Atrial Fibrillation as a Clinical Model of Multimorbidity: Current Evidence, Experimental Data and a Proposal for Management

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Ad Eugenia
A Mia Madre

Dedicato alla memoria di Giulio Regeni, che dedicando la vita a porsi domande,
ha tristemente incontrato la morte per aver perseguito la conoscenza

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1. INTRODUCTION

1.1 Atrial Fibrillation Epidemiology

Atrial fibrillation (AF) is the most prevalent and incident among the clinical arrhythmias[1]. Estimates of the prevalence of AF in the United States ranged from ≈2.7 million to 6.1 million in 2010 and AF prevalence is estimated to rise to 12.1 million in 2030. In the European Union, the prevalence of AF in adults >55 years of age was estimated to be 8.8 million (95% CI, 6.5–12.3 million) in 2010 and was projected to rise to 17.9 million in 2060 (95% CI, 13.6–23.7 million)[1].

Data retrieved from the Global Burden of Disease project showed that worldwide prevalence of AF is significant in Europe, North America and Australia, being higher in United States, as well as quite relevant in Russia [Figure 1]. Similar data can be found in relation to AF incidence [Figure 2]. Further, when the changes in prevalence and incidence are examined appears clear how, compared to 1990, significant increases for both indicators were found in the vast majority of world countries [Figure 3, Figure 4]. This evidence was also assessed in several specific report about AF epidemiology[2,3]. Furthermore, specific epidemiological data from developing countries showed that, even if on a lower magnitude, the increase in prevalence and incidence was significant even in these countries[4]. Taking together all the evidence available, it is possible to underline how we are facing a "growing global epidemic" for AF.

Both prevalence and incidence have been found to progressively increase according to age and being higher in males than in females AF patients[1,5]. A higher incidence of AF was also described in White subjects, compared to other ethnicities[1].

It has been also observed that AF is responsible of a relevant proportion of daily-adjusted life years (DALYs)[4], that was observed as significantly increasing in 2017 compared to 1990 [Figure 5]. This increase in DALYs was also evident when examined according to male and female AF patients [Figure 6].

Lastly, risk of death attributable to AF was found to be increasing compared to 1990, both in male and female AF patients, in developed and developing countries[4] [Figure 7]. This data related to epidemiology of AF are paired with increased costs both at individual and population level, significantly affection health-care systems[6].

1.2 Relationship between Risk Factors and Incident AF

The increasing incidence of AF in the worldwide scenario has been strictly associated with the increased prevalence of various cardiovascular and non-cardiovascular risk factors[7,8]. Indeed, modifiable lifestyle risk factors as alcohol consumption, physical activity, psychological distress and smoking habit, as well as specific cardiovascular risk factors as hypertension, diabetes mellitus, obesity and obstructive sleep apnea syndrome have been significantly associated with the presence of new AF (Table 1). In particular for hypertension, diabetes mellitus and obesity a dose-response relationship was identified. This was also demonstrated by a recent systematic review[9].

The strict causal relationship between risk factor and incident AF, was also verified by the effectiveness of risk factor prevention strategies in terms of AF risk reduction. In the ARREST-AF study, an aggressive risk factors control management, aimed to control at the most all the major known cardiovascular risk factors[10], reduced the risk

for AF recurrence in obese patients with at least 1 cardiovascular risk factor that underwent an ablation procedure[11]. This approach seems to suggest that to reduce at the most the risk of AF occurrence, a stricter risk factor control is needed, in order to combine all the beneficial effects of all the possible interventions. Extending this approach to the general population, we can hypothesize that interventions to obtain a strict risk factor control would be able to significantly reduce the overall risk of incident AF[8] [Figure 8]. A modelling analysis in which the impact of various prevention strategies[11,12] have been projected to the incidence rate of AF in a general population, showed how obtaining a progressively more strict control would grant to significantly reduce the rate of incident AF[8].

1.3 Thromboembolic Risk in AF Patients

Ischemic stroke is the most common cardiovascular adverse event in AF patients, with an overall 5-fold increase in stroke risk and reported incidence of 19.5 per 1000 patient-years in 2002[13]. Additionally, stroke severity and recurrence risks are higher with AF.

Evaluation of thromboembolic risk at baseline is a pivotal step in the management of thromboembolic risk in AF patients. The most largely used tool to evaluate this risk is the CHA_2DS_2-VASc score (Table 2)[14]. The almost universal adoption of CHA_2DS_2-VASc score reflects the current data available, indicating it as the clinical risk score that provides better balance between evidence, practicality and precision[15]. A recent comparative effectiveness review about the ability of the scores to predict thromboembolic and bleeding events, reported that $CHADS_2$, CHA_2DS_2-VASc and the recent ABC-Stroke[16] scores all had similarly the best predictive capacity for stroke occurrence[17]. Nonetheless, CHA_2DS_2-VASc differs from other scores for its

capacity to effectively identify those patients with very low risk, also compared to ABC-Stroke it does not need to perform expensive and time-consuming laboratory tests to be drawn[15]. Furthermore, recently a systematic review and meta-regression demonstrated that CHA_2DS_2-VASc score represent the score with the highest probability to perform as the best in predicting occurrence of all-cause death in AF patients[18].

