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CLINICAL MANAGEMENT, COMORBIDITIES, AND ASSOCIATED ADVERSE OUTCOMES IN PATIENTS WITH ATRIAL FIBRILLATION: ANALYSES FROM A EUROPEAN COHORT STUDY ON MORE THAN 11.000 PATIENTS

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INTRODUCTION

Definition, diagnosis, and classification of atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia found in clinical practice, and its incidence and prevalence are rapidly increasing worldwide (1-5). AF is associated with a fivefold increase in the risk for stroke and a twofold increase in the risk for all-cause mortality (6-10).

Atrial fibrillation is defined as a supraventricular tachyarrhythmia, and it is characterized by disorganized atrial electrical activation leading to an ineffective atrial contraction. The electrocardiographic features of AF consist of low-amplitude baseline oscillations (fibrillatory or f waves) and an irregularly irregular ventricular rhythm, more in details AF is characterized by (11):

a. Irregularly irregular R-R intervals (when atrioventricular conduction is not impaired)
b. Absence of distinct P waves and irregular atrial activations

An ECG documentation (12-lead ECG recording or a single-lead ECG tracing of ≥ 30 s) is essential to confirm the diagnosis of clinical AF (11). The presence of arrhythmia-related symptoms is not required for the definition of clinical AF, which therefore can be symptomatic or asymptomatic (12, 13)
Recently, the term Atrial High Rate Episodes (AHREs) has been introduced (14, 15). Indeed, given the ability of cardiac implantable electronic devices (CIEDs) to continuously monitor, analyze and record atrial activity, AHREs are frequently encountered in clinical practice (16-19). Despite AHREs carrying a lower risk of stroke or thromboembolic (TE) events compared to clinical AF, it is important to acknowledge that this risk is not negligible(14, 15, 20, 21). This becomes even more significant if we consider that most patients with AHRE may develop atrial tachyarrhythmias lasting more than 24 hours or progress to clinical AF during the follow-up (22).

Subclinical AF may include AHRE that are confirmed to be AF, atrial flutter, or an atrial tachycardia, or AF episodes detected by an insertable cardiac monitor or wearable monitor and confirmed by visually reviewed intracardiac electrograms or ECG-recorded rhythm (**Figure 1**)

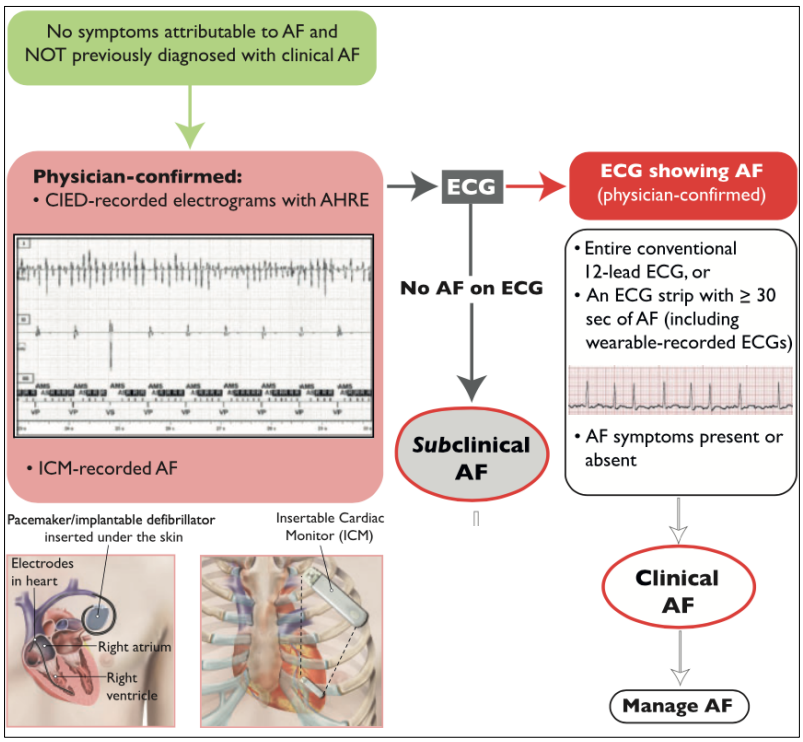

Figure 1. Diagnosis of clinical AF and AHRE/subclinical AF
From ref. (11)
AF = atrial fibrillation; AHRE = atrial high rate episode; CIED = cardiac implantable electronic device; ECG = electrocardiogram; ICM = insertable cardiac monitor

According to the latest European Society of Cardiology (ESC) Guidelines on AF published in 2020, there are five types of AF that can be distinguished based on the presentation, duration, and spontaneous termination of arrhythmia (11):

a. **First diagnosed**. AF that has not been diagnosed before, irrespective of its duration or the presence and severity of AF-related symptoms.
b. **Paroxysmal**: AF that terminates spontaneously (in most cases within 48 hours) or with intervention within 7 days of onset.
c. **Persistent**: AF episode that is continuously sustained beyond 7 days, including episodes that are terminated by cardioversion, either with drugs or by electrical cardioversion

d. **Long-standing persistent**: Continuous AF lasting for >12 months when it is decided to adopt a rhythm control strategy.
e. **Permanent**: AF that is accepted by the patient and physician and no further rhythm control interventions are pursued to restore or maintain sinus rhythm. Hence, the term permanent AF represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF.

Epidemiology

AF is a global health care problem with future projections estimating a growth in its prevalence and incidence at least two-fold by 2060 (23-26) (**Figure 2**).
Based on recent data, is it estimated more than 46.3 million individuals worldwide had prevalent AF/atrial flutter in 2016 (**Figure 3**) (1, 11, 26). Due to the aging population and increasing presence of comorbidities and cardiovascular risk factors, the prevalence and incidence of AF are estimated to exponentially rise in the next 50 years. Indeed besides age, the increasing burden of common comorbidities such as hypertension, diabetes mellitus (DM), heart failure (HF), coronary artery disease (CAD), chronic kidney disease (CKD), obesity, and obstructive sleep apnoea (OSA) are also important to determine the prevalence and incidence of AF (27-30).

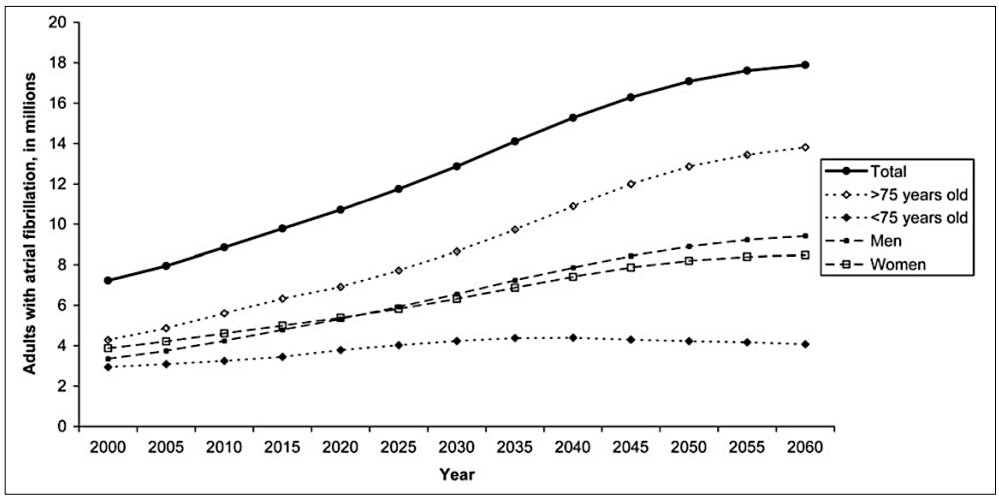

Figure 2. Projected number of adults with AF in the European Union between 2000 and 2060
From ref. (31)

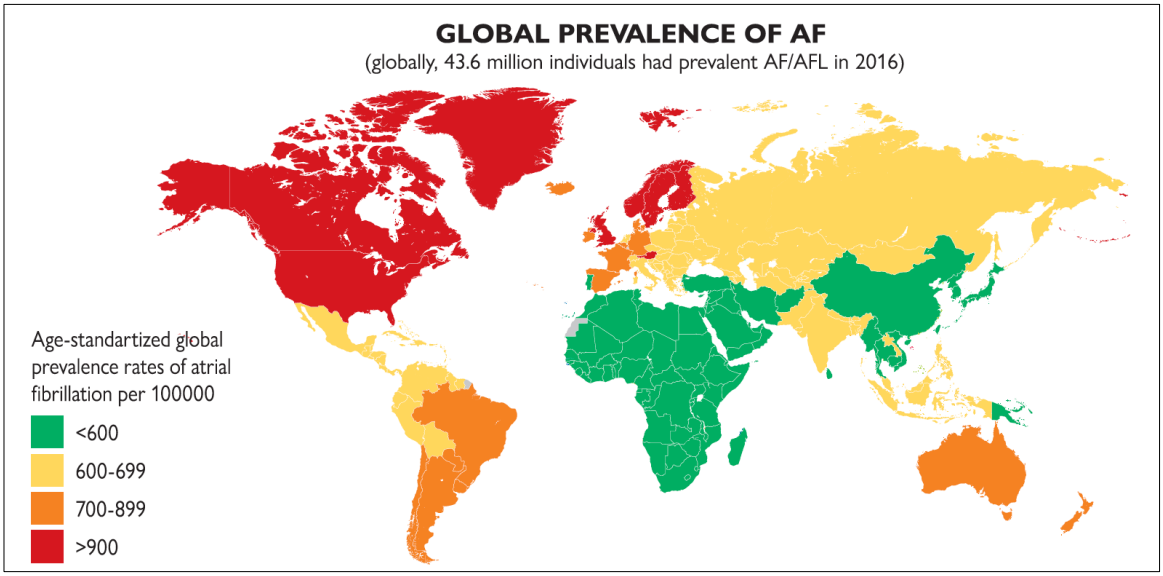

Figure 3. Global prevalence of atrial fibrillation
From ref. (11)
AF= atrial fibrillation; AFL= atrial flutter

Large epidemiological studies have been reported that the prevalence of AF in the general population of Europe ranged from 1.9% in Italy, Iceland, and England to 2.3% in Germany and 2.9% in Sweden while in the USA the prevalence of AF has increased by 0.3% per year in individual older than 65 years, with an absolute growth of 4.5% (from 4.1% to 8.6%) in the period 1993–2007 (1, 32).

Nevertheless, despite several large studies have been conducted thus far, the true prevalence of AF may be underestimated, especially across different geographic regions of the world (9). Different community-based studies investigating the racial and ethnic differences in AF prevalence, showed a large variation across different regions of the world (33, 34).

The lifetime risk of AF is 1 in 3 individuals of European ancestry at an index age of 55 years but this risk is greatly influenced by CV risk factors, comorbidities, and genetic factors (**Figure 4**)(9, 35, 36).

Interestingly, there are also some differences regarding sex differences in the epidemiology of AF with some studies reporting that age-adjusted incidence of AF may be higher in men compared with women (26, 37-39).

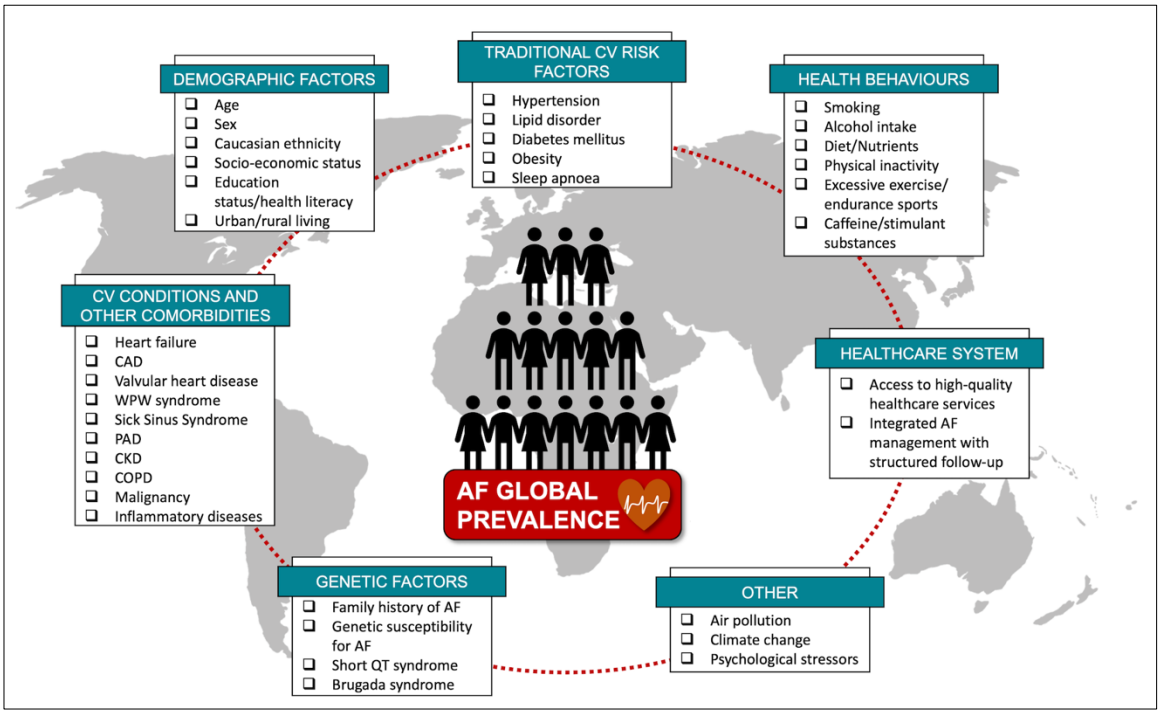

Figure 4. Determinants of variations in global AF prevalence
From ref. (9)
AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; PAD, peripheral artery disease; WPW, Wolff-Parkinson-White

Pathophysiology, clinical features, and associated adverse outcomes

The pathophysiology of AF is complex involving interconnected triggers, perpetuators, and substrate alterations (40-42). Firstly, AF often shows a natural progression from self-terminating episodes to a more sustained or permanent form which is characterized by advancing atrial structural remodelling (43-48). Importantly, a progression towards a more sustained from of AF (i.e. from paroxysmal to permanent AF) may be significantly associated with an increased risk of ischemic stroke/systemic embolism (49-51). Different comorbidities may affect the development, evolution and perpetuation of AF, as well as the clinical course of AF patients, with influences on AF temporal patterns and AF burden. The

effect of the most common comorbidities affecting AF incidence, temporal pattern and outcomes are shown in **Figure 5**.

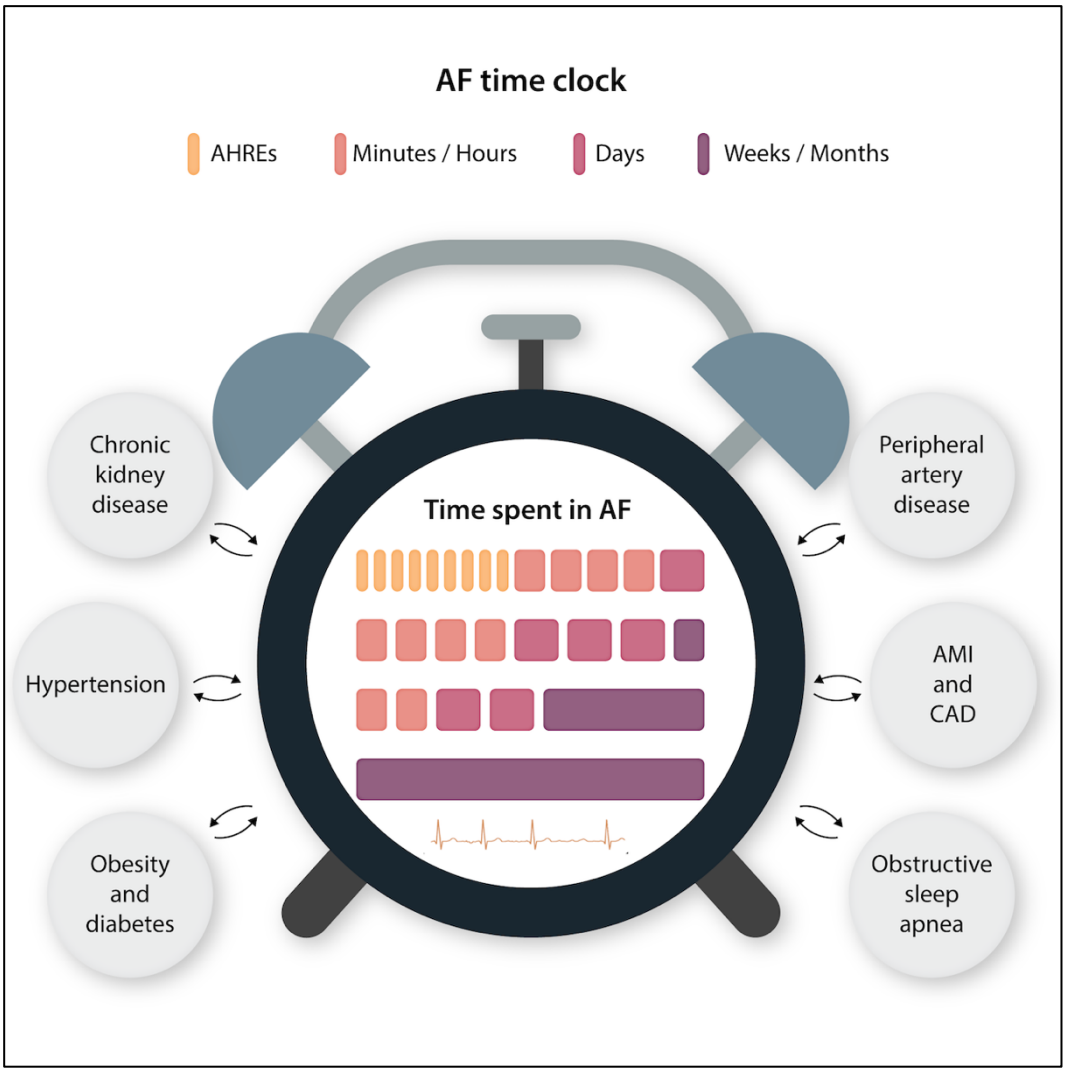

Figure 5. Atrial fibrillation time clock: the effect of a series of comorbidities affecting AF temporal pattern.
From ref. (41)
AF, atrial fibrillation; AMI, acute myocardial ischaemia; CAD, coronary artery disease.

