%) [Figure 1, 1st column]; also, 33.3% of patients treated only with antiplatelet drugs at baseline were prescribed with an OAC, both alone and associated with antiplatelet drugs, at follow-up [Figure 1, 2nd column]. The large majority of patients originally prescribed with VKA or NOACs only remained on the same drugs, even though 4.5% and 7.9% respectively stopped taking their VKA and NOACs [Figure 1, 3rd and 4th columns]. Among patients treated with antiplatelet drugs and OAC, 41.7% were switched to a single OAC at follow-up [Figure 1, 5th column].

Follow-up Analysis

After 1-year of follow-up observation, a total of 63 (0.7%) strokes, 116 (1.2%) any TE events and 148 (1.6%) ACS were recorded. A total of 222 (2.3%) hemorrhagic events, with 24 (0.3%) intracranial hemorrhages, as well as 380 (3.9%) CV death and 501 (5.2%) all-cause death events were also recorded. Overall, the composite outcome of any TE/ACS/CV death was recorded in 618 (6.5%).

Analyzing the occurrence of major adverse clinical events according to baseline antithrombotic therapy use at discharge (Table 2), a higher rate of stroke and any TE was recorded with antiplatelet drugs (1.7% [p=0.043] and 2.4% [p=0.053], respectively). No difference in rate of hemorrhagic events and intracranial hemorrhage was found. A higher rate of ACS, CV death and all-cause death was reported for both antiplatelet drugs and OAC, while the lowest rate was found in patients treated only with NOACs (all p<0.0001) (Table 2).

The composite outcome of any TE/ACS/CV death was higher with antiplatelet drugs and those treated with both antiplatelet drugs and OAC (12.1% and 12.5% respectively) while patients treated only with NOACs reported the lowest rate (3.9%) (p<0.0001). Regarding hospital readmissions, patients treated both with antiplatelet drugs and OAC reported higher crude rates of any readmission and any CV readmission (Table 2).

For the main outcomes of interest, overall incidence of any TE/ACS/CV death was 6.6 per 100 patient-years, incidence of CV death was 3.9 per 100 patient-years and incidence of all-cause death was 5.2 per 100 patient-years. Patients treated only with antiplatelet drugs and those treated with both antiplatelet drugs and OAC reported the highest incidence rates (12.7 and 13.1 per 100 patient-years, respectively), while those not treated with any antithrombotic and those treated with VKA reported a similar incidence (5.5 and 6.1 per 100 patient-years, respectively); lastly those patients treated only with NOACs reported the lowest incidence (3.9 per 100 patient-

years). Similar differences across the groups were found for CV death and all-cause death outcomes.

Kaplan-Meier curves [Figure 2] show that the cumulative survival for any TE/ACS/CV death [Figure 2, Panel A] was highest for patients treated only with NOACs and progressively lower for patients treated only with VKA, patients not treated with any antithrombotic and those treated with antiplatelet drugs or antiplatelet drugs and OAC ($p<0.0001$). Similar evidence was reported for the CV death outcome [Figure 2, Panel B], while for all-cause death outcome, patients treated only with VKA or NOACs had similar cumulative survival, higher than those in other groups ($p<0.0001$) [Figure 2, Panel C].

Cox Regression Analysis

After the univariate analysis (Table S3-S5), a Cox multivariate regression analysis (Table 3), adjusted for all the main known outcomes predictors in AF patients [Figure 3, Panels A-C], showed an independent association with lower risk for any TE/ACS/CV death for patients treated only with VKA (hazard ratio [HR]: 0.44, 95% confidence interval [CI]: 0.31-0.63) and NOACs (HR: 0.37, 95% CI: 0.26-0.54), compared to those not treated with any antithrombotic therapy.

For the CV death and all-cause death outcomes, all the antithrombotic therapies were associated to a lower risk of event occurrence, with treatment only with VKA or NOACs showing the lower risk (for CV death and all-cause death, only VKA, HR: 0.38, 95% CI: 0.25-0.57 and HR: 0.34, 95% CI: 0.24-0.47, respectively; for only

NOACs, HR: 0.25, 95% CI: 0.16-0.40 and HR: 0.26, 95% CI: 0.18-0.38, respectively).

DISCUSSION

In this 1-year follow-up report of the EORP-AF General Long-Term Registry, our principal findings are as follows: (i) we observed an overall low rate of thromboembolic, bleeding and CV events amongst a contemporary cohort of European AF patients, while conversely a higher rate of CV death and all-cause death was evident; (ii) after one year, the persistence of OAC treatments was high and most patients remained treated with at least one type of OAC; (iii) use of either VKA or NOACs was associated with a significant independent reduced risk for the composite of adverse clinical events. All the antithrombotic treatments (only antiplatelet drugs, only VKA, only NOACs and antiplatelet drugs and OAC) have been found to be associated with a lower risk of CV death and all-cause death, even though use of only VKA and only NOACs showed a stronger magnitude in risk reduction (Representative Figure).

Results presented in this paper strengthen and reinforce the evidence, already provided in the baseline paper[8], that the uptake of OAC (both VKA and NOACs) is very high and remains high persistently across 1-year of follow-up observation, also showing a significant reduction in use of aspirin. A recent study held in the UK, merging several different national databases further supported this observation in the context of a real-life scenario, reporting an increase in OAC uptake up to 78.6%, with a consensual decrease of antiplatelet drugs use up to 16.1%[15]. Notwithstanding, other nationwide real-life databases (based on general care and not on cardiology practices) even if confirmed an increase in OAC uptake (mostly based on the increased use of NOACs), reported an overall lower prescription rate compared to our data[16,17]. Further, the reduction in the use of aspirin was definitely more modest

than that described by our study[16,17]. These differences are likely to be attributed to the fact that our study is based on highly skilled and expert cardiology practices, also in the context of a specific study investigating cardiology practices in AF.

Data from worldwide registries have established that oral anticoagulation is significantly associated with reduced rates of thromboembolic events[10,11]. Data from EORP-AF Pilot Registry reported a low rate of thromboembolic events, even though it was conducted when NOAC use was limited and also with a limited number of countries included[3,14]. Our data confirm and extend previous knowledge, demonstrating a high uptake of OAC treatment after NOACs fully entered current daily clinical practice in Europe, which are associated with a significantly reduced risk for thromboembolic complications, without an excess of bleeding complications. Even though the observational nature of the study does not allow to establish the causality link, the results presented seems to strengthen the concept that NOACs use is effective and safe in real-life AF population. Moreover, despite the observed differences in OAC prescription across European regions[8], we found no impact of regions on outcomes, which did not emerge as significant independent predictors on multivariate analysis.