Oral anticoagulation (OAC) therapy with the vitamin K antagonists (VKA; e.g., warfarin), has been central for stroke prevention in the management AF. More recently, several drugs with direct inhibitory effects on thrombin and factor Xa have been developed[19]. These non-VKA oral anticoagulants (NOACs), namely, dabigatran etexilate, rivaroxaban, apixaban, and edoxaban, are proved to be as effective as warfarin for the prevention of stroke and systemic thromboembolism events in patients with AF[20]. All major guidelines recommend use of NOACs as well as well managed VKA for the prevention of stroke and thromboembolic risk in non-valvular AF patients[19,21–23]. However, OAC treatment is unavoidably associated with an increased risk of bleeding, regardless of OAC type used[24,25]. In patients treated with VKA, quality of anticoagulation control, as expressed as time in therapeutic range (TTR), is a major determinant of major adverse outcomes[26–30], including stroke and major bleeding, hence interventions to obtain an optimal TTR control can be successful to optimize stroke prevention and minimize risk of bleeding events[13]. A TTR >70% is recommended to obtain an optimal control of anticoagulation treatment[19]. Conversely, in patients treated with NOACs, an optimal adherence to treatment is strongly needed to reduce the risk of stroke and major bleeding[31].

1.4 Increased Risk of CV Death and All-Cause Death in AF

In the last years, evidence raised about an increased risk of major adverse events, beyond the above-mentioned discussed risk of stroke, in particular cardiovascular (CV) death and all-cause death, even despite the use of OAC[32–37]. It emerges from several observational studies and secondary analyses of randomized controlled trials that patients with AF have a high risk of death, even higher than the risk of stroke.

An analysis from an observational cohort in France showed how cumulative risk of death was progressively higher, even than the risk of stroke, over a long-term follow-up observation with CV death being the main contributor[36]. A pooled analysis derived from Phase 3 trials about non-vitamin K antagonist oral anticoagulants in AF showed that stroke accounted only for less than 6% of deaths, with cardiac and other vascular related deaths accounting for more than 50% of events[38].

An analysis comparing two European observational cohorts enrolled 12 years each other apart documented that risk of CV death and all-cause death significantly increased over time, and is independently associated with increased age and several concomitant CV and non-CV comorbidities[34].

1.5 Role of Specific Comorbidities in AF Clinical History

As described, several comorbidities have a significant impact in determining AF clinical history[34].

It is largely known that hypertension, defined as history of hypertension at the beginning of observation, is associated with an increased risk of adverse events in AF patients[39,40]. Indeed, hypertension is considered among CHA_2DS_2-VASc[14] and

HAS-BLED[41] risk scores as one of the main factors in predicting both thromboembolic and bleeding risk. A subgroup analysis from the 'Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation' (ARISTOTLE) trial found that clinical history of hypertension was associated with an increased risk of thromboembolic events (HR: 1.24, 95% CI: 1.03-1.49)[42], while an analysis from the 'Randomized Evaluation of Long-Term Anticoagulation Therapy' (RE-LY) trial documented, conversely, an increased risk for major bleeding (HR: 1.25, 95% CI: 1.06-1.46)[43]. In an analysis from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), blood pressure visit-to-visit variability was found to be associated independently associated with an increased risk for major adverse clinical outcomes, particularly stroke and major bleeding occurrence[44].

Also diabetes mellitus have been described as significantly associated to increased risk of major adverse outcomes in AF patients[45,46]. Some reports also described that duration of diabetes mellitus[47], as well as glycaemic control[48,49].

In the recent years accumulating evidence suggest a strong relationship between AF and peripheral arterial disease (PAD)[50–52]. In particular, AF patients affected with PAD are found to be at increased risk of major adverse outcomes[53]. Since 2000, Frost and colleagues exploring the association between AF and incident stroke occurrence found that, despite a not particularly high prevalence, PAD was independently associated with stroke occurrence, both in male and female subjects (HR: 1.3, 95% CI: 1.0-1.7 and HR: 1.3, 95% CI: 1.0-1.6)[54]. A Follow-up analysis of the "Atrial Fibrillation Registry for Ankle-brachial Index Prevalence Assessment: Collaborative Italian Study" (ARAPACIS) study further extended the evidence about

association between AF and PAD in determining adverse outcomes. Indeed, ABI ≤0.90 was found significantly associated with incident MI (HR: 2.62, 95% CI: 1.32-5.20), vascular death (HR: 2.24, 95% CI: 1.34-3.73) and the composite outcome of any vascular event (HR: 1.50, 95% CI: 1.11-2.03) over a 3 years follow-up time[55].