Recently, the term atrial cardiomyopathy, defined as “any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations” has been introduced (52). Advancements in comprehending the mechanisms and thrombogenicity of AF have prompted a re-evaluation of the significant role played by the atria in the pathophysiology of cardiomyopathies. Either structural and functional modifications of the atria may act as a favourable substrate for the development, maintenance, and progression of AF (30, 53). The pathophysiological basis of AF

alterations, either functional or anatomical, is currently more complex than in the past (**Figure 6**) (40, 54).

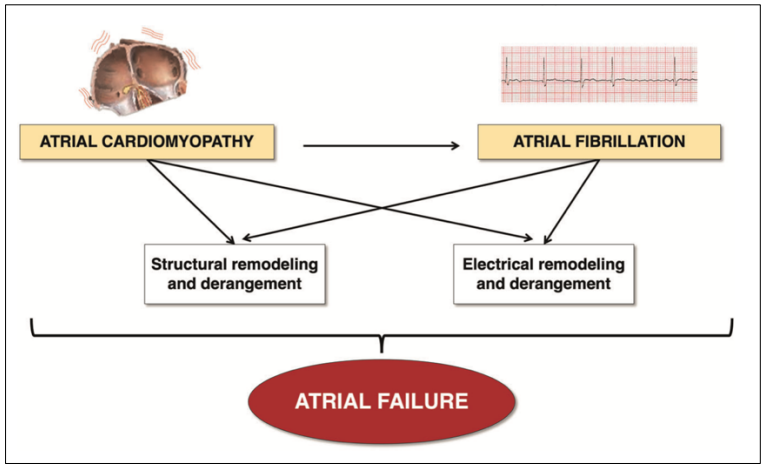

Figure 6. The complex interplay between atrial cardiomyopathy atrial fibrillation, and atrial failure
From ref. (40)

There is a complex interplay between atrial fibrillation, underlying atrial and ventricular factors, comorbidities, and adverse outcomes (stroke, cardiovascular mortality) as shown in **Figure 7** (11, 41, 55).

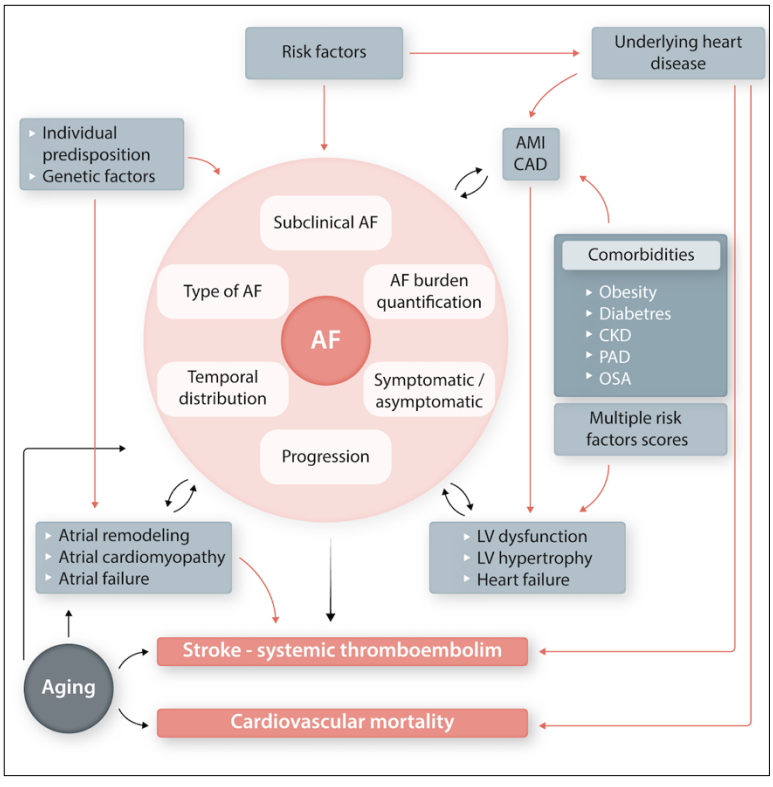

Figure 7. The complex interplay between atrial fibrillation, underlying atrial and ventricular factors, comorbidities, and adverse outcomes (stroke, cardiovascular mortality)
From ref. (41)
AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; LV, left ventricular; OSA, obstructive sleep apnoea; PAD, peripheral artery disease.

Figure 8 shows the clinical presentation of AF and AF-related outcomes (11).
It is important to note that the clinical presentation as well as associated comorbidities, and clinical management of patients with AF are dynamic processes that may change over time (56, 57).
As stated before, patients with AF are at increased risk of stroke, HF, cognitive impairment, and all-cause mortality. This risk may be independent of the clinical presentation of AF (i.e. symptomatic or asymptomatic AF) and it is be even more pronounced in asymptomatic patients since the diagnosis of AF may be delayed in these patients. The most common symptoms of AF are palpitations, fatigue, dyspnoea and/or asthenia.

Despite the presence of symptoms is a key element in the decision between rate or rhythm control therapy, it is not completely elucidated if asymptomatic or symptomatic clinical presentations are related to outcomes (58). Some studies reported similar risk for TE, in particular ischemic stroke and death, in patients with asymptomatic AF compared with symptomatic patients. On the other hand, other studies have reported an association between mortality, TE, and silent AF(13, 59-63). However, in a recent meta-analysis (12), there were no differences between symptomatic and asymptomatic patients regarding the risks of all-cause death, cardiovascular death, stroke and stroke/TE. Taken together these results highlight that adverse outcomes in AF patients are unrelated to symptomatic status of their clinical presentation and the adoption of management strategies in AF patients should not be based on symptomatic clinical status (12, 64).

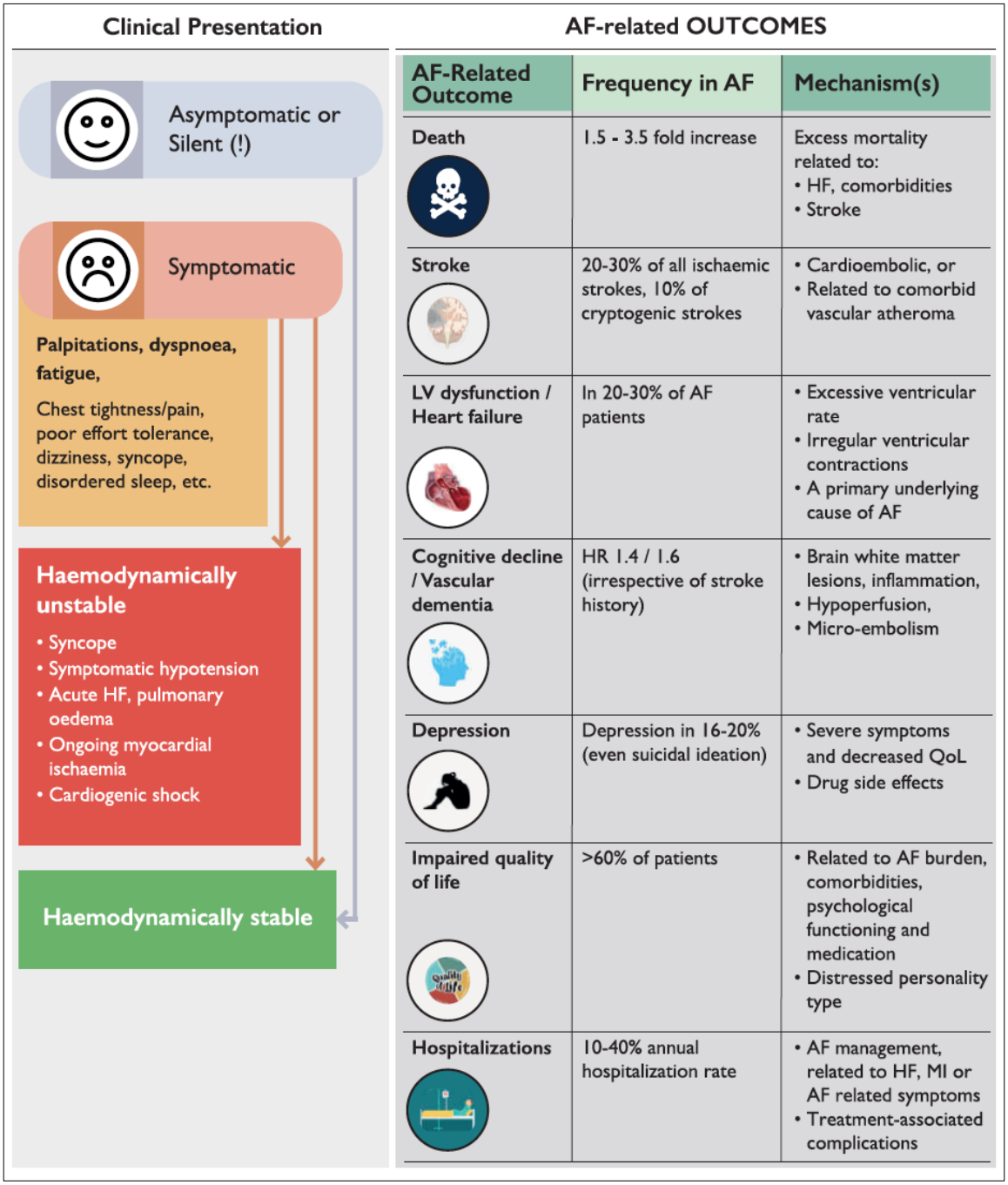

Figure 8. Clinical presentation of AF and AF-related outcomes
From ref. (11)
AF = atrial fibrillation; HF = heart failure; HR = Hazard Ratio; LV = left ventricle; MI=myocardial infarction; QoL= quality of life

Nevertheless, despite the great advances in our knowledge, AF is still associated with adverse outcomes and particularly with a significantly increased risk of all-cause mortality, dementia and hospitalization (**Figure 8**) (7, 11, 65-73). Notwithstanding the continuous improvement in clinical management, all-cause mortality remains substantially high reflecting an increasing age-dependent burden

of co-morbidities and stressing the need for an integrated and holistic approach of AF patients (5). The epidemiology of AF has significantly changed, and AF patients are often old, frail and more affected by several cardiovascular and non-CV comorbidities (3, 4, 74-78). Clinical complexity is becoming more common among individuals with AF and the growing recognition of this clinical complexity led to substantial changes in the management and care of AF patients (79, 80). Multimorbidity, polypharmacy, and frailty can be viewed as distinct facets of clinical complexity (79-81). While these conditions frequently coexist, each of them plays a unique role in shaping AF patients' prognosis (79, 80).

Integrated clinical management of patients with atrial fibrillation

The integrated "Atrial fibrillation Better Care" (ABC) Pathway

Given the complexity of AF patients, there is a need for a simple holistic pathway that streamlines the integrated care of patients across all healthcare levels and among different specialities (5). The Atrial fibrillation Better Care (ABC) pathway ('A' Anticoagulation/Avoid stroke; 'B' Better symptom management; 'C' Cardiovascular and Comorbidity optimization) has been recently introduced (11). Indeed, a more comprehensive management of AF patients which would go beyond the 'mere' prescription of OAC should be pursued (82, 83). Each step of the ABC pathway represents one of the pivotal pillars of the management of AF:

i. (A) Anticoagulation/Avoid stroke, i.e. optimizing treatment with OAC;
ii. (B) Better symptom management with patient-centred decisions on rate or rhythm control;
iii. (C) Cardiovascular and other Comorbidities management with optimal medical therapy, including lifestyle changes

The integrated holistic management of AF patients is thus essential to improve their outcomes and the formal introduction of the CC (Confirm AF and Characterize AF) to ABC (Atrial fibrillation Better Care) pathway into the guidelines addresses this (84)

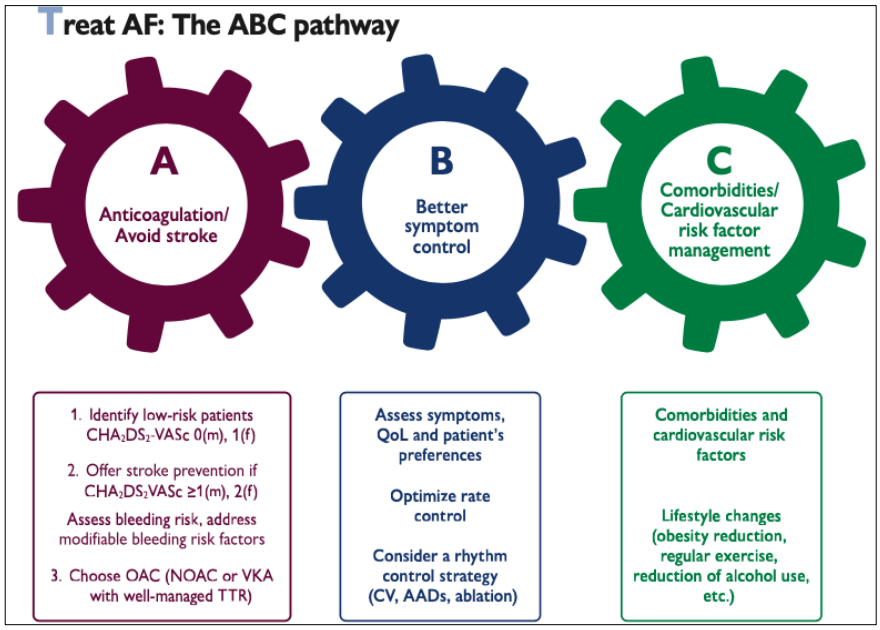

Figure 9. The ABC Pathway
From ref. (11)
AADs: antiarrhythmics drugs; CV= cardioversion; NOAC= Non-Vitamin K Oral Anticoagulants; OAC= oral anticoagulants; QoL= Quality of Life; TTR= Time in Therapeutic Range; VKA= Vitamin K Antagonists

To date, several studies extensively reported that the implementation of the ABC pathway is significantly associated with a lower risk of all-cause death and stroke, lower rates of CV events, lower health-related costs compared with usual care (84-91).

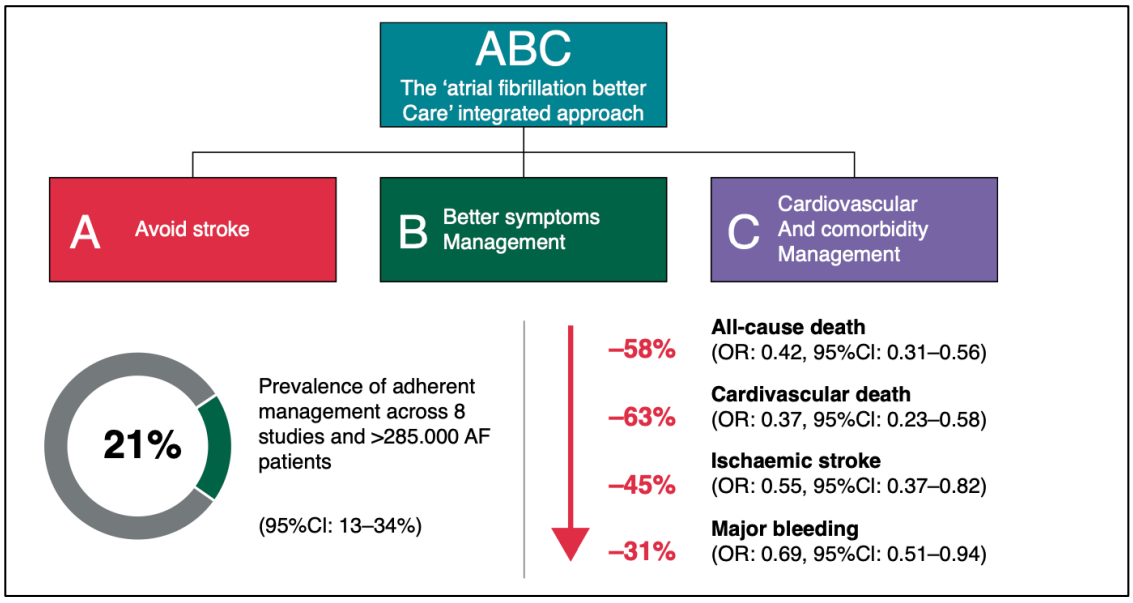

Figure 10 The ABC pathway
From refs. (5, 92)
A: Avoid stroke with Anticoagulation, where the default is stroke prevention unless the patient is at low risk; B: Better symptom control, with patient-centred, symptom-directed decisions on rate or rhythm control; and C: Cardiovascular risk factor and comorbidity optimization, including attention to lifestyle changes, patient's psychological morbidity, and consideration of patient values and preferences.

The ABC pathway has been tested in several retrospective and prospective studies, clinical trials as well as post hoc analysis from adjudicated outcomes from clinical trials from different regions of the world (5, 81, 84, 86, 88, 93-95).

For example, the prospective cluster randomized Mobile Atrial Fibrillation Application (mAFA)-II clinical trial (90), showed a significant reduction in the primary outcome with the ABC pathway intervention using a mHealth App, compared to usual care. In a recent analysis from the EORP AF General Long Term Registry, patients managed adherent to the ABC pathway compared to non-adherent, were associated with lower rates of adverse outcomes, including all-cause death (3.0% vs. 6.4%) at 1-year follow-up. Of note, ABC adherent care had a lower risk of any TE/ACS/CV death (HR: 0.59, 95% CI: 0.44–0.79), CV death (HR: 0.52, 95% CI: 0.35–0.78), and all-cause death (HR: 0.57, 95% CI: 0.43–0.78) (96).