Of note, the low rates of overall bleeding events possibly underlined how indications for appropriate management of modifiable bleeding risk score from international guidelines[1] are implemented in cardiology clinical practice and effective in containing bleeding events. This appears to be particularly true regarding the intracranial hemorrhage events, which rates are extremely low (ranging from 0.2% to 0.3% in all the groups). Notwithstanding, this very low rate of events does not allow to draw

definitive conclusions regarding the difference in terms of intracranial bleeding between the various antithrombotic therapy approach.

Despite the high use of OAC, the risk of CV death and all-cause death remained high in AF real-life patients. A post-hoc analysis derived from the ROCKET-AF trial also showed that the majority of deaths are related to cardiac causes associated with comorbidities[5]. In the Loire Valley Atrial Fibrillation project, after over a 2.5 years follow-up, 14% of patients died, with the majority of deaths associated with pre-existing cardiovascular comorbidities rather than stroke[4]. These data were also confirmed in the Phase III trials on NOACs[18]. Indeed, focus on the reduction of mortality is should be the next objective in improving outcomes for AF patients. This has led to the concept of 'integrated care' for improving management of AF patients, which has been shown to reduce mortality and hospitalizations[19]. Such 'integrated care' can be operationalized with the simple ABC pathway ('A' Avoid stroke with Anticoagulation; 'B; Better symptom management with rate or rhythm control; 'C' Cardiovascular and comorbidity risk management, including lifestyle interventions)[20]. A more integrated, comprehensive evaluation of these patients would properly manage patients in a more holistic manner[20,21].

Follow-up data from large observational registries about AF patients have provided evidence about a sustained association of OAC and NOACs antithrombotic therapy with a reduced risk of thromboembolic events and death[10,11]. Our results supplement these industry-sponsored registries with an independent ESC-conducted European-wide cohort of AF patients, where the use of VKA and NOACs was consistently associated with a reduced risk of main clinical adverse events, without an increase in

the risk of bleeding events. Our cohort included also AF patients not treated with VKA or NOACs (6% of the cohort) and this allows to make important considerations on this subgroup of “real-life” patients usually not object of analysis in other registries. Our data reinforce the concept that the use of any OAC is associated with a reduced risk of CV death and all-cause death, independently of known predictors of death in AF patients[22].

The association between use of antiplatelet drugs and reduced risk of CV death and all-cause death deserves some considerations. Current guidelines firmly contraindicate the use of antiplatelet drugs in patients with AF[1], due to inefficacy to prevent stroke and the contemporary increased risk of major bleeding. Actually, both stroke and thromboembolic events are reported to be more than doubled in patients treated with antiplatelet drugs only. Conversely, no difference was found in the rate of hemorrhagic events, even though the overall low rate is likely due to the good implementation of current recommendations for minimizing bleeding risk as reported above.

In the cohort of untreated patients more than 40% had a baseline high risk of stroke, which may have led to an overestimation of risk reduction in patients treated with antiplatelet drugs, even though still in this case the proportion of high risk is notable. Moreover, considering the high prevalence of cardiac disease associated to AF in these patients, that drive the prescription of antiplatelet drugs as described in other observational cohorts[23], the inverse association with the risk of mortality can be due to an impact on the cardiac substrate, often due to relatively recent ACS[8].

These considerations need to be extended also to those patients treated with both antiplatelet drugs and OAC. Indeed, these patients not only presented the highest baseline thromboembolic risk, but also reported the highest rate of events. Considering the baseline characteristics, we can see how these patients are the most burdened with coronary artery disease, previous myocardial infarction and peripheral artery disease. Our observations match with some recent papers specifically investigating this issue[23,24]. Even in these patients, very likely the combining action of OAC and antiplatelet drugs is able to modulate the cardiovascular risk associated with the vascular disease that goes beyond the AF-related thromboembolic risk.

Our observations surely do not allow to reconsider the role of antiplatelet drugs in thromboembolic risk management, but highlight the role of these drugs in the management of concomitant heart disease, that is often reported in AF patients, as underlined by clinical guidelines[1].

Limitations

The main limitation of the study is related to the observational nature of the study. First, a significant number of patients were lost at follow-up, notwithstanding similar proportion of losses were reported by other registries[11]. Even though the events were not centrally adjudicated, this limitation is shared by almost all real-life observational registries. Moreover, if the low rate of thromboembolic events could be due to a relatively short follow-up, longer follow-up is planned to further substantiate our observations. Another limitation is related to the study setting, based exclusively on cardiology practices. Since AF patients are also commonly managed by different

health professionals (i.e. general practitioners, internal medicine specialists, geriatricians), our data need to be cautiously interpreted when extended to the entire AF population.

CONCLUSIONS

The one-year follow-up of EORP-AF General Long-Term Registry reported an overall low occurrence of thromboembolic and hemorrhagic events, although mortality was high. Both VKA and NOACs were similarly associated with a lower risk of the composite outcome of Any TE/ACS/CV death as compared to no treatment. All antithrombotic treatments are associated to a lower risk of CV death and all-cause death, comprising antiplatelet drugs alone or in association with OAC (despite with a lower magnitude than only VKA and only NOACs) in patients with prominent cardiac disease.

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DECLARATIONS OF INTEREST

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Table 1: Demographic and Baseline Characteristics according to Antithrombotic Therapy at Baseline Discharge

	No Antithrombotic N= 586	**Only Antiplatelet Drugs N= 681**	**Only VKA N= 4066**	**Only NOACs N= 3167**	**Antiplatelet Drugs + OAC N= 1163**	**p**
Demographics						
Age, *years* Median [IQR]	61 [51-73]	72 [62-78]	71 [64-78]	70 [62-77]	72 [65-78]	<0.0001
Female, n (%)	223 (38.1)	289 (42.4)	1729 (42.5)	1272 (40.2)	374 (32.2)	<0.0001
Type of AF, n (%)						<0.0001
First Diagnosed	136 (23.9)	127 (19.2)	386 (9.6)	626 (20.0)	189 (16.7)	
Paroxysmal	231 (40.7)	285 (43.1)	821 (20.5)	844 (27.0)	288 (25.4)	
Persistent	78 (13.7)	80 (12.1)	711 (17.7)	814 (26.0)	215 (19.0)	
LS Persistent	9 (1.6)	18 (2.7)	206 (5.1)	158 (5.1)	35 (3.1)	
Permanent	114 (20.1)	151 (22.8)	1884 (47.0)	683 (21.9)	405 (35.8)	
Concomitant Diseases						
Hypertension, n (%)	188 (32.5)	412 (61.1)	2631 (65.2)	1897 (60.4)	791 (68.5)	<0.0001
CAD, n (%)	91 (16.2)	334 (52.8)	850 (22.3)	498 (16.4)	834 (76.3)	<0.0001
Previous MI, n (%)	40 (44.0)	160 (47.9)	325 (38.2)	194 (39.0)	432 (51.8)	<0.0001