Recently, the role of chronic obstructive pulmonary disease (COPD) has been assessed in determining risk of adverse outcomes in AF patients. In a subgroup analysis from the EURObservational Research Programme in AF (EORP-AF) found that COPD was associated with higher rates of CV death, all-cause death and the composite outcome of any thromboembolic event/bleeding/CV death. Also, COPD was found independently associated with a higher risk of all-cause death[56]. Data coming from an observational study in a Chinese AF population reported that patients with both AF and COPD were at higher risk for both all-cause death (hazard ratio [HR]: 1.491) and CV death (HR: 1.595)[57]. A sub-group analysis from the ARISTOTLE study reported that COPD patients had a significant risk excess for both CV and all-cause death, with a 40% to 60% relative risk increase[58]. Both studies reported no influence of COPD in determining stroke occurrence. A recent analysis from the 'Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation' (ROCKET AF) trial also showed that COPD confers an higher risk for both CV death (HR: 1.42) and all-cause death (HR: 1.65)[37].

Coronary artery disease (CAD) is also associated with worst outcomes in AF patients. A study from a large population-based cohort documented that presence of CAD was associated with an increased risk of stroke, myocardial infarction, CV death

and all-cause death. Also, the risk of events was proportionally higher according to the extent of CAD (1, 2 or 3 vessels)[59].

A recent paper derived from an observational cohort documented that also metabolic syndrome is associated with major adverse cardiac events (MACE), myocardial infarction, coronary revascularization and CV death. After a propensity matching adjustment metabolic syndrome conferred an independent risk for MACE (HR: 1.87, 95% CI: 1.21–3.01), myocardial infarction (HR: 1.72, 95% CI: 1.54–5.00), coronary revascularization (HR: 2.18, 95% CI: 1.69–3.11), and CV death (HR: 2.27, 95% CI: 1.14–5.11)[60].

Chronic kidney disease is an established risk factor for stroke, major bleeding, CV death and all-cause as it emerges from several studies[61]. The most striking issue in the relationship between chronic kidney disease and AF is the contemporary increased risk of stroke and major bleeding[62]. The Loire Valley Atrial Fibrillation Project showed that CKD, defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2, was associated with a higher incidence of ischemic stroke/thromboembolism events, but multivariable Cox regression analysis did not demonstrate an independent effect of renal impairment on predicting major adverse events, after adjusting for CHA_2DS_2-VASc score risk factors[63,64]. At the same time, in the same study the authors provided evidence for an increased risk of major bleeding. An analysis from the 'Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation' (SPORTIF) III and V studies, found that CKD was associated with risk of stroke, major bleeding and all-cause death[65]. The same study also underlined how the relationship between CKD and major adverse outcomes was strictly and significantly dependent on quality of anticoagulation control, as expressed by TTR[65].

1.6 The Concept of Multimorbidity and AF

The concept of multimorbidity (defined as the concomitant presence of two or more chronic conditions) has gained much medical attention in the last decades[66]. As with AF, the prevalence of multimorbidity increases with increasing age and is associated with a high risk of mortality, reduced functional status, increased healthcare expenditure and use of resources[67]. As part of the biological, sociological and clinical complexity associated with healthcare[68], multimorbidity demands solid integrated care and an holistic approach to the patient in order to properly manage the associated risks[67]. Moreover, multimorbidity is very common in patients with CV disease[69].

The Charlson Comorbidity Index (CCI) has been validated as a reliable tool to evaluate the burden of multimorbidity in the general population and is significantly associated with an increased risk of all-cause death during the long-term follow-up[70]. Furthermore, CCI has been extensively validated in patients with CV disease[71]. Nevertheless, despite AF being associated with several comorbidities[19], scarce data exist about the overall burden of multimorbidity, or the relationship with CCI, and AF.

2. OBJECTIVES OF THE DOCTORAL PROJECT

2.1 General Objectives of Doctoral Project

The general objectives of the project were to make a comprehensive report about prevalence of major cardiovascular and non-cardiovascular comorbidities among large AF patients cohorts derived from both contemporary randomized controlled trials (RCTs) and observational studies; further the project aimed to describe the interactions of clinical comorbidities with thromboembolic risk and antithrombotic therapy. Also, the project intended to report relationship between principal comorbidities and all-cause death occurrence. These initial general objectives of the study were achieved in the first part of the doctoral course and reported above, as part of the current available evidence regarding AF and its clinical history. Those objectives were achieved through multiple subgroup analysis, derived from several observational, randomized controlled trials and administrative databases.