CLINICAL MANAGEMENT, COMORBIDITIES, AND ASSOCIATED ADVERSE OUTCOMES IN PATIENTS WITH ATRIAL FIBRILLATION: ANALYSES FROM A EUROPEAN COHORT STUDY ON MORE THAN 11.000 PATIENTS

Background and general aim of the project

Management of AF poses significant challenges in clinical practice due to the complexity of AF patients and ongoing advances in clinical treatments. Consequently, there is a growing need for standardized programs designed to gather "real-world" clinical practice data (97). These data should encompass the epidemiology, diagnostic, therapeutic, and management practices, as well as adherence to guidelines. Moreover, given the existing differences across European countries between epidemiology, healthcare and socio-economic systems, there is a need for programmes aimed at collecting a large amount of data and assessing adherence to the guidelines (97).

There has been an exponential increase in the number of studies based on "real-world "AF patients over the past two decades. High-quality prospective studies and registries are essential to provide a "real-world snapshot" of clinical practices across European countries (98).

In 2000, the ESC initiated the European Heart Survey (EHS) that included a large series of surveys and registries in major cardiovascular fields of interest. The EHS collected a large amount of data on over 100,000 patients across 35 countries and published more than 70 scientific papers in indexed journals.

The EHS focused on AF, conducted from 2003 to 2004, was one of the first large-scale prospective studies reporting real-world AF management. It enrolled more than 5000 patients from 35 ESC member countries, providing valuable insights into AF treatment and therapy (58, 99, 100).

Given the success of the EHS, the ESC launched the Eurobservational Research Programme (EORP) in 2009. The EORP, based on observational data with robust scientific methodology, includes general registries for major cardiovascular diseases, sentinel registries for new procedures' impact, and specific registries for

rare or challenging diseases. The EORP-AF pilot registry, initiated in 2012, assessed clinical epidemiology and medical management of AF in nine European countries (65, 67, 101). In 2012, the EORP started the EORP-AF Long-Term General Registry, a multicenter prospective study collecting data from 250 centers in 27 ESC countries, enrolling more than 11,000 patients from 2013 to 2016 with long-term follow-up (3, 75).

The general aim of this PhD project was to investigate the epidemiology, comorbidities, and clinical management of AF in this contemporary cohort of European patients enrolled in the EURObservational Research Programme on AF Long-Term General study. Here, we present three distinct analyses that primarily underscore the complexity of epidemiology, pathophysiology, and clinical management of European AF patients in daily clinical practice.

Specifically, the three analyses are:

- **Analysis n° 1: Impact of AF clinical phenotypes on management and outcomes:** To describe AF patients' clinical phenotypes and analyze the differential clinical course using a machine-learning-based statistical technique (i.e. hierarchical cluster analysis)

- **Analysis n° 2: Real-world applicability and impact of early rhythm control:** To evaluate the real-world applicability and impact of an early rhythm control strategy (according to the selection criteria of recent randomized clinical trials) in patients with AF.

- **Analysis n° 3: Impact of malignancy and adherence to the ABC pathway:** To evaluate the outcomes of patients with malignancy and to evaluate the impact of adherence to ABC pathway in this high-risk subgroup of AF patients.

The rationale behind the choice to present and discuss these analyses is essentially motivated by the following: (i) Conventional classification of AF patients only based on disease subtype or arrhythmia patterns may not adequately

characterize AF population and there is a need for phenotyping characterization; (ii) The increasing role of rhythm control in AF patients and especially the so-called "early rhythm control strategy" has been one of the most debated issue in the field of AF in the last two decades and new evidence is needed; (iii) Managing high-risk subgroup patients, such as those with AF and cancer, is challenging, and there is limited evidence supporting their appropriate clinical care.

This choice aims to provide a comprehensive view supported by recent data on the clinical complexities of AF "real-world" patients.

Methods

Study design and cohort

The EORP-AF Long-Term General is a prospective, observational, large-scale multicentre study on AF patients in current cardiology practice held by the ESC and endorsed by the European Heart Rhythm Association (EHRA).

The registry enrolled AF consecutive patients in 250 centres from 27 participating ESC Countries. Both in- and outpatients were consecutively enrolled when presenting with AF as a primary or secondary diagnosis from October 2013 to September 2016. All patients were ≥ 18 years old and provided written informed consent form. The qualifying AF event had to be recorded by a 12-lead ECG, 24h ECG Holter, or other electrocardiographic documentation within the 12 months before enrolment. Exclusion criteria were the following: (i) no objective proof of AF; (ii) being previously enrolled in the EORP-AF Pilot Registry; or (iii) being or planned to be enrolled in a pharmacological interventional clinical trial.

Institutional review board approved the study protocol for every institution. The study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

All data about baseline clinical characteristics, previous clinical history, and previous interventional procedures, were collected by any investigators at the enrolment. All the characteristics regarding the main reasons for admission/consultation, symptomatic status, specific diagnostic procedures and

interventional procedures performed during the admission/consultation, were collected at the moment of enrolment.

Thromboembolic risk was defined according to CHA_2DS_2-VASc score. '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. '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 score.

Participating countries were grouped in European regions as follows: (i) Northern Europe—Denmark, Estonia, Latvia, Norway, UK; (ii) Western Europe—Belgium, France, Germany, Netherlands, Switzerland; (iii) Eastern Europe—Bulgaria, Czech Republic, Georgia, Kazakhstan, Kyrgyzstan, Poland, Romania, Russia; and (iv) Southern Europe—Albania, FYR Macedonia, Italy, Malta, Montenegro, Portugal, Serbia, Spain, Turkey.

Additional details on the EORP-AF study design, baseline, and 1-year follow-up results have been previously reported (3, 75, 96).

Multimorbidity, frailty, polypharmacy, and malignancy

Among the three different analyses, we used the following definitions: (i) Multi-morbidity was defined as the concomitant presence of at least 2 different comorbidities (102); (ii) Frailty was defined based on a 40-item frailty index ≥ 0.25 built according to Rockwood and Mitnitski (103); (iii) Polypharmacy was defined as the concomitant use of ≥ 5 drugs (104) and (iv) active malignancy was defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment had been administered within 6 months; or haematological cancer that is not in complete remission (105, 106).

Definition of early rhythm control

Early rhythm control was defined at the moment of enrolment visit or discharge following hospital admission. All patients who received a rhythm control intervention during the index episode, such as electrical cardioversion, pharmacological cardioversion, catheter ablation, or were prescribed an antiarrhythmic drug (Class Ia, Class Ic, Class III) at discharge, were included in the

'early rhythm control' group. All the other patients prescribed only with beta-blockers, digoxin, or non-dihydropyridine calcium-channel blockers, as rate control drugs, were included in the 'no rhythm control' group.

Evaluation of quality of life and health-care resources use

Quality of life was evaluated at baseline and follow- up using the EQ-5D-5L questionnaire that consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/). The descriptive system contains five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five possible levels for each dimension (no problems, slight problems, moderate problems, severe problems and extreme problems), generating 5^5 = 3125 unique health states. Using a trade-off value set according to previous report, we transformed each of the levels into a single numeric value, with the lowest values corresponding to better health (47). Additionally, by combining the single values, we translated the five-digit health state into a single index, the Health Utility Score (HUS) by subtracting each value from 1. The best possible health in each dimension (= 11,111) corresponded to an HUS of 1.0 (perfect health). An HUS of 0 is equivalent to death. The visual analogue scale (VAS) was used for patients to self-rate their current health status, ranging from 0 (worst health imaginable) to 100 (best health imaginable). We also assessed the use of health-care resources, the overall length of stay, the occurrence and number of cardiology and internal medicine/general practitioner visits, as well as the emergency room (ER) admissions and hospital readmissions (both CV and non-CV related) during the follow-up.

ABC pathway adherence

The ABC pathway was evaluated according to its original definition (87) and specific criteria used for ABC adherence definitions were:

- The **"A" criterion** was fulfilled if the patient was properly treated with OAC according to thromboembolic risk; patients not qualifying for OAC (i.e. CHA_2DS_2VASc=0 in males or =1 in females) and not treated with OAC, also qualified for the 'A' criterion; in case of treatment with a vitamin K antagonist (VKA) we considered a time in therapeutic range (TTR) ≥70%

- The “**B” criterion** was fulfilled if the patient presented with an EHRA score of I (no symptoms) or II (mild symptoms not affecting daily life); The ‘B’ criterion refers to the actual symptoms control, which is considered pivotal, rather than the attempt to control the symptomatic presentation.

- The **“C” criterion** was fulfilled if the patient was appropriately managed for the most frequent comorbidities associated with AF [i.e. hypertension, CAD, PAD, HF, stroke/ TIA, and diabetes mellitus]. In detail, a patient qualified for adherence to the “C” criterion when was treated according to the best medical regimens defined by current clinical guidelines. Optimal medical treatment was defined as follows: (i) for hypertension, a controlled blood pressure ≤ 140/90 mmHg; (ii) for CAD, treatment with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and statins; (iii) for PAD, treatment with statins; (iv) for previous stroke/TIA, treatment with statins; (v) for HF, treatment with ACE inhibitors/angiotensin receptor blockers and beta- blockers; (vi) for diabetes mellitus, treatment with insulin or oral antidiabetics. If the patient had ≥ 1 comorbidity described above, proper treatment for all the conditions was required to qualify for adherence to the “C” criterion.

Patients who met all the three criteria were defined as “ABC-adherent”, otherwise they were considered “ABC non-adherent”. Furthermore, we evaluated the number of ABC criteria fulfilled.

Follow-up and adverse outcomes

All follow-up was performed at 1 and 2 years after enrolment. The following incident major adverse clinical events were recorded: (i) all-cause death; (ii) any haemorrhagic events; (iii) any TE (including stroke, TIA, and any peripheral embolism); (iv) any ACS; (v) CV-death and (vi) any myocardial revascularization (including percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]). Haemorrhagic events were not specifically defined, but all significant events which investigators became aware, were reported. All data about

hospital admissions (any admission, AF-related, CV-related and non CV-related) were also recorded.

All-cause death, Major Adverse Cardiovascular Events (MACE, as the composite of the any TE/ACS/CV death), the composite outcome of any TE/any ACS/CV death/all-cause death and the net clinical outcome (NCO), defined as a composite of all-cause death, any TE, ACS and major bleeding, were the main endpoints of the analyses.

Investigators reported all available details about incident major adverse clinical events on the centralized electronic case report form.

Statistical analysis

Continuous variables were expressed as mean [SD] or median [IQR]. Among-group comparisons were made using parametric or non-parametric tests, Mann-Whitney U or Kruskal–Wallis test when appropriate. Categorical variables were reported as counts and percentages. Among-group comparisons were made using a $\chi 2$ test or Fisher's exact test (if any expected cell count was less than five). All logistic regression analysis results were reported as odds ratio (OR) and 95% confidence interval (CI). All Cox regression analysis results were reported as hazard ratio (HR) and 95% CI. All linear regression analyses were reported as Beta coefficient and 95% CI. Missing data were considered as missing with no imputation analysis performed. A two-sided $p<0.05$ was considered statistically significant. All analyses were performed using SPSS statistical software (IBM Corp. Released 2019. IBM SPSS Statistics for Macintosh, NY: IBM Corp).

A detailed description of the statistical analyses performed for each of the three sub-analyses is reported below.

Analysis n°1 – Statistical analysis and clustering process

For the purpose of this analysis, we performed an agglomerative hierarchical cluster analysis to find clusters of patients based on pre-specified clinical variables. The hierarchical cluster analysis was based on Ward's Minimum Variance Method

to minimize the total within-cluster variance and we selected the squared Euclidean as measure of distance or dissimilarity. The squared Euclidean distance was used since only dichotomous variables were selected. The aim of the analysis was to identify the optimal number of clusters that were homogenous and indicative of a clinically relevant phenotypic subgroup of AF patients without a priori knowledge of the outcomes. We a priori selected 22 clinical variables as follows: age, sex, heart failure, coronary artery disease, valvular disease, hypertension, diabetes mellitus, ischemic stroke, peripheral ischemic events, liver disease, chronic obstructive pulmonary disease, anaemia, dementia, any cardiomyopathy, hyperthyroidism, hypothyroidism, chronic kidney disease, obstructive sleep apnoea syndrome, malignancy, body mass index. All variables were considered as categorical (i.e. present or absent). Age and body mass index were dichotomized, according to usual clinical practice, as age < 75 and ≥ 75years and body mass index <25kg/m2 (normal BMI) and ≥ 25 kg/m2 (overweight/obese). The clustering algorithm begins with each element (i.e. patient) as a separate cluster and then proceeds with a 'bottom-up' approach grouping each cluster with the most similar one until all clusters become one. The hierarchical clustering process is visually represented by a dendrogram graph in which vertical lines represent clusters that are joined together and the position of an horizontal line on the scale indicates the rescaled distance at which clusters were joined. By examining the dendrogram produced by the clustering process and considering the Ward Linkage coefficients, we found that the distance between the points in which the elements grouped together (between 10 and 15 on the y-axis) became larger and consequently the groupings became more heterogeneous after being expanded to 3 clusters. Therefore, the 3-cluster model was used in this analysis. Once clusters were identified, we assessed the association between clusters and clinical characteristics and outcomes.

A logistic regression model, adjusted for the type of AF and EHRA score, was used to examine the association between clusters and use OAC. To evaluate the differences in length of hospital stay between the three clusters, a one-way analysis of covariance (ANCOVA) model, adjusted for type of AF and EHRA score, was used. To analyse the association between clusters and other healthcare use resources, a logistic regression model was used, adjusted for type of AF, EHRA score and use of OAC. Differences in cumulative risk for the three main study

outcomes were evaluated using log-rank test and drafted according to Kaplan-Meier curves. To investigate the association between the three clusters and the clinical outcomes a Cox or logistic regression analyses (if time-to-event data were not available) adjusted for type of AF, EHRA score and use of OAC were used.
We also performed a sensitivity analysis to assess the impact of adherence to the ABC pathway on the composite outcome of CV events and all-cause death, according to the three clusters. A Cox regression model for ABC vs. non-ABC and each ABC criterion, adjusted for type of AF, EHRA score and use of OAC, was performed.

Analysis n°2 – Statistical analysis

A univariate and multivariate logistic regression model was used to evaluate which clinical factors were associated with the choice of early rhythm control.
To evaluate the relationship between the use of early rhythm control and length of hospital stay, in addition to the number of medical visits during the follow-up, we performed a linear regression analysis adjusted for type of AF, CHA_2DS_2-VASc score and EHRA score. To analyse the association between the use of early rhythm control and the occurrence of medical visits, a logistic regression model was used, adjusted for type of AF, CHA_2DS_2-VASc score and EHRA score. We also performed a linear regression analysis adjusted for type of AF, CHA_2DS_2-VASc score and EHRA score to evaluate the relationship between the use of early rhythm control and quality of life measures. The association between the use of early rhythm control and readmission outcomes was tested using a logistic regression model, adjusted for type of AF, CHA_2DS_2-VASc score, EHRA score and use of OAC.

Cumulative risk differences for the main study outcome were evaluated using log-rank tests and Kaplan–Meier curves. A Cox regression analysis was also performed to investigate the independent associations between the use of early rhythm control and the clinical outcomes. Two different models were used: (i) adjusted for type of AF, CHA_2DS_2-VASc score and EHRA score and use of OAC; (ii) adjusted for type of AF, EHRA score, age, sex, hypertension, diabetes mellitus, heart failure, severe coronary artery disease, valvular disease, left ventricular hypertrophy, peripheral artery disease, stroke/transient ischaemic attack, chronic

kidney disease, chronic obstructive pulmonary disease, malignancy and use of OAC. Finally, we performed a sensitivity analysis regarding the occurrence of study primary outcome, comparing the early rhythm control strategy to a 'no rhythm control' approach adherent to the ABC pathway.

Analysis n°3 – Statistical analysis

For this analysis, Cox regression models were used to establish the relationship between ABC adherent care and the primary outcome (i.e. NCO) as well as other major adverse outcomes (i.e. MACE, all-cause death and major bleeding). We performed different analyses: first, we evaluated full ABC pathway adherence vs non-adherence (or incomplete); second, we explored the relationship between increasing number of ABC adherent criteria and the risk of the main study outcomes. The Cox regression analysis was adjusted for a pre-specified list of covariates that were selected on the basis of their known ability to predict outcomes in AF patients. The CHA_2DS_2-VASc score, chronic kidney disease (i.e. creatinine clearance <60 ml/min calculated with Cockcroft-Gault equation) and type of AF were used as adjustments for NCO, MACE and all-cause death. For major bleeding, the model was adjusted for HAS-BLED score, sex and type of AF.

Plots of Kaplan–Meier curves for time to NCO according to ABC pathway status (full adherence vs non-adherence) and number of ABC adherent criteria in both cancer and non-cancer patients were also performed and compared using the log-rank test.

Results

A total of 11096 patients were enrolled in 250 centres from 27 participating countries, 40.7% female; median (IQR) age 71 (63–77) years. Overall, 5161 (68.5%) patients were enrolled in a specialized centre, whereas 52.2% of patients were enrolled in-hospital and 47.8% were enrolled as outpatients.

Analysis n°1 –Phenotype classification of AF patients using cluster analysis and impact of clinical management and outcomes

For this analysis, a total of 9363 (84.8%) were included. Median [IQR] age was 71 [62-77], with 3706 (39.6%) females and a median [IQR] CHA_2DS_2-VASc equal to 3 [2–4]. Based on baseline characteristics (**Table 1**), we labelled three clusters (**Figure 11**) as follows: (i) *Cluster 1*: older patients with prevalent non-cardiac comorbidities; (ii) *Cluster 2*: younger patients with an overall low thrombo-embolic risk and low comorbidity burden; and (iii) *Cluster 3*: patients with prevalent cardiovascular risk factors and comorbidities, at highest risk of adverse events.