Heart Failure, n (%)	135 (23.4)	323 (47.9)	1735 (42.9)	934 (29.8)	590 (51.1)	<0.0001
Valvular Disease, n (%)	157 (27.4)	305 (46.0)	2362 (59.1)	1316 (42.5)	625 (54.6)	<0.0001
Dilated Cardiomyopathy, n (%)	24 (4.2)	54 (8.0)	419 (10.4)	185 (5.9)	142 (12.4)	<0.0001
Hypertrophic Cardiomyopathy, n (%)	9 (1.6)	16 (2.4)	154 (3.8)	76 (2.4)	41 (3.6)	0.0007
Restrictive Cardiomyopathy, n (%)	2 (0.3)	1 (0.1)	11 (0.3)	4 (0.1)	2 (0.2)	0.5788
Other Cardiomyopathy, n (%)	12 (2.1)	24 (3.6)	161 (4.0)	97 (3.1)	56 (4.8)	0.0102
Congenital Heart Disease, n (%)	6 (1.0)	9 (1.3)	50 (1.2)	25 (0.8)	12 (1.0)	0.3852
PAH, n (%)	21 (3.7)	53 (8.0)	345 (8.6)	128 (4.1)	93 (8.1)	<0.0001
Cardiovascular Risk Factors						
Diabetes Mellitus, n (%)	86 (14.8)	161 (23.7)	943 (23.3)	595 (18.9)	409 (35.5)	<0.0001
Lipid Disorder, n (%)	148 (26.6)	295 (45.7)	1651 (42.5)	1138 (37.5)	617 (55.1)	<0.0001
Current Smoker, n (%)	85 (15.5)	71 (11.2)	305 (8.2)	244 (8.2)	124 (11.3)	<0.0001
No Regular Exercise, n (%)	170 (33.4)	290 (47.6)	1483 (42.5)	989 (37.0)	525 (50.9)	<0.0001
Other Comorbidities						
Previous Stroke, n (%)	14 (2.4)	40 (6.0)	262 (6.5)	189 (6.0)	83 (7.2)	0.0005
Previous TIA, n (%)	6 (1.0)	18 (2.7)	126 (3.1)	119 (3.8)	41 (3.6)	0.0048
Previous Bleedings, n (%)	39 (6.8)	59 (8.8)	166 (4.1)	163 (5.2)	68 (5.9)	<0.0001
PAD, n (%)	26 (4.5)	84 (12.8)	299 (7.5)	176 (5.7)	175 (15.5)	<0.0001

Chronic Kidney Disease, n (%)	37 (6.3)	123 (18.2)	504 (12.5)	304 (9.6)	223 (19.3)	<0.0001
COPD, n (%)	34 (5.9)	60 (8.9)	388 (9.6)	226 (7.2)	147 (12.7)	<0.0001
Malignancy, n (%)	47 (8.0)	54 (8.0)	285 (7.0)	262 (8.3)	89 (7.7)	0.3309
Thyroid Disease/Disorder, n (%)	57 (9.9)	75 (11.4)	615 (15.4)	452 (14.5)	166 (14.5)	0.0017
Main Reason for						<0.0001
Admission/Consultation, n (%)						
AF	447 (76.3)	368 (54.0)	2565 (63.1)	2557 (80.7)	537 (46.2)	
ACS	13 (2.2)	84 (12.3)	36 (0.9)	19 (0.6)	161 (13.8)	
Valvular Disease	9 (1.5)	19 (2.8)	177 (4.4)	17 (0.5)	52 (4.5)	
Hypertension	21 (3.6)	10 (1.5)	94 (2.3)	51 (1.6)	19 (1.6)	
Heart Failure	22 (3.8)	67 (9.8)	502 (12.3)	207 (6.5)	142 (12.2)	
Other CAD	8 (1.4)	41 (6.0)	80 (2.0)	36 (1.1)	96 (8.3)	
Other CV	28 (4.8)	65 (9.5)	363 (8.9)	159 (5.0)	105 (9.0)	
Other Non-CV	38 (6.5)	27 (4.0)	248 (6.1)	121 (3.8)	51 (4.4)	
Symptomatic Status*, n (%)*						<0.0001
EHRA I	261 (44.5)	337 (49.5)	1942 (47.8)	1328 (41.9)	519 (44.6)	
EHRA II-III-IV	325 (55.5)	344 (50.5)	2124 (52.2)	1839 (58.1)	644 (55.4)	

Legend: ACS= Acute Coronary Syndrome; AF= Atrial Fibrillation; CAD= Coronary Artery Disease; COPD= Chronic Obstructive Pulmonary Disease; CV= Cardiovascular; EHRA= European Heart Rhythm Association; IQR= Interquartile Range; MI= Myocardial Infarction; NOACs= Non-vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulants; PAD= Peripheral Artery Disease; PAH= Pulmonary Artery Hypertension; TIA= Transient Ischemic Attack; VKA= Vitamin K Antagonist.

Table 2: Major Adverse Clinical Events according to Antithrombotic Therapy at Baseline Discharge

	No Antithrombotic N= 586	Only Antiplatelet Drugs N= 681	Only VKA N= 4066	Only NOACs N= 3167	Antiplatelet Drugs + OAC N= 1163	p
Stroke, n (%)	2 (0.3)	11 (1.7)	22 (0.6)	20 (0.6)	8 (0.7)	0.0453
Any TE, n (%)	9 (1.6)	16 (2.4)	40 (1.0)	37 (1.2)	14 (1.2)	0.0530
Hemorrhagic Events, n (%)	8 (1.4)	15 (2.3)	95 (2.4)	74 (2.4)	30 (2.7)	0.5797
Intracranial Hemorrhage, n (%)	1 (0.2)	2 (0.3)	12 (0.3)	6 (0.2)	3 (0.3)	0.8932
Acute Coronary Syndrome, n (%)	6 (1.1)	27 (4.1)	49 (1.2)	24 (0.8)	42 (3.7)	<0.0001
CV Death, n (%)	17 (2.9)	47 (6.9)	157 (3.9)	64 (2.0)	95 (8.2)	<0.0001
All-Cause Death, n (%)	30 (5.1)	60 (8.8)	196 (4.8)	100 (3.2)	115 (9.9)	<0.0001
Any TE/ACS/CV Death, n (%)	31 (5.4)	81 (12.1)	240 (6.0)	122 (3.9)	144 (12.5)	<0.0001
Any Readmission, n (%)	120 (21.4)	176 (27.6)	912 (23.4)	723 (23.5)	326 (29.7)	<0.0001
Any AF Readmission, n (%)	48 (8.5)	67 (10.4)	405 (10.3)	354 (11.5)	135 (12.3)	0.0915
Any CV Readmission, n (%)	85 (15.2)	151 (23.6)	745 (19.1)	561 (18.2)	278 (25.2)	<0.0001

Legend: ACS= Acute Coronary Syndrome; AF= Atrial Fibrillation; CV= Cardiovascular; NOACs= Non-vitamin K Antagonist Oral Anticoagulants; TE= Thromboembolism; OAC= Oral Anticoagulation; VKA= Vitamin K Antagonist.