In detail, the clusters had the following characteristics (**Table 1**):

- **Cluster 1 – "Older patients with non-cardiac comorbidities"**. A total of 3634 (38.8%) patients were in Cluster 1. Median [IQR] age was 73 [65-78] years, with 1553 (42.7%) patients being ≥ 75 years and the largest proportion of females compared to the other clusters (p<0.001). The proportion of overweight/obese patients was the lowest in Cluster 1 compared to Clusters 2 and 3 (p<0.001). Patients in Cluster 1 had also a clinical history more burdened with previous stroke, thromboembolic and bleeding events and a higher prevalence of several non-cardiovascular comorbidities, compared to other clusters (**Table 1**). Mean CHA_2DS_2-VASc and HAS-BLED scores were higher than in patients in Cluster 2, but lower than in patients in Cluster 3 (both p<0.001).
- **Cluster 2 – "Younger patients with few comorbidities".** A total of 2774 (29.6%) patients were clustered in this group. This cluster included younger patients (median [IQR] age 65 [56-72] years) compared to the other two

clusters (p<0.001). This cluster had the largest proportion of overweight/obese patients. Patients in this cluster were those more likely smoking and drinking alcohol. In addition, patients in Cluster 2 were more likely to have first detected or paroxysmal AF and were more symptomatic. Patients in Cluster 2 generally had less comorbidities than patients in other clusters (p<0.001). Thromboembolic and bleeding risks were the lowest. Of note, there was the lowest prevalence of multimorbidity, polypharmacy and frailty.

- **Cluster 3 – "Older patients with high prevalence of cardiovascular risk factors and comorbidities".** A total of 2955 (31.6%) patients were included in Cluster 3. Median [IQR] age was 73 [66-78] years, with 1257 (42.5%) females. Patients in Cluster 3 were more likely to be admitted for cardiovascular reasons other than AF (p<0.001) and more commonly had permanent AF. Patients in this Cluster had more prevalent CV risk factors and clinical history of cardiac and vascular disease, with 2771 (93.8%) patients with high thrombo-embolic risk and 809 (27.4%) with high bleeding risk. The prevalence of multi-morbidity, frailty and polypharmacy was highest in Cluster 3 compared to the other clusters (all p <0.001). Interestingly, when examining the median number of comorbidities and concomitant drugs, both were highest in Cluster 3 and progressively lower in Cluster 1 followed by Cluster 2.

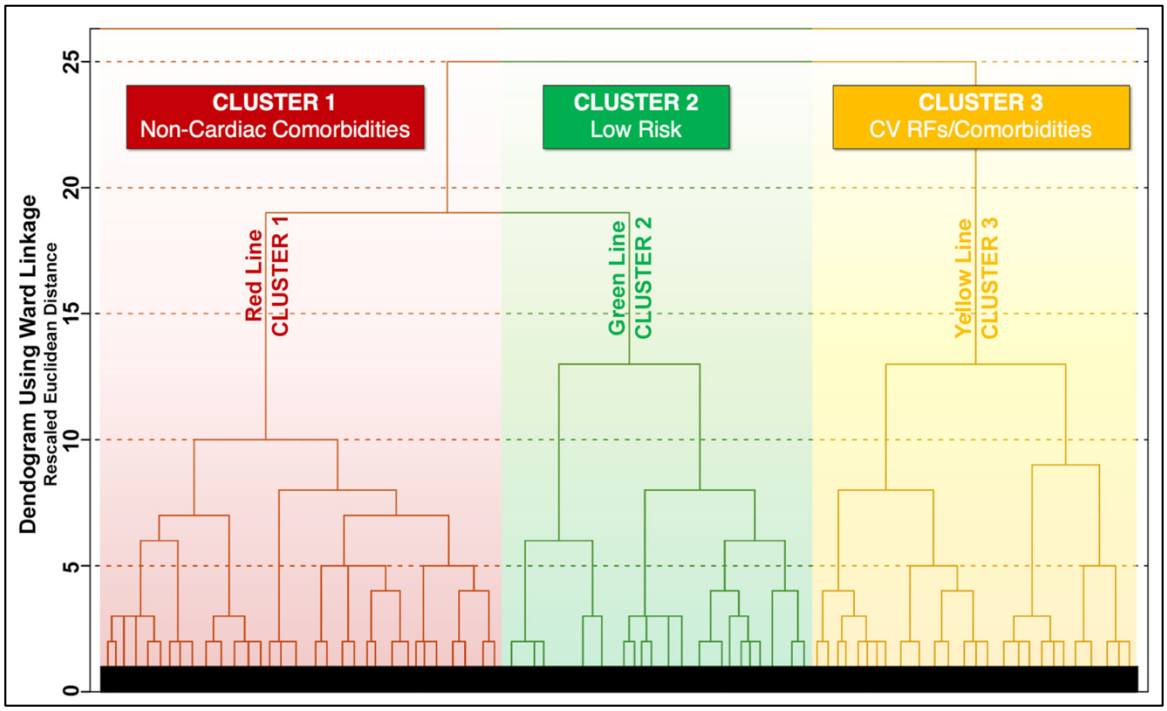

Figure 11 Patients' cluster membership

Dendrogram generated by hierarchical clustering process showing the three AF clusters. The dendrogram graph is the visual representation of the hierarchical clustering process. Vertical lines are clusters that are joined together and the position of the line on the scale indicates the distance at which clusters were joined (the greater the difference in height, the more dissimilarity exists between clusters). CV = cardiovascular; RFs = risk factors

Management of AF according to the three clusters is shown in **Table 2**. Use of antiplatelet drugs was highest in Cluster 3 (p<0.001), while use of OAC was lowest in Cluster 2 (p<0.001). Among OAC, VKAs were more likely used in Cluster 3, while NOACs use were more prevalent in Cluster 2 (p<0.001). After adjustment for type of AF and EHRA score, compared to those in Cluster 2, both patients in Cluster 1 and in Cluster 3 were more likely prescribed with OAC (OR 1.20, 95% CI 1.05–1.39 and OR 1.17, 95% CI 1.01–1.36, respectively). Among OAC users, Cluster 1 and Cluster 3 were significantly associated with greater VKA use compared to non-vitamin K antagonist OACs, when compared to Cluster 2 (adjusted OR 1.21, 95% CI 1.08–1.36 and OR 1.45, 95% CI 1.29-1.63, respectively).

Use of healthcare resources according to the three Clusters are shown in **Table 3**. Among the 4694 patients enrolled during a hospital admission, mean [SD] length of stay was progressively lower in patients in Cluster 3 (8.07 [8.50] days), Cluster 1 (6.52 [7.29] days) and Cluster 2 (4.36 [6.33] days) (p<0.001 for the overall model and for differences between each cluster). After adjustment for EHRA score and type of AF, differences in overall length of stay remained significant (F = 72.215, p

<0.001). As shown in **Table 3**, during follow-up, use of healthcare resources differed significantly among the three clusters.

Outcomes events are shown in **Table 4**. A progressively higher rate of events was found from Cluster 2 to Cluster 1 and Cluster 3 for the occurrence of cardiovascular events, all-cause death, composite outcomes and any cardiovascular non-AF-related hospital re-admission (all p<0.001). The occurrence of any bleeding and any non-CV-related hospital readmission was significantly lower in Cluster 2, while a higher rate of AF-related readmission was found. Adjusted logistic regression analyses (**Figure 12**) found a higher risk for all the secondary outcomes in Cluster 1 and Cluster 3, except the risk for any AF-related readmission, which was lower for both these clusters. Kaplan-Meier curves show a progressively higher cumulative risk across the three clusters for all the main study outcomes (**Figure 13**). Adjusted Cox regression analyses (**Table 5)** found that compared to Cluster 1, Cluster 2 and Cluster 3 were associated with a progressively higher risk for all the three study primary outcomes.

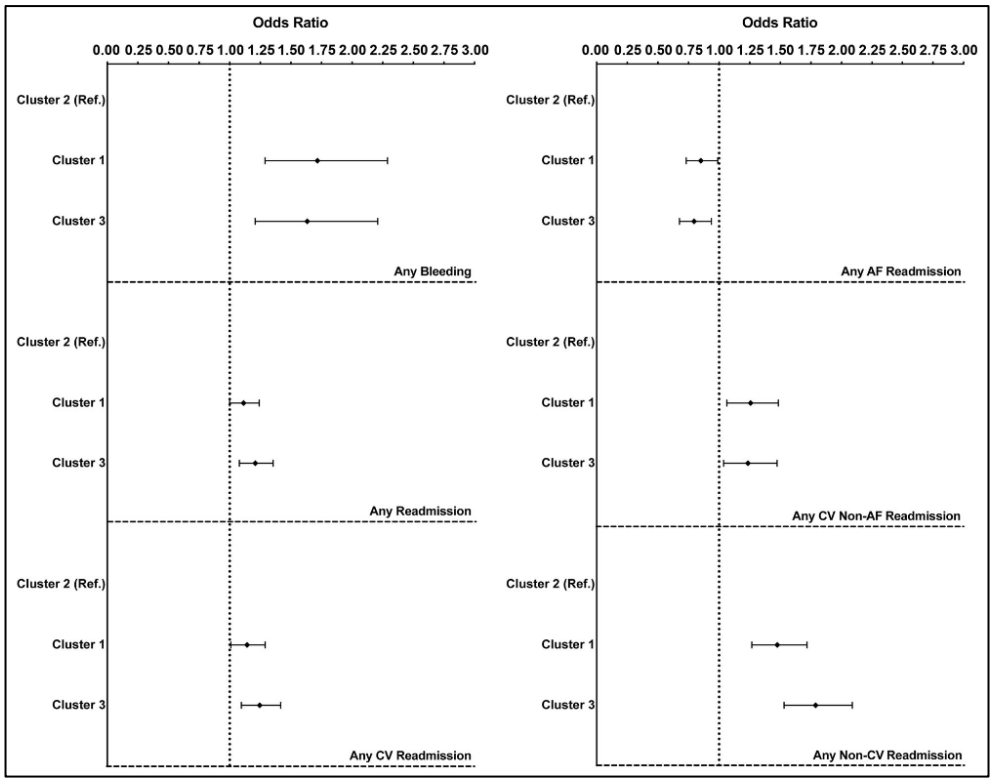

Figure 12. Multivariable logistic regression analysis

Adjusted for type of AF, EHRA score, use of OAC; AF = atrial fibrillation; CV = cardiovascular; OAC = oral anticoagulant

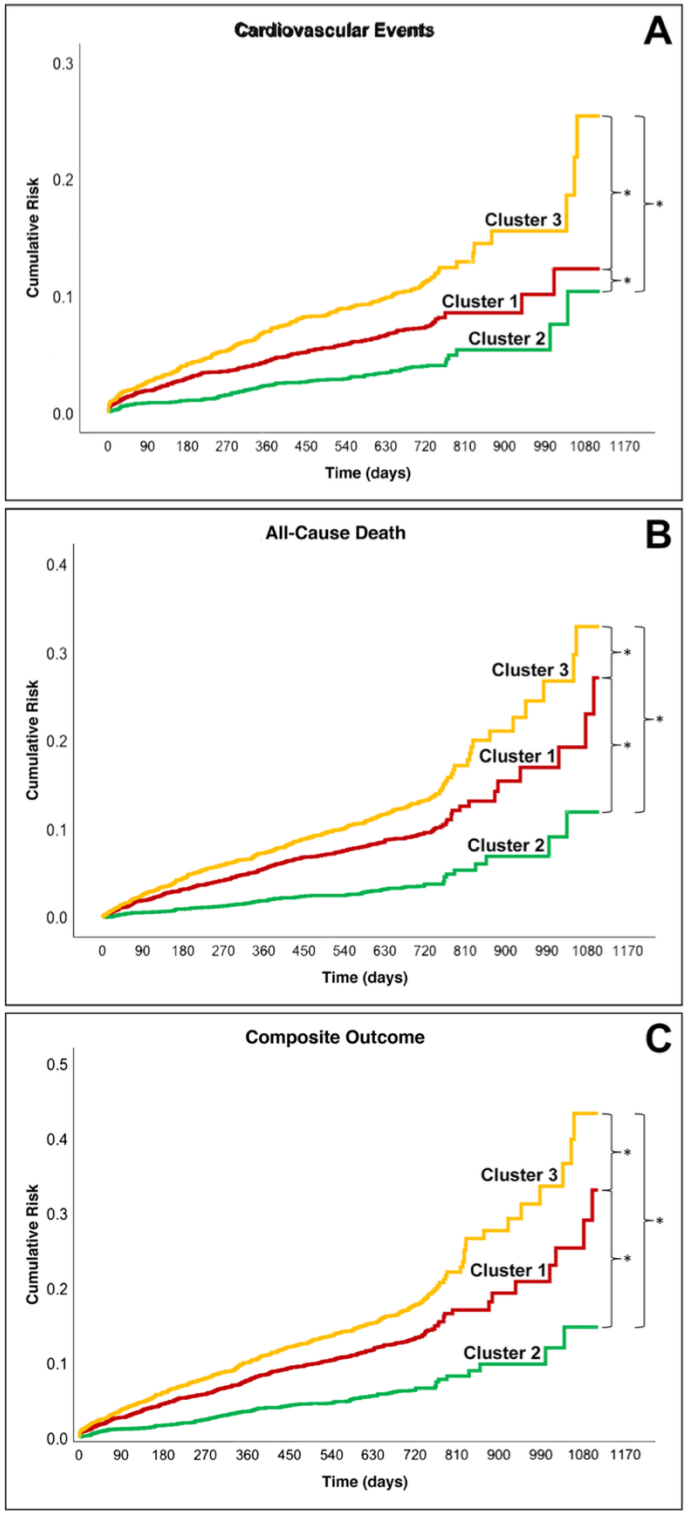

Figure 13. Kaplan-Meier curves for primary clinical study outcomes

Legend: A Cardiovascular events = log-rank 85.975, p<0.001. B All-cause death = log-rank 132.790 p<0.001. C Composite outcome = log-rank 132.997, p<0.001. All pairwise comparisons were significant for p<0.001. Green line = Cluster 2; Red line = Cluster 1; Yellow line = Cluster 3

Table 1. Baseline Characteristics according to Patient Clusters

N= 9363	**Cluster 1 Non-CV Comorbidities N= 3634**	**Cluster 2 Low Risk N= 2774**	**Cluster 3 CV RFs/Comorbidities N= 2955**	**p**
Age, *years* Median [IQR]	73 [65-78]	65 [56-72]	73 [66-78]	<0.001
Age ≥75 years, n (%)	1553 (42.7)	513 (18.5)	1257 (42.5)	<0.001
Females, n (%)	1604 (44.1)	964 (34.8)	1138 (38.5)	<0.001
Overweight/Obese, n (%)	755 (20.8)	1666 (60.1)	1619 (54.8)	<0.001
Reason for Admission, n (%)				<0.001
AF	2427 (66.8)	2299 (82.9)	1571 (53.2)	
Other CV	1034 (28.5)	400 (14.4)	1221 (41.3)	
Other Non-CV	173 (4.8)	75 (2.7)	163 (5.5)	
Site of Admission, n (%)				<0.001
Hospital Facility	1783 (49.1)	1261 (45.5)	1650 (55.8)	
Outpatient Facility	1851 (50.9)	1513 (54.5)	1305 (44.2)	
Type of AF, n (%) *9360*				<0.001
First Detected	547 (15.1)	532 (19.2)	373 (12.6)	
Paroxysmal	936 (25.8)	865 (31.2)	692 (23.4)	
Persistent	693 (19.1)	641 (23.1)	496 (16.8)	
Long-standing persistent	143 (3.9)	114 (4.1)	134 (4.5)	
Permanent	1256 (34.6)	577 (20.8)	1210 (41.0)	
Unknown	58 (1.6)	44 (1.6)	49 (1.7)	
CHA_2DS_2-VASc Score, median [IQR] *9358*	3 [2-4]	2 [1-3]	4 [3-5]	<0.001
High TE Risk, n (%) *9358*	2865 (78.9)	1351 (48.7)	2771 (93.8)	<0.001
HAS-BLED Score, median [IQR]	2 [1-2]	1 [0-2]	2 [1-3]	<0.001
High Bleeding Risk, n (%)	616 (17.0)	172 (6.2)	809 (27.4)	<0.001
EHRA Score, median [IQR] *9362*	2 [1-2]	2 [1-2]	2 [1-2]	0.002
EHRA II-IV, n (%) *9362*	1892 (52.1)	1613 (58.2)	1536 (52.0)	<0.001
Previous Stroke, n (%)	358 (9.9)	40 (1.4)	157 (5.3)	<0.001
Previous Thromboembolic Events, n (%)	529 (14.6)	193 (7.0)	325 (11.0)	<0.001
Hypertension, n (%)	2230 (61.4)	1253 (45.2)	2266 (76.7)	<0.001
Heart Failure, n (%)	1327 (36.5)	419 (15.1)	1658 (56.1)	<0.001
Diabetes Mellitus, n (%)	297 (8.2)	177 (6.4)	1613 (54.6)	<0.001
Lipid Disorder, n (%)	1356 (38.4)	874 (32.5)	1512 (52.5)	<0.001

Congenital Heart Disease, n (%)	50 (1.4)	24 (0.9)	29 (1.0)	0.243
Valvular Disease, n (%)	2200 (60.5)	615 (22.2)	1724 (58.3)	<0.001
CAD, n (%)	1093 (30.1)	273 (9.8)	1311 (44.4)	<0.001
Chronic Kidney Disease, n (%)	138 (3.8)	58 (2.1)	911 (30.8)	<0.001
History of Bleeding, n (%)	311 (8.6)	23 (0.8)	156 (5.3)	<0.001
COPD, n (%)	446 (12.3)	80 (2.9)	267 (9.0)	<0.001
Anaemia, n (%)	176 (4.8)	14 (0.5)	268 (9.1)	<0.001
Predisposition to Bleeding, n (%)	76 (2.1)	18 (0.6)	81 (2.7)	<0.001
Peripheral Arterial Disease, n (%)	297 (8.2)	131 (4.7)	318 (10.8)	<0.001
Liver Disease, n (%)	125 (3.4)	17 (0.6)	79 (2.7)	<0.001
OSAS, n (%)	83 (2.3)	230 (8.3)	127 (4.3)	<0.001
Neoplasm, n (%)	513 (14.1)	40 (1.4)	162 (5.5)	<0.001
Hyperthyroidism, n (%)	305 (8.4)	47 (1.7)	84 (2.8)	<0.001
Hypothyroidism, n (%)	509 (14.0)	49 (1.8)	334 (11.3)	<0.001
Multi-morbidity, n (%)	3151 (86.9)	1312 (47.3)	2877 (97.6)	<0.001
Frailty, n (%)	571 (16.5)	185 (7.0)	1003 (35.5)	<0.001
Polypharmacy, n (%) *9301*	1801 (49.9)	941 (34.1)	2162 (73.7)	<0.001

Legend: AF= Atrial Fibrillation; CAD= Coronary Artery Disease; CKD= Chronic Kidney Disease; COPD= Chronic Obstructive Pulmonary Disease; CV= Cardiovascular; IQR= Interquartile Range; NOAC= Non-Vitamin K Antagonist Oral Anticoagulant; OAC= Oral Anticoagulant; OSAS= Obstructive Sleep Apnoea Syndrome; PAD= Peripheral Artery Disease; RFs= Risk Factors; TE= Thromboembolic; VKA= Vitamin K Antagonist.

Table 2. Atrial Fibrillation Clinical Management according to Patient Clusters

	Cluster 1	Cluster 2	Cluster 3	p
Antithrombotic Treatment				
Any Antiplatelet, n (%) 9356	708 (19.5)	304 (11.0)	812 (27.5)	<0.001
Any OAC, n (%) 9359	3143 (86.5)	2306 (83.2)	2563 (86.7)	<0.001
Any VKA, n (%) 9358	1833 (50.5)	1163 (42.0)	1639 (55.5)	<0.001
Any NOAC, n (%) 9354	1314 (36.2)	1145 (41.3)	925 (31.3)	<0.001
Antithrombotic Pattern, n (%)				<0.001
No Antithrombotic	217 (6.0)	318 (11.5)	142 (4.8)	
Only Antiplatelet	273 (7.5)	147 (5.3)	250 (8.5)	
Only VKA	1524 (42.0)	1059 (38.2)	1228 (41.6)	
Only NOAC	1182 (32.6)	1089 (39.3)	773 (26.2)	
Antiplatelet + OAC	435 (12.0)	157 (5.7)	562 (19.0)	
Primary Management (Before Admission)				
Primary Management Strategy, n (%) *7753*				<0.001
Rate Control	1371 (45.3)	802 (36.5)	1317 (52.0)	
Rhythm Control	1203 (39.8)	1083 (49.3)	852 (33.7)	
Observation	452 (14.9)	311 (14.2)	362 (14.3)	
Primary ECV, n (%) *7350*	693 (24.1)	604 (28.5)	476 (20.2)	<0.001
Primary PCV, n (%) *7281*	730 (25.6)	629 (29.9)	621 (26.6)	0.003
Primary Catheter Ablation, n (%) *7531*	171 (5.8)	181 (8.4)	108 (4.4)	<0.001
Management during Admission/Consultation				
Intervention Planned/Performed, n (%) *9363*	1285 (34.6)	1150 (41.5)	984 (33.3)	<0.001
ECV, n (%) *3392*	566 (45.0)	628 (54.6)	379 (38.5)	<0.001
PCV, n (%) *3392*	304 (24.2)	204 (17.7)	245 (24.9)	<0.001
Catheter Ablation, n (%) *3392*	176 (14.0)	261 (22.7)	100 (10.2)	<0.001
Management Strategy at Discharge, n (%)				<0.001
Rate Control	1724 (47.5)	984 (35.5)	1522 (51.7)	
Rhythm Control	1365 (37.6)	1333 (48.1)	981 (33.3)	
Observation	537 (14.8)	452 (16.3)	442 (15.0)	
ABC Pathway Adherence, n (%)	666 (30.8)	655 (34.5)	431 (26.2)	<0.001

Legend: ECV= Electrical Cardioversion; PCV= Pharmacological Cardioversion.

Table 3. Health-Resources Use during Follow-Up according to Patient Clusters

	Cluster 1	Cluster 2	Cluster 3	p
Cardiology Visits 1Y, n (%)	2227 (75.1)	1802 (74.5)	1693 (73.3)	0.338
*OR [95% CI]**	1.06 [0.93-1.20]	Ref.	0.97 [0.85-1.20]	-
Internal Medicine/GP Visits 1Y, n (%)	1208 (51.3)	909 (46.5)	1006 (52.4)	<0.001
*OR [95% CI]**	**1.24 [1.10-1.40]**	Ref.	**1.30 [1.14-1.48]**	-
ER Admissions 1Y, n (%)	494 (17.1)	390 (16.7)	490 (21.9)	<0.001
*OR [95% CI]**	1.08 [0.93-1.26]	Ref.	**1.50 [1.29-1.75]**	-
Cardiology Visits 2Y, n (%)	1788 (68.9)	1442 (68.2)	1355 (68.6)	0.877
*OR [95% CI]**	1.03 [0.91-1.17]	Ref.	1.00 [0.88-1.15]	-
Internal Medicine/GP Visits 2Y, n (%)	1124 (51.0)	808 (45.5)	876 (51.2)	0.001
*OR [95% CI]**	**1.27 [1.18-1.44]**	Ref.	**1.29 [1.13-1.48]**	-
ER Admissions 2Y, n (%)	352 (14.1)	287 (14.0)	297 (15.7)	0.250
*OR [95% CI]**	1.02 [0.86-1.21]	Ref.	1.16 [0.97-1.39]	-

Legend: adjusted for type of AF, EHRA score, use of OAC; 1Y= 1 Year Follow-Up; 2Y= 2 Years Follow-Up; CI= Confidence Interval; ER= Emergency Room; GP= General Practitioner; OR= Odds Ratio; for other acronyms please see previous tables' legends.

Table 4. Major Adverse Clinical Events according to Patient Clusters

N= 8701	Cluster 1	Cluster 2	Cluster 3	p
Cardiovascular Events, n (%)	295 (8.7)	121 (4.7)	385 (14.1)	<0.001
All-Cause Death, n (%)	331 (9.8)	101 (3.9)	370 (13.6)	<0.001
Composite Outcome, n (%)	502 (14.9)	187 (7.2)	571 (20.9)	<0.001
Any Bleeding, n (%)	156 (4.6)	71 (2.7)	121 (4.5)	<0.001
Any Readmission, n (%)	1264 (37.7)	940 (36.3)	1063 (39.3)	0.086
Any CV Readmission, n (%)	816 (24.4)	592 (22.9)	694 (25.6)	0.064
Any AF Readmission, n (%)	413 (12.3)	396 (15.3)	304 (11.2)	<0.001
Any CV Non-AF Readmission, n (%)	546 (16.3)	306 (11.8)	516 (19.1)	<0.001
Any Non-CV Readmission, n (%)	406 (12.1)	260 (10.0)	322 (11.9)	0.029

Legend: for acronyms, please see previous tables' legends. Composite outcome of CV events and/or all- cause death

Table 5. Cox Regression Analysis for Main Study Outcomes

	Univariate		Multivariable*	
	HR (95% CI)		**HR (95% CI)**	**p**
Cardiovascular Events, n (%)				
Cluster 1	1.85 [1.46-2.34]	<0.001	1.88 [1.48-2.38]	<0.001
Cluster 2 (Ref.)	-	-	-	-
Cluster 3	2.82 [2.24-3.55]	<0.001	2.87 [2.27-3.62]	<0.001
All-Cause Death, n (%)				
Cluster 1	2.55 [2.03-3.21]	<0.001	2.50 [1.98-3.15]	<0.001
Cluster 2 (Ref.)	-	-	-	-
Cluster 3	3.55 [2.83-4.46]	<0.001	3.42 [2.72-4.31]	<0.001
Composite Outcome, n (%)				
Cluster 1	2.09 [1.74-2.51]	<0.001	2.09 [1.74-2.51]	<0.001
Cluster 2 (Ref.)	-	-	-	-
Cluster 3	2.81 [2.34-3.37]	<0.001	2.79 [2.32-3.35]	<0.001

Legend: *adjusted for type of AF, EHRA score, use of OAC; HR= Hazard Ratio; for other acronyms please see previous tables' legends. Composite outcome of CV events and/or all-cause death

Adherence to ABC pathway and outcomes according to clusters are shown in **Table 6**.

In Cluster 1, we found that while the adherence to the overall ABC pathway was not significantly associated with a lower risk of the composite outcome, the 'B' criterion showed a non-significant trend in inverse association with the risk of event occurrence. In Cluster 2, which was at a generally low thromboembolic risk, adherence to ABC pathway was found to be associated to a lower risk for the composite outcome, with no single criterion being independently associated with lower risk. Cluster 3 showed that full adherence to the ABC pathway was strongly associated with a significant reduction in the risk of adverse outcomes, but that the risk reduction was mainly associated with adherence to the 'C' criterion

Table 6. Adherence to ABC Pathway and Outcomes according to Clusters

	Composite Outcome		
	HR*	95% CI	p
Cluster 1			
ABC vs. Non-ABC	0.89	0.66-1.21	0.45
A Criterion	1.25	0.80-1.96	0.34
B Criterion	0.59	0.34-1.01	0.06
C Criterion	0.82	0.63-1.05	0.12
Cluster 2			
ABC vs. Non-ABC	0.62	0.40-0.97	0.04
A Criterion	1.23	0.78-1.95	0.38
B Criterion	0.63	0.28-1.41	0.26
C Criterion	0.55	0.37-0.81	0.002
Cluster 3			
ABC vs. Non-ABC	0.53	0.36-0.76	<0.001
A Criterion	1.14	0.38-3.38	0.82
B Criterion	0.96	0.57-1.62	0.87
C Criterion	0.71	0.54-0.93	0.01

Legend: *adjusted for type of AF, CHA_2DS_2-VASc score, EHRA score, use of OAC; for acronyms, please see previous tables' legends. Composite outcome of CV events and/or all-cause death

Analysis n°2 - Real-world applicability and impact of early rhythm control on clinical management and outcomes

Recently, the EAST-AFNET 4 trial (107) described how early rhythm control strategy was associated with a lower risk of adverse clinical outcomes. Then, we aim to evaluate how many patients in our cohort would have been eligible to be enrolled in the EAST-AFNET 4 trial (107). Accordingly, we applied the same inclusion criteria to our population (108). In brief, we included all the patients that were aged ≥ 75 years or had a clinical history positive for previous stroke or transient ischaemic attack. Additionally, we included all the patients that fulfilled at least two of the following criteria: (i) age ≥ 65 years; (ii) female sex; (iii) hypertension; (iv) diabetes mellitus; (v) previous myocardial infarction or any coronary revascularization procedure; (vi) stable heart failure (NYHA II or ejection fraction < 50%); (vii) left ventricular hypertrophy: (viii) chronic kidney disease (creatinine clearance 15–59 mL/ min); (ix) peripheral arterial disease.

From the original 11,096 patients enrolled in the EORP- AF, 10,707 (96.5%) were evaluated for eligibility to EAST- AFNET 4 inclusion criteria. Overall, 3774 (34.0%) patients fulfilled the study's inclusion criteria and were selected for this analysis. Among those not selected, 2654 (38.3%) did not fulfil the study main criteria; 3682 (53.1%) did not fulfil the study additional criteria; 4013 (57.9%) had long-standing persistent or permanent AF or did not report the type of AF.

Among EORP-AF patients, 2052 (54.4%) were treated according to an early rhythm control strategy and 1722 (45.6%) with no rhythm control at baseline. Patients in the early rhythm control group were younger, more likely male, with persistent AF and a higher burden of AF symptoms. The early rhythm control group had more prevalent hypertension, but less comorbidities, with lower thromboembolic and bleeding risk factors, and a greater proportion receiving OAC (**Table 7**). EAST-AFNET 4 patients reported higher proportions of hypertension and diabetes mellitus, while EORP-AF patients had more structural heart disease (heart failure, severe coronary artery disease, valvular disease, left ventricular hypertrophy) (**Table 7**).

Mean (SD) time from AF diagnosis to enrolment was not significantly different between patients treated with and without early rhythm control [48.6 (84.4) days vs. 51.2 (88.6) days, respectively; p = 0.426], nor was the mean (SD) time from enrolment to discharge [0.4 (14.1) days vs. 1.5 (16.7) days, respectively; p = 0.381]. Distribution of rate/rhythm control treatments according to groups at baseline are shown in **Figure 14**

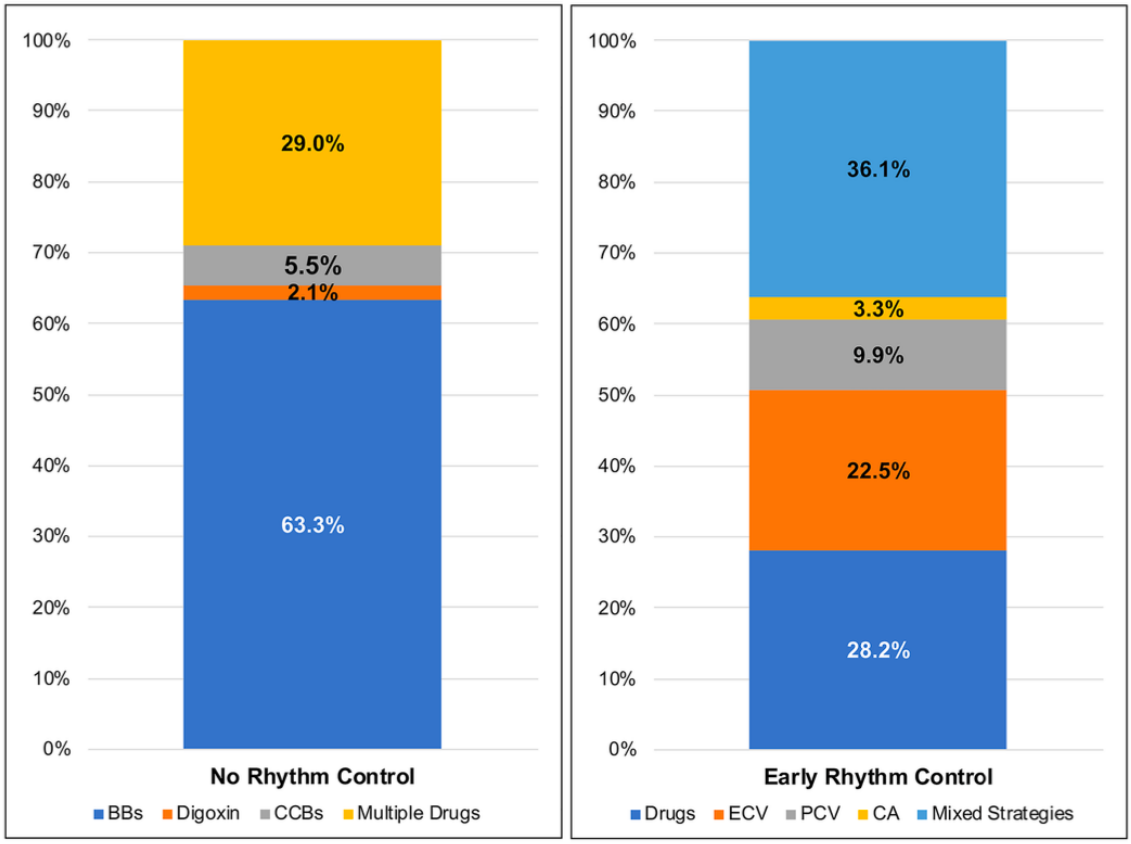

Figure 14. Distribution of rate/rhythm control treatments according to groups at baseline*.*
BBs beta blockers, CA catheter ablation, CCBs calcium- channel blockers, ECV electric cardioversion, PCV pharmacological cardioversion

At the multivariable analysis**,** paroxysmal and persistent AF, progressively increasing symptom burden and presence of hypertension were significantly associated with the use of an early rhythm control strategy. Increasing age, higher NYHA class and concomitant diabetes mellitus, stroke/transient ischaemic attack and chronic obstructive pulmonary disease were all inversely associated with early rhythm control**.**

Evaluation of quality of life is shown in **Table 8.** The analysis showed that patients managed with early rhythm control were more able to attend to their self-care ($p = 0.001$) and their usual activities ($p < 0.001$), but were more likely anxious, even after adjustment for CHA_2DS_2-VASc score, type of AF and EHRA score**.** In the multivariate analysis, at 1-year follow-up, those patients with early rhythm control had better levels of mobility ($p < 0.001$), self-care ($p = 0.009$) and participation in their usual activities ($p = 0.005$), with an overall better health state according to the Health Utility Score (HUS) ($p = 0.002$), compared to those not prescribed with early rhythm control. At 2 years follow-up, patients prescribed early rhythm control reported less impairment in all five dimensions of the EQ-5D-5L questionnaire and a better overall health state according to both HUS ($p < 0.001$) and VAS ($p = 0.053$), after the adjustments.

Use of health-care resources is reported in **Table 9.** Patients managed with early rhythm control attended more cardiology and internal medicine/general practitioner appointments at both follow-up time points (all $p < 0.001$). Among hospitalized patients, those prescribed early rhythm control had a shorter mean hospital stay. Among those who attended cardiology visits, those with early rhythm control reported a higher number of visits both at 1 year ($p < 0.001$) and 2 years ($p = 0.023$) of follow-up. Among patients attending internal medicine/general practitioner visits, those with early rhythm control attended more often within the first year of follow-up than those with 'no rhythm control' ($p = 0.015$).

Patients treated with an early rhythm control strategy had a higher rate of any readmission, and admissions related to CV reasons or AF (all $p < 0.001$). The adjusted logistic regression analysis found that an early rhythm control strategy was associated with higher odds of any hospital readmission, any CV readmission and any AF readmission (**Table 9**).