Table 3: Cox Regression Analysis for Major Adverse Clinical Events according to Antithrombotic Therapy at Baseline Discharge

	Any TE/ACS/CV Death*			CV Death†			All-Cause Death‡		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
No Antithrombotic (*ref.*)	-	-	-	-	-	-	-	-	-
Only Antiplatelet Drugs	0.83	0.55-1.24	0.3619	0.56	0.34-0.91	0.0195	0.55	0.36-0.83	0.0041
Only VKA	0.44	0.31-0.63	<0.0001	0.38	0.25-0.57	<0.0001	0.34	0.24-0.47	<0.0001
Only NOACs	0.37	0.26-0.54	<0.0001	0.25	0.16-0.40	<0.0001	0.26	0.18-0.38	<0.0001
Antiplatelet Drugs + OAC	0.71	0.48-1.04	0.0776	0.64	0.41-0.98	0.0402	0.57	0.40-0.83	0.0031

Legend: *Hosmer and Lemeshow Goodness-of-Fit: 17.349, Harrell's C statistic: 0.734; †Hosmer and Lemeshow Goodness-of-Fit: 19.754, Harrell's C statistic: 0.796; ‡Hosmer and Lemeshow Goodness-of-Fit: 19.152, Harrell's C statistic: 0.780; ACS= Acute Coronary Syndrome; AF= Atrial Fibrillation; CV= Cardiovascular; NOACs= Non-vitamin K Antagonist Oral Anticoagulants; TE= Thromboembolism; OAC= Oral Anticoagulation; VKA= Vitamin K Antagonist.

FIGURE LEGENDS

Figure 1: Antithrombotic Therapy at 1-year Follow-up Discharge according to Antithrombotic Therapy at Baseline Discharge

Legend: NOACs= Non-vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulation; VKA= Vitamin K Antagonist.

Figure 2: Kaplan-Meier Curves for Major Adverse Clinical Events according to Antithrombotic Therapy at Baseline Discharge

Legend: ACS= Acute Coronary Syndrome; AF= Atrial Fibrillation; CV= Cardiovascular; NOACs= Non-vitamin K Antagonist Oral Anticoagulants; TE= Thromboembolism; OAC= Oral Anticoagulation; VKA= Vitamin K Antagonist.

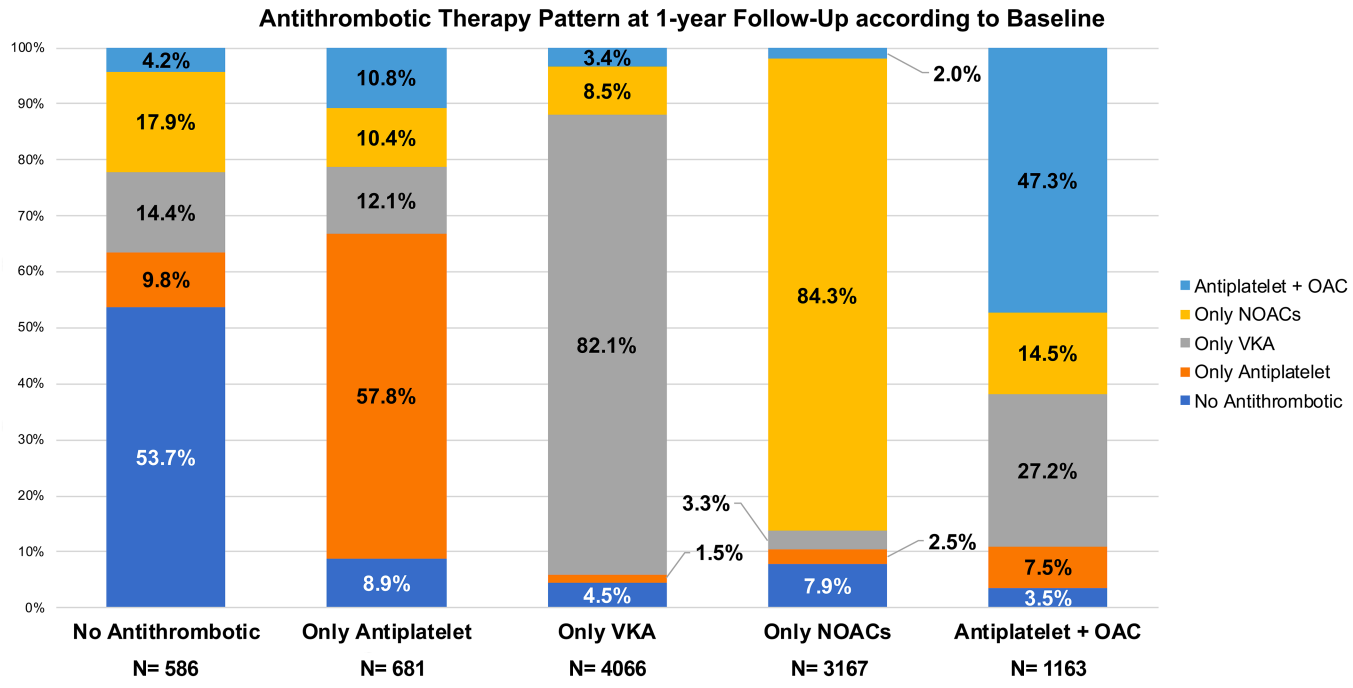
Figure 3: Cox Multivariate Regression Analysis for Major Clinical Adverse Events according to Antithrombotic Therapy at Baseline Discharge

Legend: Dashes stand for hazard ratio and 95% confidence interval. Reference for type of AF is first diagnosed, for enrollment year is 2013/2014 and for antithrombotic therapy is no antithrombotic; ACS= Acute Coronary Syndrome; AF= Atrial Fibrillation; CV= Cardiovascular; LS= Long-Standing; NOACs= Non-vitamin K Antagonist Oral Anticoagulants; TE= Thromboembolism; OAC= Oral Anticoagulation; TIA= Transient Ischemic Attack; VKA= Vitamin K Antagonist.