Follow-up data were available for 3354 (88.9%) of the patients. The primary main outcome of this analysis was equivalent to the original EAST-AFNET 4 trial primary outcome, being a composite of (i) CV death; (ii) any stroke; (iii) worsening heart failure; and (iv) acute coronary syndrome. The secondary clinical outcomes were: (i) major adverse cardiovascular events (MACEs): as the composite of any thromboembolic events, any acute coronary syndrome and CV death; and (ii) all-cause death. Over a mean (SD) follow-up of 675.4 (181.3) days, a total of 532

(14.1%) EAST-AFNET 4 defined primary outcome events were reported with an overall incidence of 8.9 per 100 patient-years. Death occurred in 321 (8.5%) and 380 (10.1%) experienced MACEs. Compared to those treated with an early rhythm control approach, the no rhythm control group had a higher proportion of patients with the EAST-AFNET 4 defined primary outcome, MACEs and all-cause death events (Table 10). The incidence of EAST-AFNET 4 defined primary outcome was 10.8 per 100 patient-years in patients with no rhythm control and 7.4 per 100 patient-years in patients with early rhythm control.

Table 7. Baseline Characteristics in EAST-AFNET 4 and EORP-AF and according to Early Rhythm Control Prescription

Variables	EAST-AFNET 4 (N= 2789)	EORP-AF (N= 3774)	No Rhythm Control (N= 1722)	Early Rhythm Control (N= 2052)	p*
Age, *years* mean (SD)	70.3 (8.3)	69.8 (10.4)	71.9 (10.3)	68.0 (10.2)	<0.001
Age, *years* median [IQR]	71 [66-76]	71 [63-78]	74 [66-79]	69 [62-76]	<0.001
Age ≥75 years, n (%)	812 (29.1)	1483 (39.3)	855 (49.7)	628 (30.6)	<0.001
Male Sex, n (%)	1496 (53.6)	2026 (53.7)	878 (51.0)	1148 (55.9)	0.002
BMI, *kg/m*^{2} median [IQR]	28.6 [25.5-32.1]	27.8 [24.8-31.2]	27.5 [24.6-31.2]	27.9 [25.0-31.3]	0.024
Type of AF, n (%)					<0.001
First Detected	1048 (37.6)	1031 (27.3)	564 (32.8)	467 (22.8)	
Paroxysmal	994 (35.7)	1538 (40.8)	742 (43.1)	796 (38.8)	
Persistent	743 (26.7)	1205 (31.9)	416 (24.2)	789 (38.5)	
EHRA Score, n (%)					<0.001
EHRA I	801 (30.4)	1390 (36.8)	784 (45.5)	606 (29.5)	
EHRA II	1358 (51.6)	1465 (38.8)	581 (33.7)	884 (43.1)	
EHRA III	447 (17.0)	808 (21.4)	310 (18.0)	498 (24.3)	
EHRA IV	27 (1.0)	110 (2.9)	47 (2.7)	63 (3.1)	
Hypertension, n (%)	2450 (87.8)	2559 (68.0)	1122 (65.4)	1437 (70.1)	0.002
Diabetes Mellitus, n (%)	694 (24.9)	860 (22.8)	440 (25.6)	420 (20.5)	<0.001
Prior Stroke/TIA, n (%)	328 (11.8)	379 (10.1)	191 (11.2)	188 (9.2)	0.049
Severe CAD, n (%)	479 (17.2)	827 (21.9)	392 (22.8)	435 (21.2)	0.247
Valvular Disease, n (%)	1251 (45.0)	1807 (48.6)	847 (50.3)	960 (47.2)	0.064
LVH, n (%)	132 (4.7)	988 (28.5)	463 (30.1)	525 (27.3)	0.070
PAD, n (%)	122 (4.4)	303 (8.1)	142 (8.4)	161 (7.9)	0.608
CKD, n (%)	351 (12.6)	454 (12.0)	234 (13.6)	220 (10.7)	0.006
COPD, n (%)	209 (7.5)	279 (7.4)	168 (9.8)	111 (5.4)	<0.001
Malignancy, n (%)					0.003
No Malignancy	2563 (92.2)	3467 (91.9)	1560 (90.6)	1907 (92.9)	
Active Malignancy	19 (0.7)	79 (2.1)	52 (3.0)	27 (1.3)	
Prior Malignancy	197 (7.1)	216 (5.7)	104 (6.0)	112 (5.5)	
CHA_2DS_2-VASc, mean (SD)	3.3 (1.3)	3.3 (1.6)	3.6 (1.6)	3.1 (1.5)	<0.001
CHA_2DS_2-VASc, median [IQR]	3 [2-4]	3 [2-4]	4 [2-5]	3 [2-4]	<0.001

HAS-BLED, mean (SD)	-	1.6 (1.0)	1.7 (1.1)	1.5 (1.0)	<0.001
HAS-BLED, median [IQR]	-	2 [1-2]	2 [1-2]	1 [1-2]	<0.001
Multimorbidity, n (%)	-	2681 (83.3)	1218 (84.3)	1463 (82.4)	0.158
Frailty, n (%)	-	555 (21.7)	236 (20.6)	319 (22.5)	0.246
Polypharmacy, n (%)	-	2375 (63.3)	999 (58.3)	1376 (67.5)	<0.001
ABC Pathway Adherence, n (%)	-	758 (29.9)	344 (29.3)	414 (30.5)	0.483
ABC Pathway Criteria, n (%)	-				0.335
0		59 (2.3)	33 (2.8)	26 (1.9)	
1		494 (19.5)	239 (20.3)	255 (18.8)	
2		1221 (48.2)	560 (47.6)	661 (48.7)	
3		758 (29.9)	344 (29.3)	414 (30.5)	
Pharmacological Treatments					
Any Antiplatelet, n (%)	455 (16.4)	921 (24.4)	441 (25.6)	480 (23.4)	0.111
Any OAC, n (%)	2517 (90.5)	3255 (86.3)	1426 (82.8)	1829 (89.2)	<0.001
Any VKA, n (%)	-	1644 (43.6)	687 (39.9)	957 (46.7)	<0.001
Any NOAC, n (%)	-	1613 (42.8)	740 (43.0)	873 (42.6)	0.777
ACEi/ARBs, n (%)	1932 (69.4)	2541 (67.4)	1156 (67.3)	1385 (67.5)	0.875
Diuretics, n (%)	1120 (40.3)	1900 (50.4)	902 (52.5)	998 (48.7)	0.020
MRAs, n (%)	182 (6.5)	577 (15.3)	276 (16.1)	301 (14.7)	0.240
Statins, n (%)	1196 (43.0)	1832 (48.6)	843 (49.0)	989 (48.3)	0.636
Oral Antidiabetics, n (%)	459 (16.5)	599 (15.9)	314 (18.3)	285 (13.9)	<0.001
Insulin, n (%)	121 (4.3)	205 (5.4)	102 (5.9)	103 (5.0)	0.220

Legends: *p value is referred to the comparison between No Rhythm Control and Early Rhythm Control; ABC= Atrial Fibrillation Better Care; AF= Atrial Fibrillation; BMI= Body Mass Index; CAD= Coronary Artery Disease; CKD= Chronic Kidney Disease; COPD= Chronic Obstructive Pulmonary Disease; EHRA= European Heart Rhythm Association; HF= Heart Failure; IQR= Interquartile Range; LVH= Left Ventricular Hypertrophy; NYHA= New York Heart Association; PAD= Peripheral Artery Disease; SD= Standard Deviation; TIA= Transient Ischemic Attack.

Table 8. Quality of Life Indicators according to Early Rhythm Control

	No Rhythm Control	Early Rhythm Control	p	Early Rhythm Control Beta (95% CI)*	p
Baseline					
EQ-5D-5L Mobility	0.049 (0.063)	0.043 (0.061)	0.019	-0.003 (-0.007 / 0.001)	0.156
EQ-5D-5L Self-Care	0.020 (0.039)	0.014 (0.035)	<0.001	**-0.005 (0.007 / -0.002)**	**0.001**
EQ-5D-5L Usual Activities	0.037 (0.047)	0.031 (0.044)	<0.001	**-0.006 (-0.009 / -0.003)**	**<0.001**
EQ-5D-5L Pain/Discomfort	0.049 (0.068)	0.044 (0.063)	0.024	-0.004 (-0.009 / 0.000)	0.062
EQ-5D-5L Anxiety	0.046 (0.066)	0.054 (0.072)	0.001	**0.007 (0.002 / 0.012)**	**0.004**
Health Utility Score	0.80 (0.21)	0.81 (0.19)	0.068	0.010 (-0.004 / 0.025)	0.142
Visual Analog Scale	68.3 (20.6)	68.3 (20.8)	0.992	0.093 (-1.486 / 1.673)	0.908
1 Year Follow-Up					
EQ-5D-5L Mobility	0.046 (0.059)	0.036 (0.056)	<0.001	**-0.009 (-0.014 / -0.004)**	**<0.001**
EQ-5D-5L Self-Care	0.018 (0.035)	0.013 (0.033)	0.002	**-0.004 (-0.007 / -0.001)**	**0.009**
EQ-5D-5L Usual Activities	0.033 (0.042)	0.027 (0.041)	0.001	**-0.005 (-0.009 / -0.002)**	**0.005**
EQ-5D-5L Pain/Discomfort	0.044 (0.067)	0.039 (0.062)	0.056	-0.005 (-0.010 / 0.001)	0.118
EQ-5D-5L Anxiety	0.042 (0.066)	0.040 (0.057)	0.536	-0.004 (-0.009 / 0.002)	0.197
Health Utility Score	0.817 (0.203)	0.844 (0.185)	0.001	**0.026 (0.009 / 0.043)**	**0.002**
Visual Analog Scale	69.7 (19.8)	70.9 (19.8)	0.169	1.283 (-0.505 / 3.071)	0.159
2 Years Follow-Up					
EQ-5D-5L Mobility	0.051 (0.062)	0.040 (0.056)	<0.001	**-0.009 (-0.015 / -0.004)**	**0.001**
EQ-5D-5L Self-Care	0.021 (0.040)	0.012 (0.027)	<0.001	**-0.009 (-0.012 / -0.005)**	**<0.001**
EQ-5D-5L Usual Activities	0.038 (0.045)	0.028 (0.041)	<0.001	**-0.008 (-0.012 / -0.004)**	**<0.001**
EQ-5D-5L Pain/Discomfort	0.048 (0.068)	0.039 (0.062)	0.004	**-0.008 (-0.014 / -0.001)**	**0.016**
EQ-5D-5L Anxiety	0.043 (0.065)	0.037 (0.058)	0.052	**-0.007 (-0.013 / -0.001)**	**0.020**
Health Utility Score	0.80 (0.21)	0.84 (0.18)	<0.001	**0.042 (0.023 / 0.060)**	**<0.001**
Visual Analog Scale	69.8 (19.4)	72.1 (19.8)	0.016	**1.943 (-0.026 / 3.911)**	**0.053**

Legend: *adjusted for CHA_2DS_2-VASc score, type of AF, EHRA score; CI= Confidence Interval; for other acronyms please see previous tables' legends.

Table 9. Use of Health-Care Resources according to Early Rhythm Control Use

	No Rhythm Control	**Early Rhythm Control**	**p**	**Early Rhythm Control** OR (95% CI)*	**p**
Cardiology Visits 1Y, n (%)	940 (68.3)	1386 (83.0)	<0.001	**2.07 (1.73-2.47)**	**<0.001**
IM/GP Visits 1Y, n (%)	481 (43.9)	822 (58.9)	<0.001	**1.87 (1.58-2.21)**	**<0.001**
ER Admissions 1Y, n (%)	290 (21.6)	371 (22.4)	0.577	1.08 (0.90-1.29)	0.422
Cardiology Visits 2Y, n (%)	738 (61.6)	1130 (76.2)	<0.001	**1.88 (1.58-2.23)**	**<0.001**
IM/GP Visits 2Y, n (%)	430 (42.1)	760 (58.9)	<0.001	**2.02 (1.70-2.40)**	**<0.001**
ER Admissions 2Y, n (%)	181 (15.8)	242 (16.8)	0.497	1.08 (0.87-1.35)	0.482
	No Rhythm Control	**Early Rhythm Control**	**p**	**Early Rhythm Control** Beta (95% CI)*	**p**
Length of Staying, *days* mean (SD)	7.6 (7.1)	5.9 (6.7)	<0.001	**-0.992 (-1.572 / -0.412)**	**0.001**
Cardiology Visits 1Y, *N* mean (SD)	2.4 (1.9)	2.7 (2.2)	<0.001	**0.349 (0.168 / 0.530)**	**<0.001**
IM/GP Visits 1Y, *N* mean (SD)	3.9 (3.4)	4.6 (3.9)	0.004	**0.589 (0.115 / 1.062)**	**0.015**
ER Admissions 1Y, *N* mean (SD)	1.7 (1.3)	1.7 (1.4)	0.704	0.005 (-0.209 / 0.219)	0.963
Cardiology Visits 2Y, *N* mean (SD)	2.0 (1.4)	2.2 (1.8)	0.004	**0.184 (0.025 / 0.342)**	**0.023**
IM/GP Visits 2Y, *N* mean (SD)	3.5 (3.4)	3.7 (3.3)	0.505	0.094 (-0.348 / 0.536)	0.676
ER Admissions 2Y, *N* mean (SD)	1.6 (1.2)	1.6 (1.3)	0.610	0.061 (-0.193 / 0.315)	0.637
	No Rhythm Control	**Early Rhythm Control**	**p**	**Early Rhythm Control**	**p**
				OR (95% CI)†	
Any Readmission, n (%)	624 (38.6)	857 (46.2)	<0.001	**1.34 (1.16-1.54)**	**<0.001**
Any CV Readmission, n (%)	415 (25.7)	607 (32.7)	<0.001	**1.40 (1.20-1.63)**	**<0.001**
Any AF Readmission, n (%)	205 (12.7)	408 (22.0)	<0.001	**1.76 (1.45-2.12)**	**<0.001**
Any CV Non-AF Readmission, n (%)	303 (18.8)	317 (17.1)	0.203	0.95 (0.79-1.14)	0.540
Any Non-CV Readmission, n (%)	207 (12.8)	213 (11.5)	0.232	0.91 (0.74-1.13)	0.369

Legend: *adjusted for CHA_2DS_2-VASc score, type of AF, EHRA score; †adjusted for CHA_2DS_2-VASc score, type of AF, EHRA score, use of OAC; bold values depict significant association; 1Y= 1 year follow-up; 2YR= 2 years follow-up; ER= Emergency Room; GP= General Practitioner; IM= Internal Medicine; OR= Odds Ratio; for other acronyms please see previous tables' legends.

Table 10. Major Clinical Outcomes Comparing Early Rhythm Control Versus No Rhythm Control in the EORP-AF Registry Patients Eligible for EAST-AFNET 4

	No Rhythm Control	Early Rhythm Control	p
EAST-AFNET 4 Primary Outcome	287 (18.5)	245 (13.6)	<0.001
MACEs	204 (12.5)	176 (9.4)	0.003
All-Cause Death	191 (11.9)	130 (6.7)	<0.001

Legend: AF= Atrial Fibrillation; CV= Cardiovascular; MACEs= Major Adverse Cardiovascular Events.

Kaplan–Meier curves for the EAST- AFNET 4 trial defined primary outcome showed that an early rhythm control strategy was associated with a progressively lower cumulative risk ($p < 0.001$) (**Figure 15**).

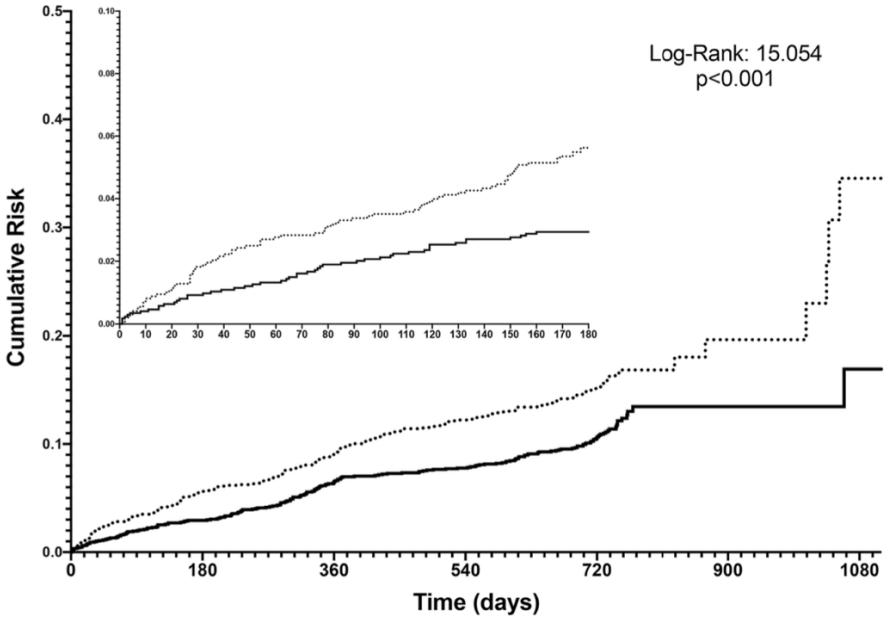

Figure 15. Kaplan–Meier curves for EAST-AFNET 4 primary outcome.
Black solid line=early rhythm control; black dotted line=no early rhythm control

The Cox regression analysis was performed to establish the association between use of an early rhythm control strategy and the risks of primary and secondary outcomes (**Table 11**). While the univariate analysis showed that prescription of an early rhythm control strategy was associated with a lower risk for all primary and secondary outcomes, the progressive adjustment process showed a gradual and subsequent loss in association, with the fully adjusted Model 2 showing no significant differences between patients treated with and without an early rhythm

control strategy (HR 0.84, 95% CI 0.66–1.19 for EAST-AFNET 4 defined primary outcome; HR 0.95, 95% CI 0.73–1.24 for MACEs; HR 0.96, 95% CI 0.75–1.24 for all-cause death).