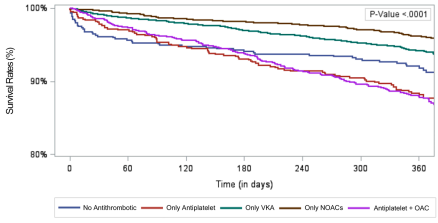
Representative Figure: EORP-AF General Long-Term Follow-Up

Legend: *the logical signs are intended as expressing the association between antithrombotic therapies and risk of outcomes occurrence and do not imply a

causative link; AP= Antiplatelet; CV= Cardiovascular; TE= Thromboembolism; NOACs= Non-vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulation; VKA= Vitamin K Antagonist;


Antithrombotic Therapy Pattern at 1-year Follow-Up according to Baseline
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
4.2%
17.9%
14.4%
9.8%
53.7%
10.8%
10.4%
12.1%
57.8%
8.9%
3.4%
8.5%
82.1%
4.5%
3.3%
1.5%
2.0%
84.3%
2.5%
7.9%
47.3%
14.5%
27.2%
7.5%
3.5%
Antiplatelet + OAC
Only NOACs
Only VKA
Only Antiplatelet
No Antithrombotic
No Antithrombotic
N= 586
Only Antiplatelet
N= 681
Only VKA
N= 4066
Only NOACs
N= 3167
Antiplatelet + OAC
N= 1163

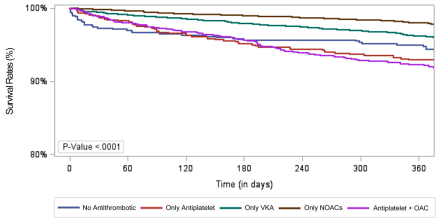
A) Any TE/ACS/CV Death



Number of Subjects at risk for event

1	593	564	556	547	531	518	397
2	671	643	625	610	596	584	460
3	4018	3954	3913	3867	3815	3731	2869
4	3139	3104	3071	3043	3003	2929	2253
5	1150	1118	1093	1069	1034	1000	796

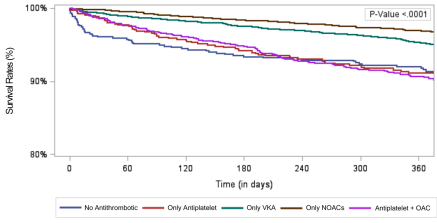
B) CV Death



Number of Subjects at risk for event

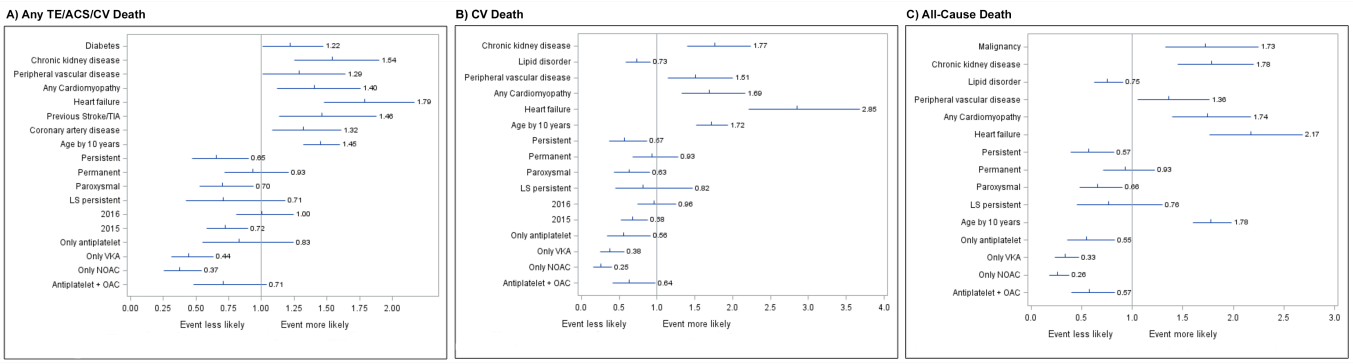
1	698	606	597	587	573	560	436
2	813	699	682	667	656	641	515
3	4514	4118	4082	4048	4005	3930	3033
4	3475	3258	3230	3201	3155	3083	2388
5	1349	1183	1162	1143	1112	1085	871

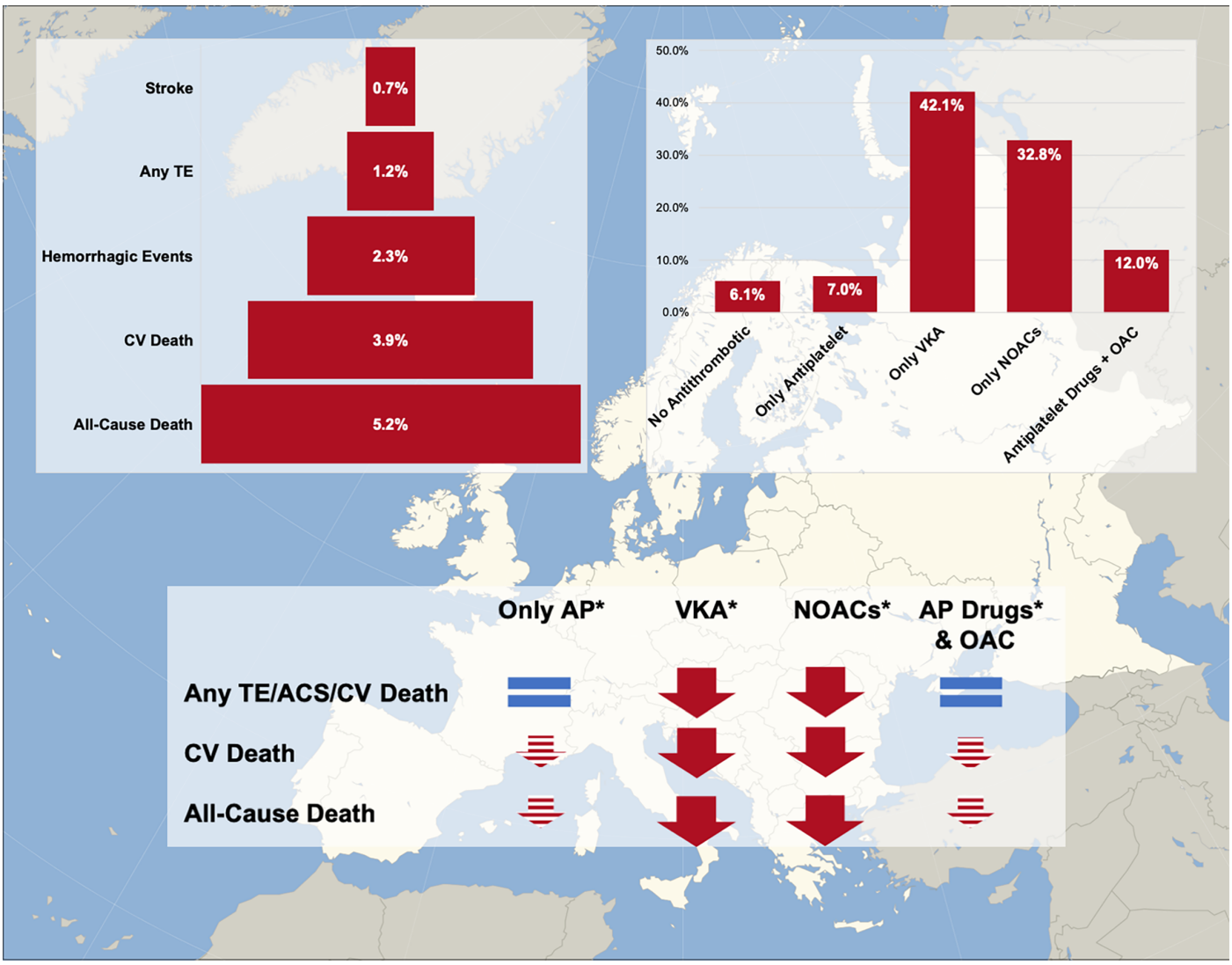
C) All-Cause Death



Number of Subjects at risk for event

1	698	606	597	587	573	560	436
2	813	699	682	667	656	641	515
3	4514	4118	4082	4048	4005	3930	3033
4	3475	3258	3230	3201	3155	3083	2388
5	1349	1183	1162	1143	1112	1085	871


A) Any TE/ACS/CV Death
Diabetes 1.22
Chronic kidney disease 1.54
Peripheral vascular disease 1.29
Any Cardiomyopathy 1.40
Heart failure 1.79
Previous Stroke/TIA 1.46
Coronary artery disease 1.32
Age by 10 years 1.45
Persistent 0.65
Permanent 0.93
Paroxysmal 0.70
LS persistent 0.71
2016 1.00
2015 0.72
Only antiplatelet 0.83
Only VKA 0.44
Only NOAC 0.37
Antiplatelet + OAC 0.71
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
Event less likely
Event more likely
B) CV Death
Chronic kidney disease 1.77
Lipid disorder 0.73
Peripheral vascular disease 1.51
Any Cardiomyopathy 1.69
Heart failure 2.85
Age by 10 years 1.72
Persistent 0.57
Permanent 0.93
Paroxysmal 0.63
LS persistent 0.82
2016 0.96
2015 0.58
Only antiplatelet 0.56
Only VKA 0.38
Only NOAC 0.25
Antiplatelet + OAC 0.64
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Event less likely
Event more likely
C) All-Cause Death
Malignancy 1.73
Chronic kidney disease 1.78
Lipid disorder 0.75
Peripheral vascular disease 1.36
Any Cardiomyopathy 1.74
Heart failure 2.17
Persistent 0.57
Permanent 0.93
Paroxysmal 0.66
LS persistent 0.76
Age by 10 years 1.78
Only antiplatelet 0.55
Only VKA 0.33
Only NOAC 0.26
Antiplatelet + OAC 0.57
0.0 0.5 1.0 1.5 2.0 2.5 3.0
Event less likely
Event more likely


Stroke
0.7%
Any TE
1.2%
Hemorrhagic Events
2.3%
CV Death
3.9%
All-Cause Death
5.2%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
6.1%
7.0%
42.1%
32.8%
12.0%
No Antithrombotic
Only Antiplatelet
Only VKA
Only NOACs
Antiplatelet Drugs + OAC
Only AP*
VKA*
NOACs*
AP Drugs* & OAC
Any TE/ACS/CV Death
CV Death
All-Cause Death

Association between Antithrombotic Treatment and Outcomes at 1-year Follow-Up in Patients with Atrial Fibrillation: The EORP-AF General Long-Term Registry

Giuseppe Boriani, Marco Proietti, Cécile Laroche, Laurent Fauchier, Francisco Marin, Michael Nabauer, Tatjana Potpara, Gheorghe-Andrei Dan, Zbigniew Kalarus, Luigi Tavazzi, Aldo P Maggioni, Gregory Y H Lip
on behalf of the EORP-AF Long-Term General Registry Investigators

Supplementary Materials

Table S1: Pharmacological Treatments at Discharge according to Antithrombotic Therapy at Discharge

	No Antithrombotic	Only Antiplatelet Drugs	Only VKA	Only NOACs	Antiplatelet Drugs + OAC	p
	N= 586	**N= 681**	**N= 4066**	**N= 3167**	**N= 1163**	
Any Antiarrhythmic Drug, n (%)	144 (25.0)	175 (25.8)	1037 (25.6)	960 (30.3)	352 (30.4)	<0.0001
ACE Inhibitors, n (%)	119 (20.7)	331 (48.8)	1765 (43.6)	1174 (37.1)	645 (55.5)	<0.0001
ARBs, n (%)	43 (7.5)	94 (13.9)	793 (19.6)	704 (22.3)	220 (19.0)	<0.0001
DRI, n (%)	1 (0.2)	2 (0.3)	17 (0.4)	14 (0.4)	5 (0.4)	0.9605
Beta Blockers, n (%)	257 (44.6)	497 (73.1)	2814 (69.4)	2184 (69.0)	911 (78.5)	<0.0001
Digoxin, n (%)	35 (6.1)	79 (11.7)	796 (19.6)	333 (10.5)	168 (14.5)	<0.0001
Diuretics, n (%)	107 (18.6)	309 (45.5)	2454 (60.6)	1312 (41.5)	742 (64.1)	<0.0001
Aldosterone Blockers, n (%)	32 (5.6)	112 (16.5)	903 (22.3)	338 (10.7)	324 (27.9)	<0.0001
DHP Calcium Channel Blockers, n (%)	50 (8.7)	125 (18.5)	668 (16.5)	568 (18.0)	222 (19.1)	<0.0001
Statins, n (%)	95 (16.5)	370 (54.7)	1632 (40.3)	1164 (36.8)	821 (70.8)	<0.0001
Oral Antidiabetics, n (%)	41 (7.1)	106 (15.6)	635 (15.7)	418 (13.2)	271 (23.4)	<0.0001
Insulin, n (%)	10 (1.7)	53 (7.8)	215 (5.3)	100 (3.2)	139 (12.0)	<0.0001
Thyroid Hormones, n (%)	28 (4.9)	47 (6.9)	388 (9.6)	266 (8.4)	109 (9.4)	0.0004
Thyroid-Suppressing Drugs, n (%)	10 (1.7)	8 (1.2)	89 (2.2)	50 (1.6)	26 (2.2)	0.1777

Legend: ACE= Angiotensin-Converting Enzyme; ARB= Angiotensin Receptor Blockers; DHP= Dihydropyridine; DRI= Direct Renin Inhibitor; NOACs= Non-vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulation; VKA= Vitamin K Antagonist.