Table 11. Cox Regression Analysis for Main Adverse Events for those receiving early rhythm control versus no rhythm control

	Univariate	Model 1*	Model 2†
	HR [95% CI]	HR [95% CI]	HR [95% CI]
EAST-AFNET 4 Primary Outcome	0.69 [0.57-0.83]	0.83 [0.68-1.01]	0.84 [0.66-1.19]
MACEs	0.70 [0.55-0.89]	0.88 [0.69-1.13]	0.95 [0.73-1.24]
All-Cause Death	0.56 [0.45-0.70]	0.73 [0.58-0.93]	0.96 [0.75-1.24]

Legend: *adjusted for type of AF, EHRA score, CHA_2DS2-VASc score, use of OAC; †adjusted for type of AF, EHRA score, age, sex, hypertension, diabetes mellitus, heart failure, severe coronary artery disease, valvular disease, left ventricular hypertrophy, peripheral artery disease, stroke/transient ischemic attack, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, use of OAC; HR= Hazard Ratio; MACEs= Major Adverse Cardiovascular Events; for other acronyms please see previous tables' legends.

Finally, we conducted a sensitivity analysis comparing the occurrence of the primary outcome in patients managed with early rhythm control and those with no rhythm control approach but adherent to the ABC pathway management. We selected all patients with data on ABC pathway adherence (2532, 67.1%) and compared those managed with early rhythm control (1356, 53.6%), to those not treated with rhythm control but managed with a clinical management adherent to the ABC pathway (344, 13.6%). There was no difference in the cumulative risk of primary outcome between early rhythm control and no rhythm control adherent to ABC pathway (log- rank: 0.099, p = 0.753). Cox regression analysis showed no association between early rhythm control strategy vs. no rhythm control ABC adherent management in univariate (HR: 1.03, 95% CI 0.71–1.49) or multivariable (HR: 0.99, 95% CI 0.65–1.52) analyses.

Analysis n°3 – Atrial fibrillation and cancer: adherence to the "Atrial fibrillation Better Care" (ABC) Pathway and associated clinical outcomes

For the purpose of this analysis, we divided the population into two categories: (i) 'No cancer' group and (ii) 'Cancer' group (including those with prior or active diagnosis of cancer) and subsequently stratified each group according to

adherence to the ABC pathway (i.e. ABC-adherent vs ABC non-adherent). A net clinical outcome (NCO), defined as a composite of all-cause death, any TE, ACS and major bleeding, was the primary endpoint of the present analysis. The composite outcome of any TE/any ACS/CV death, defined as major adverse cardiovascular events (MACE) was also evaluated.

Among the original 11 096 patients enrolled, a total of 6550 (59.0%) patients with available data to evaluate the ABC pathway and malignancy status were included (median age 69 years, interquartile range [IQR] 61–77, females 40.1%). Of these, 6005 (91.7%) had no cancer while 545 (8.3%) had a diagnosis of active or prior cancer at baseline.

In the cancer and no cancer groups, respectively, 25.7% and 30.6% of the patients met all three ABC criteria and therefore were defined as ABC-adherent. Baseline characteristics for ABC adherent vs. ABC non- adherent care patients, stratified according to malignancy status are shown in **Table 12**. Patients in the ABC non-adherent groups had a higher burden of comorbidities such as diabetes mellitus, HF, CAD, CKD and previous TE events (**Table 12**). Pharmacological management, including antithrombotic treatments are shown in **Table 13**. Non- vitamin K oral anticoagulants were the most prevalent oral anticoagulants prescribed both in cancer and no-cancer patients. Overall, 216/6547 (3.3%) patients had also a prescription of low- molecular-weight heparin (LMWH) at low/intermediate dosage with no full-anticoagulant effect with a slightly higher prevalence in the cancer group compared with no cancer group (5.5% vs 3.1%, $p = 0.003$). In consideration of the lack of evidence on stroke-reduction with these regimens of LMWH, adherence to “A” criterion was not assumed in these cases.

Distribution of ABC criteria among the study groups are shown in **Table 14**. Most patients qualified for 2 out of 3 ABC criteria in both cancer and no-cancer groups (49.3% vs 48.2%, respectively). The proportion of patients with adherence to “C” criterion was not high in either group, and was significantly lower in the cancer group (51.5% vs 43.9%, $p < 0.001$). Conversely, adherence to “A” and “B” criteria did not significantly differ between the two groups (Table 14).

Table 12. Baseline characteristics of study population according to ABC pathway status and cancer

	No Cancer group N=6005			Cancer group N=545		
	ABC Adherent n=1836 (30.6%)	**ABC Non-adherent** n=4169 (69.4%)	**p**	**ABC Adherent** n=140 (25.7%)	**ABC Non-adherent** n=405 (74.3%)	**p**
Age (years), median (IQR)	69 (61-76)	69 (61-77)	0.65	73 (66-78)	75 (68-80)	0.02
Female, n (%)	674/1836 (36.7)	1679/4169 (40.7)	0.004	61/140 (43.6)	193/405 (47.7)	0.40
BMI (kg/m^2), median (IQR)	27.4 (24.9-30.8)	27.7 (24.8-31.2)	0.07	27.2 (23.9-30.6)	27.4 (24.4-30.8)	0.58
AF type, n (%)			0.05			0.40
First diagnosed	402/1813 (22.2)	833/4088 (20.4)		33/138 (23.9)	86/394 (21.8)	
Paroxysmal	493/1813 (27,7)	1239/4088 (30.3)		27/138 (19.6)	108/394 (27.4)	
Persistent	379/1813 (20,9)	841/4088 (20.6)		29/138 (21.0)	80/394 (20.3)	
Long-standing persistent	88/1813 (4.9)	157/4088 (3.8)		5/138 (3.6)	17/394 (4.3)	
Permanent	451/1813 (24.9)	1018/4088 (24.9)		44/138 (31.9)	103/394 (26.1)	
Hypertension, n (%)	1098/1824 (60.2)	2406/4125 (58.3)	0.17	77/139 (55.4)	256/401 (63.8)	0.07
Diabetes mellitus, n (%)	298/1825 (16.3)	954/4143 (23.0)	<0.001	26/140 (18.6)	120/405 (29.6)	0.01
Smoking (current), n (%)	183/1756 (10.4)	391/3884 (10.1)	0.68	11/135 (8.1)	27/386 (7.0)	0.65
Lipid disorder, n (%)	671/1761 (38.1)	1606/4000 (40.2)	0.14	46/135 (34.1)	159/383 (41.5)	0.12
Heart failure, n (%)	485/1823 (26.6)	1598/4126 (38.7)	<0.001	36/140 (25.7)	153/401 (38.2)	0.008
NYHA III/IV, n (%)	118/485 (24.3)	556/1597 (34.8)	<0.001	7/36 (19.4)	67/152 (44.1)	0.007
Dilated CMP, n (%)	141/1819 (7.8)	288/4109 (7.0)	0.31	3/139 (2.2)	22/399 (5.5)	0.11
Hypertrophic CMP, n (%)	37/1821 (2.0)	124/4105 (3.0)	0.03	1/139 (0.7)	15/399 (3.8)	0.08
PAH, n (%)	70/1812 (3.9)	255/4083 (6.2)	<0.001	4/138 (2.9)	25/395 (6.3)	0.12
LVEF (%), median (IQR)	58 (48-64)	56 (47-62)	0.007	58 (50-62)	57 (46-63)	0.07
Bundle Branch Block, n (%)			0.27			0.44
No	1504/1722 (87.3)	3356/3862 (86.9)		109/128 (85.2)	293/360 (81.4)	
LBBB	130/1722 (7.5)	270/3862 (7.0)		11/128 (8.6)	31/360 (8.6)	
RBBB	88/1722 (5.1)	236/3862 (6.1)		8/128 (6.3)	36/360 (10.0)	
Coronary artery disease, n (%)	284/1743 (16.3)	1208/3949 (30.6)	<0.001	20/138 (14.5)	133/385 (34.5)	<0.001
Previous MI	152/284 (53.5)	514/1208 (42.5)	0.001	10/20 (50.0)	67/133 (50.4)	0.97
Valvular alterations, n (%)	771/1804 (42.7)	1801/4079 (44.2)	0.31	65/131 (49.6)	195/398 (49.0)	0.90
Previous TE events, n (%)	135/1825 (7.4)	490/4127 (11.9)	<0.001	15/140 (10.7)	74/401 (18.5)	0.03
Previous ischaemic stroke, n (%)	75/1825 (4.1)	248/4127 (6.0)	0.003	5/140 (3.6)	41/401 (10.2)	0.01
Previous TIA, n (%)	29/1825 (1.6)	149/4127 (3.6)	<0.001	5/140 (3.6)	21/401 (5.2)	0.42
Previous PE/DVT, n (%)	32/1825 (1.8)	74/4127 (1.8)	0.91	3/140 (2.1)	15/401 (3.7)	0.36
Previous haemorrhagic events, n (%)	73/1828 (4.0)	238/4124 (5,8)	0.004	11/140 (7.9)	45/400 (11.3)	0.25
PAD, n (%)	60/1814 (3.3)	339/4088 (8.3)	<0.001	11/137 (8.0)	60/399 (15.0)	0.03
Liver disease, n (%)	21/1834 (1.1)	115/4149 (2.8)	<0.001	5/140 (3.6)	11/404 (2.7)	0.61
COPD, n (%)	128/1828 (7.0)	306/4138 (7.4)	0.59	14/139 (10.1)	46/403 (11.4)	0.66
Dementia, n (%)	8/1832 (0.4)	60/4159 (1.4)	0.001	0/140	8/404 (2.0)	0.12
Anaemia, n (%)	46/1834 (2.5)	228/4161 (5.5)	<0.001	9/140 (6.4)	41/405 (10.1)	0.19
Hyperthyroidism, n (%)	75/1801 (4.2)	183/4088 (4.5)	0.59	6/138 (4.3)	19/397 (4.8)	0.83
Hypothyroidism, n (%)	158/1805 (8.8)	373/4094 (9.1)	0.65	11/139 (7.9)	51/396 (12.9)	0.11

CKD, n (%)	138/1830 (7.5)	490/4151 (11.8)	<0.001	17/140 (12.1)	86/404 (21.3)	0.01
CrCl (C-G) (ml/min), median (IQR)	80.2 (59.6-102.7)	78.1 (57.1-101.2)	0.02	75.1 (57.9-92.1)	64.9 (47.3-87.1)	0.006
CHA_2DS_2VASc, median (IQR)	3 (2-4)	3 (2-4)	<0.001	3 (2-1)	4 (3-5)	<0.001
HASBLED, median (IQR)	1 (1-2)	1 (1-2)	<0.001	1 (1-2)	2 (1-3)	0.001
EHRA score, median (IQR)	1 (1-2)	2 (1-3)	<0.001	1 (1-2)	2 (1-3)	<0.001
Multimorbidity*, n (%)	1061/1571 (67.5)	2586/3466 (74.6)	<0.001	110/119 (92.4)	320/335 (95.5)	0.19
Frailty, n (%)	76/1294 (5.9)	583/2752 (21.2)	<0.001	10/96 (10.4)	101/267 (37.8)	<0.001

Legend: ABC= Atrial fibrillation Better Care pathway; AF= atrial fibrillation; BMI= body mass index; CAD= coronary artery disease; CKD= chronic kidney disease; CMP= cardiomyopathy; CrCl C-G=creatinine clearance according to Cockroft-Gault formula; COPD=chronic obstructive pulmonary disease; DVT= deep vein thrombosis; EHRA= European Heart Rate Association; IQR, interquartile range; LBBB= left bundle branch block; LVEF, left ventricular ejection fraction; NYHA=New York Heart Association; PAD= peripheral artery disease; PAH= pulmonary arterial hypertension; PE= pulmonary embolism; RBBB= right bundle branch block; TE= thromboembolic; TIA= transient ischaemic attack. *Multimorbidity= defined as the concomitant presence of at least 2 different comorbidities.

After a median follow-up of 730 days [IQR 698–748], a total of 1050 (16.7%) events of the primary composite endpoint of NCO occurred. Event rates for the primary outcome were significantly lower in ABC-adherent patients as compared to ABC non-adherent patients (12.1% vs 17.2%, p <0.001 and 18.0% vs 31.8%, p=0.002, in non- cancer and cancer group respectively). The ABC-adherent patients in both groups also experienced significantly lower crude rates of MACE, all-cause death, CV death and any hospital readmissions.

Kaplan-Meier curves for the primary composite outcome of NCO, showed a significantly lower cumulative risk for full ABC-adherence vs non-adherence (**Figure 16**, Panel A and Panel B) and a progressive lower cumulative risk of the outcome for increasing number of ABC-adherent criteria both in no-cancer and cancer patients (**Figure 16**, Panel C and Panel D).

The Cox regression analyses adjusted for CHA_2DS_2-VASc score, CKD and type of AF found that full ABC adherence (compared to non- adherence/incomplete adherence) was independently associated with a lower risk of the primary composite endpoint of NCO in both groups [aHR 0.78, 95% CI 0.66–0.92 and aHR 0.59, 95% CI 0.37–0.96, in no cancer and cancer group respectively, Table 15]. Of note, adherence to increasing number of ABC criteria was independently associated with a lower risk of the primary outcome, being lowest for those with 3 ABC criteria fulfilled (vs 0 criteria; non-cancer group: aHR 0.54, 95% CI 0.36–0.81; cancer group: aHR 0.32, 95% CI 0.13–0.78, Table 15).

Similar results were found for MACE and all-cause death with some differences in the cancer group. The association between increasing number of ABC adherent criteria and a lower risk of all-cause death was confirmed in the cancer group

(Table 15). Finally, adherence to 2 or 3 ABC criteria (compared to adherence to 1-0 criteria) was associated with a significantly lower risk of NCO, all-cause death and MACE in both groups (Table 15). Conversely, no significant differences were observed for major bleeding (Table 15).

Table 13. Pharmacological and non-pharmacological management

	No Cancer group N=6005			**Cancer group** N=545		
	ABC Adherent n=1836 (30.6%)	**ABC Non-adherent** n=4169 (69.4%)	**p**	**ABC Adherent** n=140 (25.7%)	**ABC Non-adherent** n=405 (74.3%)	**p**
Pharmacological management, n (%)						
Any antiarrhythmic treatment	560/1834 (30.5)	1234/4151 (29.7)	0.53	40/140 (28.6)	101/404 (25.0)	0.41
Beta-blockers	1229/1832 (67.1)	2858/4154 (68.8)	0.18	103/140 (73.6)	265/405 (65.4)	0.07
Digoxin	185/1834 (10.1)	501/4149 (12.1)	0.02	14/139 (10.1)	50/404 (12.4)	0.46
ACE-inhibitors	890/1832 (48.6)	1510/4152 (36.4)	<0.001	68/139 (48.9)	121/404 (30.0)	<0.001
ARBs	335/1833 (18.3)	800/4149 (19.3)	0.36	19/139 (13.7)	84/404 (20.8)	0.06
Diuretics	768/1833 (41.9)	1887/4150 (45.5)	0.01	59/139 (42.4)	202/404 (50.0)	0.12
Aldosterone blockers	240/1833 (13.1)	592/4149 (14.3)	0.22	18/139 (12.9)	57/405 (14.1)	0.74
Calcium channel blockers	313/1834 (17.1)	685/4151 (16.5)	0.58	21/139 (15.1)	74/404 (18.3)	0.39
Non-DHP - CCB	111/1834 (6.1)	206/4151 (5.0)	0.08	3/139 (2.2)	25/404 (6.2)	0.06
Statins	758/1833 (41.4)	1642/4148 (39.6)	0.19	49/139 (35.3)	169/404 (41.8)	0.17
Oral antidiabetics	256/1834 (14.0)	571/4152 (13.8)	0.83	25/139 (18.0)	73/405 (18.0)	0.99
Insulin	70/1833 (3.8)	206/4151 (5.0)	0.05	7/139 (5.0)	33/405 (8.1)	0.22
Antithrombotic treatment, n (%)			<0.001			<0.001
None	159/1835 (8.7%)	455/4168 (10.9)		7/140 (5.0)	64/405 (15.8)	
Only antiplatelets	40/1835 (2.2)	566/4168 (13.6)		2/140 (1.4)	53/405 (13.1)	
VKA	413/1835 (22.5)	929/4168 (22.3)		32/140 (22.9)	80/405 (19.8)	
NOACs	1029/1835 (56.1)	1806/4168 (43.3)		85/140 (60.7)	171/405 (42.2)	
OAC plus antiplatelet	194/1835 (10.6)	412/4168 (9.9)		14/140 (10.0)	37/405 (9.1)	
Polypharmacy[#], n (%)	914/1830 (49.9)	1928/4138 (46.6)	0.01	65/139 (46.8)	209/402 (52.0)	0.28

Legend: ACE, angiotensin converting enzyme; AF= atrial fibrillation; ARB, angiotensin receptor blocker; CCB= calcium channel blockers, DHP, Dihydropyridine; NOAC= Non-Vitamin K Oral Anticoagulants; OAC= oral anticoagulants; VKA= Vitamin K antagonist. [#]Polypharmacy= contemporary use of five or more drugs.

Table 14. Adherence to ABC criteria within the study cohort

	No Cancer group (n=6005)	**Cancer group (n=545)**	p value
Number of ABC adherent criteria			0.03
0 ABC Criteria	134 (2.2)	18 (3.3)	
1 ABC Criterion	1139 (19.0)	118 (21.7)	
2 ABC Criteria	2896 (48.2)	269 (49.3)	
3 ABC Criteria	1836 (30.6)	140 (25.7)	
Specific ABC adherent criterion (alone or in combination)			
A Criterion	4520 (75.3)	409 (75.0)	0.91
B Criterion	4825 (80.3)	428 (78.5)	0.31
C Criterion	3094 (51.5)	239 (43.9)	0.001

Legend: ABC= Atrial fibrillation Better Care pathway. The "A" criterion was fulfilled if the patient was properly treated with oral anticoagulant (OAC) according to thromboembolic risk; patients not qualifying for OAC (i.e. CHA_2DS_2-VASc 0 in males or 1 in females) and not treated with OAC, also qualified for the 'A' criterion; the "B" criterion was fulfilled if the patient presented with an EHRA score of I (no symptoms) or II (mild symptoms not affecting daily life); the "C" criterion was fulfilled if the patient were appropriately managed for the most frequent comorbidities associated with AF (i.e. hypertension, coronary artery disease, peripheral artery disease, heart failure, stroke/ transient ischaemic attack, and diabetes mellitus).