Table S2: Baseline Thromboembolic and Bleeding Risks according to Antithrombotic Therapy at Baseline Discharge

	No Antithrombotic	Only Antiplatelet Drugs	Only VKA	Only NOACs	Antiplatelet Drugs + OAC	p
	N= 586	N= 681	N= 4066	N= 3167	N= 1163	
CHA_2DS_2-VASc *9659**						
Mean (SD)	1.94 (1.92)	3.38 (1.89)	3.26 (1.69)	2.89 (1.68)	3.75 (1.69)	<0.0001
Median [IQR]	1 [0-3]	3 [2-5]	3 [2-4]	3 [2-4]	4 [3-5]	<0.0001
TE Risk Classes, n (%)						<0.0001
Low	238 (40.6)	67 (9.8)	244 (6.0)	311 (9.8)	28 (2.4)	
Moderate	70 (11.9)	56 (8.2)	407 (10.0)	374 (11.8)	74 (6.4)	
High	278 (47.4)	558 (81.9)	3415 (84.0)	2478 (78.3)	1061 (91.2)	
HAS-BLED						
Mean (SD)	0.95 (1.05)	2.08 (1.14)	1.60 (1.01)	1.26 (0.93)	2.28 (1.06)	<0.0001
Median [IQR]	1 [0-2]	2 [1-3]	2 [1-2]	1 [1-2]	2 [2-3]	<0.0001
Bleeding Risk Classes, n (%)						<0.0001
Low	534 (91.1)	451 (66.2)	3381 (83.2)	2871 (90.7)	730 (62.8)	
High	52 (8.9)	230 (33.8)	685 (16.8)	296 (9.3)	433 (37.2)	

Legend: *refers to patients with available data to calculate CHA_2DS_2-VASc score; IQR= Interquartile Range; NOACs= Non-vitamin K Antagonist Oral Anticoagulants; TE= Thromboembolic; OAC= Oral Anticoagulation; SD= Standard Deviation; VKA= Vitamin K Antagonist.

Table S3: Univariate Cox Regression Analysis for Any TE/ACS/CV Death

		Univariate analysis		
	Effect*	**Hazard Ratio**	**95% CI**	**p**
Antithrombotic pattern	Antiplatelet + OAC	1.512	[1.094-2.091]	<.0001
	Only NOAC	0.459	[0.330-0.638]	.
	Only VKA	0.704	[0.518-0.956]	.
	Only antiplatelet	1.505	[1.058-2.141]	.
Entry Year	2015	0.660	[0.546-0.799]	<.0001
	2016	0.885	[0.731-1.071]	.
Region	Northern Europe	0.640	[0.484-0.847]	<.0001
	Southern Europe	0.900	[0.736-1.101]	.
	Western Europe	0.533	[0.424-0.670]	.
Age (per ten years)		1.603	[1.478-1.739]	<.0001
Female gender	Female	1.096	[0.937-1.281]	0.2503
AF type	LS persistent	0.691	[0.432-1.104]	<.0001
	Paroxysmal	0.725	[0.559-0.939]	.
	Permanent	1.312	[1.049-1.640]	.
	Persistent	0.586	[0.438-0.784]	.
Hypertension		1.075	[0.915-1.262]	0.3791
Diabetes mellitus		1.600	[1.354-1.890]	<.0001
Coronary artery disease		2.494	[2.118-2.937]	<.0001
Previous Stroke/TIA		1.756	[1.406-2.193]	<.0001
Heart failure		2.809	[2.393-3.298]	<.0001
Any Cardiomyopathy		1.920	[1.595-2.312]	<.0001
Congenital Heart Disease		1.011	[0.480-2.130]	0.9768
Peripheral vascular disease		2.094	[1.680-2.611]	<.0001
Chronic kidney disease		2.654	[2.227-3.162]	<.0001
Chronic obstructive pulmonary disease		1.701	[1.360-2.127]	<.0001
Lipid disorder		0.992	[0.845-1.165]	0.9210
Malignancy		1.430	[1.109-1.845]	0.0059
EHRA II-III-IV		1.003	[0.859-1.171]	0.9689
Any Antiarrhythmic drug		0.667	[0.551-0.807]	<.0001
ACE-inhibitors		1.007	[0.861-1.177]	0.9342
ARBs		0.914	[0.747-1.118]	0.3813
DRI. Aliskiren		0.354	[0.050-2.516]	0.2995
Beta Blockers		1.021	[0.863-1.208]	0.8084
Digoxin		1.845	[1.536-2.216]	<.0001
Diuretics		2.120	[1.796-2.504]	<.0001
Aldosterone blockers		1.969	[1.661-2.333]	<.0001
DHP Calcium Channel Blockers		1.015	[0.827-1.247]	0.8842
Statins		1.250	[1.071-1.459]	0.0046
Oral antidiabetics		1.335	[1.097-1.625]	0.0040
Insulin		2.115	[1.642-2.724]	<.0001
Thyroïd hormones		1.066	[0.816-1.394]	0.6376
Thyroid-suppressing drugs		1.070	[0.618-1.853]	0.8097

Legend: Antithrombotic pattern: no Antithrombotic as reference; Type of AF: First diagnosed; Entry Year: 2013/2014; Region: Eastern Europe; Symptomatic status: EHRA I as Reference; CI= Confidence Interval.