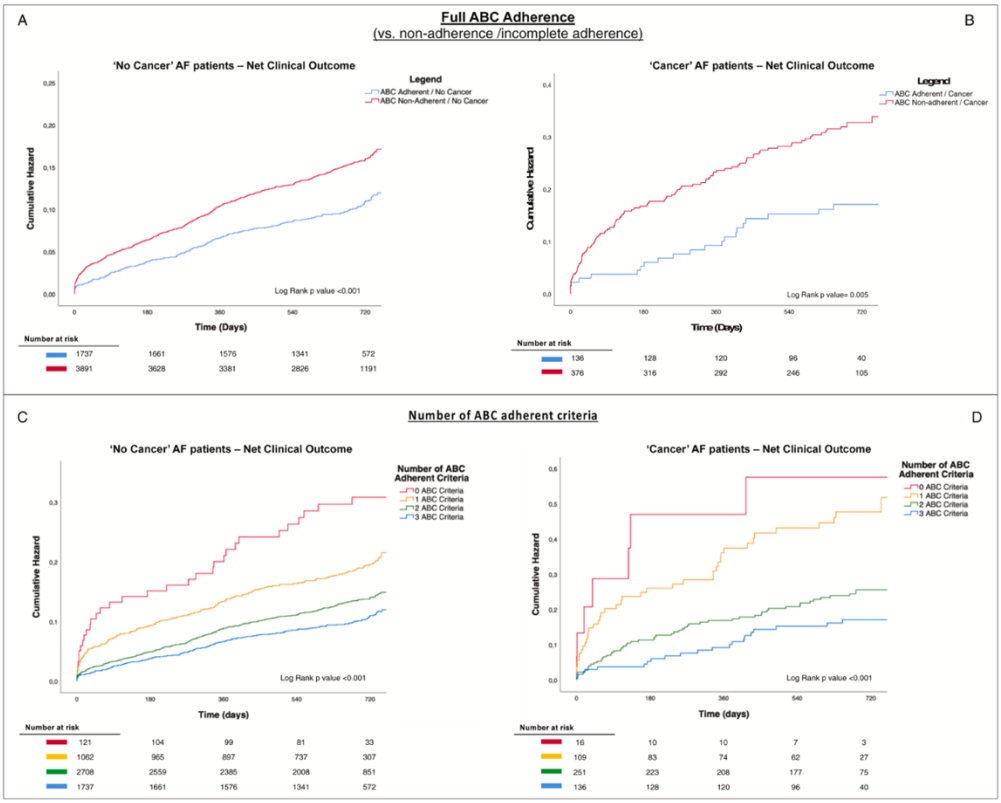

Figure 16. Kaplan-Meier Curves for the primary outcome according to ABC pathway adherence

Table 15. Adjusted Cox Regression analysis for the main outcomes according to adherence to ABC Pathway

	Number of ABC adherent criteria								**Full Adherence** (vs. Non-adherence /incomplete adherence)	
	1 Criteria (vs. 0)		**2 Criteria** (vs.0)		**3 Criteria** (vs.0)		**2-3 Criteria** (vs.1-0)			
No Cancer group										
	aHR* [95% CI]	**p value**	**aHR* [95% CI]**	**p value**	**aHR* [95% CI]**	**p value**	**aHR* [95% CI]**	**p value**	**aHR* [95% CI]**	**p value**
NCO†	0.86 [0.58-1.29]	0.48	0.61 [0.41-0.89]	0.01	0.54 [0.36-0.81]	0.03	0.66 [0.56-0.77]	<0.001	0.78 [0.66-0.92]	0.005
MACE‡	0.67 [0.42-1.06]	0.09	0.43 [0.27-0.67]	<0.001	0.33 [0.21-0.54]	<0.001	0.56 [0.45-0.69]	<0.001	0.65 [0.51-0.83]	<0.001
All-cause death	0.71 [0.45-1.12]	0.14	0.47 [0.31-0.73]	0.001	0.43 [0.27-0.68]	<0.001	0.61 [0.51-0.75]	<0.001	0.77 [0.62-0.96]	0.02
Major bleeding	0.73 [0.25-2.13]	0.56	0.66 [0.23-1.85]	0.43	0.98 [0.34-2.79]	0.97	1.01 [0.64-1.57]	0.97	1.41 [0.95-2.11]	0.08
Cancer group										
	aHR* [95% CI]	**p value**	**aHR* [95% CI]**	**p value**	**aHR* [95% CI]**	**p value**	**aHR* [95% CI]**	**p value**	**aHR* [95% CI]**	**p value**
NCO†	0.77 [0.34-1.74]	0.53	0.44 [1.19-0.98]	0.04	0.32 [0.13-0.78]	0.01	0.51 [0.35-0.74]	<0.001	0.59 [0.37-0.96]	0.03
MACE‡	1.59 [0.36-6.94]	0.53	0.51 [0.11-2.27]	0.37	0.39 [0.07-2.11]	0.39	0.31 [0.16-0.59]	<0.001	0.49 [0.18-1.27]	0.14
All-cause death	0.69 [0.28-1.67]	0.41	0.40 [0.16-0.95]	0.04	0.29 [0.11-0.79]	0.01	0.51 [0.33-0.78]	0.002	0.60 [0.33-1.06]	0.08
Major bleeding	0.78 [0.09-6.47]	0.82	0.66 [0.08-5.13]	0.69	0.39 [0.04-3.49]	0.41	0.71 [0.32-1.58]	0.41	0.55 [0.20-1.48]	0.24

Legend: ABC= Atrial fibrillation Better Care pathway aHR, adjusted hazard ratio; CI confidence interval; †NCO= composite of all-cause death, any thromboembolism (TE), acute coronary syndrome (ACS) and major bleeding; ‡MACE= composite of any TE/ACS/cardiovascular death. *Adjusted analysis for CHA_2DS_2-VASc score, chronic kidney disease and type of atrial fibrillation (for NCO, MACE and all-cause death) or for HASBLED score, sex, and type of atrial fibrillation (for major bleedin

Discussion

Our analyses were derived from a prospective, observational, large-scale multicentre study on AF patients. The study enrolled more than 11,000 consecutive patients in 250 centres from 27 participating European countries thus providing a real-world and updated snapshot of current cardiology practice and contemporary clinical management of AF.

First, our analyses highlighted the complexity of the pathophysiology, epidemiology, and clinical management of European AF patients. Our results reinforce the importance of comprehensive management in the care of AF patients who may be burdened by poor prognosis and increased risk of outcomes if not properly treated.

Phenotype classification of AF patients using cluster analysis and impact on clinical management and outcomes

The first analysis (i.e. Clinical Phenotype Classification Using Cluster Analysis) showed that three key clinical phenotypes can be identified among European AF patients. The first cluster comprised older patients with a prevalent high burden of non-cardiac comorbidities (Cluster 1); the second cluster was characterized by younger patients, with a low burden of comorbidities and an overall low thromboembolic risk (Cluster 2); the third cluster included older AF patients with a high burden of CV risk factors and comorbidities and exhibiting an overall high burden of multimorbidity and frailty, along with the highest thromboembolic risk (Cluster 3). The three clusters showed significant differences in terms of clinical management, particularly in anticoagulant therapy, leading to a differential risk in long-term major adverse events. Lastly, both Cluster 1 and Cluster 3, showed a higher utilization of healthcare resources during follow-up and a higher risk of major adverse events, particularly those patients in Cluster 3.

Machine-learning-based data analysis has been increasingly applied to biomedical scientific research, even in cardiovascular health (109-111). Given the heterogeneity of AF, conventional classification only based on disease subtype or arrhythmia patterns may not adequately characterize the AF patient population (112). Accordingly in the recent years, several efforts have been made to improve

the taxonomy of clinical classification of AF and other diseases (e.g., heart failure, valvular aortic stenosis, pulmonary arterial hypertension) by using different machine learning approaches (109-111). Cluster analysis, is one of the most popular unsupervised algorithms and it is an excellent statistical approach for capturing relevant dissimilarities in disease phenotypes and identifying different patients' clusters with distinct outcomes (113).

In brief, cluster analysis is an exploratory statistical tool aimed at generating natural groups (or clusters) within the data. The analysis can identify patients who are phenotypically homogenous and group them based only on measured different clinical characteristics between cases without investigators' supervision. Using this statistical approach, we can identify different groups of AF patients who shared common clinical phenotypes and evaluate the association between identified clusters and clinical outcomes. Use of this analytic technique indeed allows us to perform insightful epidemiological analysis, allowing better risk stratification, which could lead to more focused management and treatment (113-115).

Cluster analysis has been recently applied in other observational AF cohorts. One of the first studies that applied cluster analysis in a large cohort of AF patients was conducted by Inohara et al. (116) The authors, using data from the ORBIT-AF Registry, showed that unsupervised cluster analysis identified four clinically relevant AF phenotypes (i.e., low comorbidity cluster, young/behavioural disorder cluster, device implantation cluster, atherosclerotic-comorbid cluster). Interestingly, similar to our analysis, when compared to the low comorbidity cluster, the occurrence of adverse outcomes was significantly higher in the three other clusters. A Japanese cluster analysis based on the KiCS-AF registry similarly found an atherosclerotic comorbid AF cluster phenotype, as was found in the US cohort from the ORBIT-AF registry (116, 117). More recently, a cluster analysis conducted by using pooled individual patient data from two randomized, open-label AF trials (AMADEUS and BOREALIS) identified four different clinically relevant phenotypes that had unique clinical characteristics and different outcomes (118).

In this context, our analysis provides novel evidence, representing the first large cluster analysis focused on European AF patients. Our findings underline the pivotal role of comorbidities in influencing the occurrence of major adverse events, shedding light on the differential impact of non-CV and CV comorbidities in AF

patients. While some previous analyses have raised some concerns about methodological limitations that may affect the reliability and reproducibility of machine-learning-based data, we believe that contextualizing our data within existing literature underscores important insights (113). Indeed, our study emphasizes not only the significance of individual comorbidities in determining outcomes but also highlights the interconnected nature of these comorbidities and their collective influence on the overall disease trajectory. The findings of this analysis data are also in line with more recent research in the area of multi-morbidity, which now distinguishes patterns/clusters of conditions, clearly defined in terms of sociodemographic, clinical and functional characteristics, beyond the mere presence of multiple conditions (119). Our results also underline the importance of stratifying patients' characteristics and identify those clinical phenotypes who are associated with adverse events, beyond the mere focus on thromboembolic risk. Cluster analysis is not to be considered as a formal proposal of a new classification system for AF since the clustering process may be not easily applicable in clinical daily life. However, the information gathered from this analysis reinforces the concept that the presence of comorbidities increases the risk of AF patients. The aim of this intriguing and validated statistical approach to a large cohort of European AF patients is to capture relevant clinical factors and phenotypic similarities often overlooked in conventional classifications. Defining phenotype groups could be a step toward precision medicine and a more comprehensive characterization of AF patients (41). Taken together these results highlight the high degree of heterogeneity in patients with AF suggesting the need for a phenotype-driven approach to comorbidities which could provide a more holistic approach to management aimed at improving patients' outcomes.

Real-world applicability and impact of early rhythm control on clinical management and outcomes

Our second analysis was focused on the long-debated issue whether rate vs. rhythm control strategy could have a differential impact on major clinical outcomes, especially the risk of all-cause death occurrence.

The "Early Treatment of Atrial Fibrillation for Stroke Prevention Trial" (EAST-AFNET 4) study (107) recently tested the hypothesis that early initiation of rhythm control therapy may have an advantage in terms of the risk of major adverse

events. Despite some important limitations, the EAST-AFNET 4 trial provides useful insight for early rhythm control to reduce the rate of stroke in selected patients with AF. In particular, the study found a 21% relative risk reduction (6–34% CI) for a composite primary outcome of CV death, stroke, acute coronary syndrome and hospitalization/worsening of heart failure. However, given that the intervention arm had structured follow-up and a 'package of care', additional data was needed to assess the applicability of these findings to real-world clinical practice.

In our analysis we found that only about one-third of European AF patients would be eligible for the original EAST-AFNET 4 study. Second, patients treated with early rhythm control were more likely to be younger, burdened with less comorbidities, were more symptomatic and had a more established form of AF. However, early rhythm control was associated with better quality of life during follow-up, but with a significantly increased use of health-care resources, as well as a higher risk of hospital readmissions.

Importantly, our analysis found that early rhythm control was associated with a lower rate of major adverse events, but this difference was non-significant in the fully adjusted multivariable regression models, being mediated by differences in baseline characteristics and clinical risk profile. In particular, clinical outcomes were not different to the 'no rhythm control' group who were fully adherent to the ABC pathway.

The debate on rate vs. rhythm control has been running for the last two decades. In the 'Atrial Fibrillation Follow-Up Investigation of Rhythm Management' study, more than 4000 AF patients were randomized to rate vs. rhythm control strategies but the trial did not find any differences in mortality between the two groups in terms of adverse clinical outcomes (120). Several large meta-analyses have failed to show any significant differences in clinical outcomes between rate and rhythm control strategies (121, 122).

However, based on evidence from recent randomized controlled trials and registries, the primary objectives of rhythm control should aim at improving AF-related symptoms and the quality of life (122). Our findings indeed showed that an early rhythm control strategy was associated with an overall better quality of life, consistent with previous data.

Nevertheless, contemporary practice is shifting towards advocating rhythm control not only for persistent symptoms but also to mitigate the risk of adverse cardiovascular outcomes in individuals with new-onset or recently diagnosed AF(122). In this context, it should be highlighted that in our analysis, based on real-world practice, only one-third of patients could be considered for management with early rhythm control based on the EAST-AFNET 4 criteria. While a difference in risk of major adverse outcomes exists when comparing early rhythm control to no rhythm control, this difference may be partly due to the differences in baseline characteristics, as shown in the fully adjusted model. Our results reinforce the concept that early rhythm control is a key component of AF patients but should be integrated into a structured and holistic follow-up, aligning with the ABC pathway (5, 123).

Atrial fibrillation and cancer: adherence to the ABC pathway and associated clinical outcomes

Finally, our third analysis based on this large dataset of European AF patients was focused on the highly clinically complex subgroup of patients with cancer. The concomitant presence of cancer and AF poses a significant challenge due to the inherent clinical complexity within this group of patients (124, 125). There is a well-documented higher risk of AF in cancer patients, attributed partly to shared epidemiological backgrounds and comorbidities, and partly to specific anti-cancer treatments that may contribute to arrhythmia itself (126-130). Adherence to the ABC pathway is recommended by the most recent guidelines on AF management and a positive impact on outcomes was reported in different analyses, but a specific focus on AF patients with cancer was lacking. Indeed, there is a need to assess adherence to the ABC pathway in specific high-risk populations under-represented in large randomised trials, such as AF patients with cancer who are characterized by a high degree of complexity in clinical management and more severe outcomes. For these reasons, we performed this analysis aimed at investigating the adherence to ABC pathway and its impact on adverse outcomes in patients with active or prior cancer.

The main findings of the present analysis, which is the first specifically focused on evaluating the ABC-pathway in AF patients with cancer, were: (i) ABC-adherence

in patients with cancer was suboptimal; (ii) overall, adherence to the “C” criterion was more critical, being specifically lower in cancer patients; (iii) adherence to the ABC pathway was independently associated with a lower risk of the composite endpoint of NCO in cancer AF patients, with progressively lower risks when more ABC criteria were fulfilled.

While the primary attention in the management of AF patients with cancer has been focused on anticoagulation and the associated risk of bleeding(128, 131-133), the application of guidelines recommendations also implies a comprehensive and structured management based on the ABC-pathway, even if no data on the potential impact of this approach were available in literature.

Despite the implementation of oral anticoagulants in AF patients with cancer and the general safety and effectiveness profile of NOACs in this setting, there is a need for improved adherence to all components of the ABC pathway to enhance patient survival (127, 134). Notably, adherence to the ABC pathway was found to be particularly suboptimal in cancer patients, especially in fulfilling the "C" criterion. Both the complexity of patients with cancer and, likely, a polarization of medical care on the neoplasm in patients with active cancer may help to explain this finding. Given the shared pathophysiological mechanisms between AF and cancer, addressing cardiovascular risk factors in cancer patients is crucial, as concomitant cardiovascular conditions may be undertreated during follow-up, impacting long-term outcomes (124).

Our findings stress the positive impact of ABC pathway adherence in both general AF patients and those with cancer, highlighting a significant reduction in net clinical outcomes and all-cause mortality even when patients were partial adherence to the ABC criteria demonstrated with a dose-dependent risk reduction.

Our results emphasized how a structured approach based on the ABC pathway is the appropriate way to reduce the risk of adverse outcomes even in the high and complex population of AF patients with cancer. Additionally, the individual components of the ABC pathway act synergistically and a structured and holistic approach to AF patients, involving different specialists, should be even more encouraged. Indeed, an integrated care following the ABC pathway and,

encompassing different healthcare professionals such as cardiologists, oncologists, intensive care unit specialists, geriatricians, general practitioners, and others, should be further promoted (124). In conclusion, management of AF patients with cancer demands a collaborative involvement of various healthcare professionals, positioning the patient at the center of this multidisciplinary team.

Limitations

Our analyses have inherent limitations that should be acknowledged. The main limitation relates to their observational nature and data presented do not imply causality, but report associations. Given the observational cohort design, the completeness of data is not as high as clinical trial; hence, this aspect may have partially limited our analytical capability.

Conclusions

Our analyses highlighted the complexity of the epidemiology, pathophysiology, and clinical management of AF patients. Our results reinforce the importance of comprehensive and holistic management in the care of AF patients who may face a poor prognosis and an increased risk of adverse outcomes without proper treatment. These analyses, derived from a large European observation cohort study, will help to adapt and strengthen practice guidelines recommendations for “real-world” AF patients, identifying where care deviates from guidelines and highlighting existing treatment gaps.

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