Table S4: Univariate Cox Regression Analysis for CV Death

		Univariate analysis		
	Effect*	Hazard Ratio	95% CI	p
Antithrombotic pattern	Antiplatelet + OAC	1.444	[0.977-2.136]	<.0001
	Only NOAC	0.363	[0.241-0.549]	.
	Only VKA	0.685	[0.473-0.991]	.
	Only antiplatelet	1.279	[0.828-1.978]	.
Entry Year	2015	0.584	[0.461-0.739]	<.0001
	2016	0.744	[0.586-0.944]	.
Region	Northern Europe	0.468	[0.324-0.675]	<.0001
	Southern Europe	0.795	[0.624-1.013]	.
	Western Europe	0.458	[0.346-0.607]	.
Age (per ten years)		1.954	[1.752-2.179]	<.0001
Female gender	Female	1.159	[0.953-1.410]	0.1401
AF type	LS persistent	0.796	[0.445-1.423]	<.0001
	Paroxysmal	0.657	[0.464-0.931]	.
	Permanent	1.628	[1.224-2.165]	.
	Persistent	0.543	[0.367-0.805]	.
Hypertension		1.080	[0.882-1.323]	0.4560
Diabetes mellitus		1.543	[1.249-1.905]	<.0001
Coronary artery disease		2.355	[1.914-2.898]	<.0001
Previous Stroke/TIA		1.658	[1.244-2.208]	0.0006
Heart failure		4.462	[3.580-5.561]	<.0001
Any Cardiomyopathy		2.591	[2.086-3.218]	<.0001
Congenital Heart Disease		1.166	[0.482-2.816]	0.7335
Peripheral vascular disease		2.591	[2.000-3.357]	<.0001
Chronic kidney disease		3.468	[2.816-4.273]	<.0001
Chronic obstructive pulmonary disease		1.746	[1.322-2.305]	<.0001
Lipid disorder		0.830	[0.674-1.021]	0.0783
Malignancy		1.628	[1.198-2.214]	0.0019
EHRA II-III-IV		0.977	[0.804-1.188]	0.8177
Any Antiarrhythmic drug		0.661	[0.519-0.843]	0.0008
ACE-inhibitors		1.002	[0.823-1.221]	0.9831
ARBs		0.768	[0.587-1.005]	0.0541
DRI. Aliskiren		0.626	[0.088-4.434]	0.6389
Beta Blockers		1.023	[0.828-1.264]	0.8349
Digoxin		2.347	[1.890-2.915]	<.0001
Diuretics		3.532	[2.789-4.473]	<.0001
Aldosterone blockers		2.588	[2.111-3.174]	<.0001
DHP Calcium Channel Blockers		0.790	[0.596-1.048]	0.1017
Statins		1.039	[0.854-1.265]	0.6999
Oral antidiabetics		1.249	[0.971-1.607]	0.0834
Insulin		2.309	[1.698-3.138]	<.0001
Thyroïd hormones		1.036	[0.736-1.459]	0.8381
Thyroid-suppressing drugs		1.463	[0.803-2.663]	0.2136

Legend: Antithrombotic pattern: no Antithrombotic as reference; Type of AF: First diagnosed; Entry Year: 2013/2014; Region: Eastern Europe; Symptomatic status: EHRA I as Reference; CI= Confidence Interval.

Table S5: Univariate Cox Regression Analysis for All-Cause Death

		Univariate analysis		
	Effect*	**Hazard Ratio**	**95% CI**	**p**
Antithrombotic pattern	Antiplatelet + OAC	1.118	[0.810-1.542]	<.0001
	Only NOAC	0.352	[0.253-0.489]	.
	Only VKA	0.539	[0.399-0.728]	.
	Only antiplatelet	1.029	[0.716-1.478]	.
Entry Year	2015	0.727	[0.590-0.896]	0.0073
	2016	0.915	[0.740-1.130]	.
Region	Northern Europe	0.678	[0.497-0.925]	<.0001
	Southern Europe	0.984	[0.786-1.231]	.
	Western Europe	0.627	[0.489-0.805]	.
Age (per ten years)		2.032	[1.846-2.236]	<.0001
Female gender	Female	1.143	[0.964-1.356]	0.1232
AF type	LS persistent	0.656	[0.391-1.101]	<.0001
	Paroxysmal	0.626	[0.469-0.837]	.
	Permanent	1.383	[1.089-1.757]	.
	Persistent	0.490	[0.351-0.685]	.
Hypertension		1.106	[0.927-1.321]	0.2636
Diabetes mellitus		1.557	[1.296-1.869]	<.0001
Coronary artery disease		2.084	[1.740-2.496]	<.0001
Previous Stroke/TIA		1.557	[1.207-2.008]	0.0007
Heart failure		3.216	[2.687-3.850]	<.0001
Any Cardiomyopathy		2.290	[1.885-2.782]	<.0001
Congenital Heart Disease		1.059	[0.474-2.367]	0.8884
Peripheral vascular disease		2.333	[1.849-2.944]	<.0001
Chronic kidney disease		3.268	[2.721-3.925]	<.0001
Chronic obstructive pulmonary disease		2.192	[1.753-2.741]	<.0001
Lipid disorder		0.811	[0.677-0.971]	0.0224
Malignancy		2.240	[1.766-2.841]	<.0001
EHRA II-III-IV		0.908	[0.767-1.076]	0.2653
Any Antiarrhythmic drug		0.637	[0.515-0.789]	<.0001
ACE-inhibitors		0.945	[0.795-1.123]	0.5232
ARBs		0.755	[0.596-0.955]	0.0190
DRI. Aliskiren		0.942	[0.235-3.770]	0.9323
Beta Blockers		0.917	[0.765-1.098]	0.3464
Digoxin		1.983	[1.630-2.413]	<.0001
Diuretics		2.824	[2.326-3.427]	<.0001
Aldosterone blockers		2.114	[1.759-2.540]	<.0001
DHP Calcium Channel Blockers		0.814	[0.639-1.038]	0.0967
Statins		0.997	[0.840-1.183]	0.9693
Oral antidiabetics		1.237	[0.993-1.541]	0.0579
Insulin		2.320	[1.777-3.028]	<.0001
Thyroïd hormones		1.047	[0.778-1.408]	0.7615
Thyroid-suppressing drugs		1.411	[0.830-2.399]	0.2029

Legend: Antithrombotic pattern: no Antithrombotic as reference; Type of AF: First diagnosed; Entry Year: 2013/2014; Region: Eastern Europe; Symptomatic status: EHRA I as Reference; CI= Confidence Interval.

APPENDIX

EURObservational Research Programme Atrial Fibrillation (EORP-AF) Long-Term General Registry Committees and Investigators

Executive committee: G.Boriani (Chair), G.Y.H. Lip, L. Tavazzi, A. P. Maggioni, G-A. Dan, T. Potpara, M. Nabauer, F. Marin, Z. Kalarus, L. Fauchier, R. Ferrari, A. Shantsila.

Steering Committee (National Coordinators): A. Goda, G. Mairesse, T.Shalganov, L. Antoniades, M. Taborsky, S. Riahi, P. Muda, I. García Bolao, O. Piot, M. Nabauer, K. Etsadashvili, E.Simantirakis, M. Haim, A. Azhari, J. Najafian, M. Santini, E. Mirrakhimov, K.a Kulzida, A. Erglis, L. Poposka, M. Burg, H. Crijns, Ö. Erküner, D. Atar, R. Lenarczyk, M. Martins Oliveira, D. Shah, G-A. Dan, E. Serdechnaya, T. Potpara, E. Diker, G.Y.H. Lip, D. Lane.

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