After the first part of the doctoral course was completed, the project moved to describe in more detail, among the role of single conditions and comorbidities, the burden of multimorbidity in AF in various specific scenarios. Further, the project aimed to describe the impact of multimorbidity in AF in determining OAC prescription, quality of OAC control, functional status, quality of life and major adverse outcomes.

2.2 Specific Aims of the Thesis

Moving from the general objectives of the doctoral project, this thesis will describe results derived from multiple analysis about the impact of multimorbidity on various health indexes and outcomes, derived from several different populations.
More precisely, data from the following populations and studies will be reported:

- 'Atrial Fibrillation Follow-up Investigation of Rhythm Management' (AFFIRM)
  - The aims for this analysis were to analyse in a cohort derived from a randomised controlled trial the relationship between multimorbidity, expressed as the cumulative addition of the various comorbidities and TTR, quality of life and stroke, major bleeding, CV death and all-cause death.
- 'EURObservational Research Programme in Atrial Fibrillation' (EORP-AF) General Pilot Study
  - The aims for this analysis were to analyse in a cohort derived from a multicentre observational European-wide study the relationship between multimorbidity, expressed as the cumulative addition of the various comorbidities, prescription of OAC and major adverse events, in particular CV death and all-cause death.
- 'REgistro POliterapie SIMI' (REPOSI) Study
  - The aims for this analysis were to analyse in a cohort of hospitalised elderly (≥65 years old) patients the impact of multimorbidity, expressed as the Cumulative Illness Rating Scale Index of Comorbidity (CIRS-IC), in terms of functional status and its impact on CV death and all-cause death.
- Lombardy Region Administrative Health Databases
  - The aims for this analysis were to retrospectively analyse in a population-based cohort the relationship between multimorbidity, expressed as CCI, and AF and its impact on OAC prescription and stroke, major bleeding and all-cause death occurrence
- 'Fibrilacion Auricular: influencia del Nivel y Tipo de Anticoagulacion Sobre la Incidencia de Ictus y Accidentes hemorragico' (FANTASIIA) Study
  - The aims for this analysis were to analyse in a multicentre observational nationwide cohort the impact of multimorbidity, expressed as baseline

calculated CCI, on TTR and stroke, major bleeding, CV death and all-cause death.

Hence, on the basis of previous evidence, experimental data provided will be discussed and interpreted in order to give an overall picture of the impact of multimorbidity in the context of AF. Lastly, a proposal for an improved management of these patients, originated by the results provided, will be presented.

3. MATERIALS AND METHODS

3.1 General Characteristics of the Studies and Analyses Performed

In this section the general characteristics of the studies used to perform the analyses above described. The specific methods related to indexes and outcomes, where it does apply will be also provided.

3.1.1 The AFFIRM Study

The AFFIRM study was a nationwide multicentre open-label randomized controlled trial, held in US and Canada from 1995 to 2001 by the US National Institute of Health. The original study aimed to compare the rate and rhythm control management strategies in terms of risk of death prevention. A total of 4060 patients were enrolled, followed up for a mean (SD) time of 3.5 (1.3) years. Patients were assigned to rate or rhythm control at baseline and then managed according to physicians' discretion in relation to the current evidence-based practice[72].

Multimorbidity was evaluated as the cumulative addition of the 12 conditions available from the study database. On the basis of the distribution of the total number of conditions that were reported for each patient, the cohort was divided into four quartiles. Quality of anticoagulation control was evaluated according to TTR, for those patients prescribed with OAC. In a reduced cohort of patients (795, 19.5%) physical and mental health were evaluated according to Short Form 36 Health Survey (SF-36) (https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html), quality of life was evaluated according to Ferrans & Powers Cardiac III Quality of Life Index (https://qli.org.uic.edu/index.htm).

First stroke, first major bleeding, CV death, all-cause death, first hospitalization and first CV hospitalization were the outcomes considered.

3.1.2 The EORP-AF General Pilot Study

The EORP-AF General Pilot Study was a prospective multi-national survey conducted by the European Society of Cardiology in 9 European countries (Belgium, Denmark, Netherlands, Norway, Poland, Romania, Greece, Italy, and Portugal) to determine clinical features, treatment patterns and outcomes amongst patients with AF managed by cardiologists[73]. The study enrolled both in- and outpatients accessing to cardiology services (either hospital or office-based centres) with AF as a primary or secondary diagnosis. The qualifying AF event was recorded by a 12-lead ECG, 24 h ECG Holter or other electrocardiographic documentation and should have been occurred within the 12 months before the enrolment. From February 2012 to March 2013, a total of 3,119 AF patients were enrolled. Follow-up observation was extended up to 3 years. The present analysis considered the 2119 patients available for the 3 years follow-up analysis, with a final number of 1629 of patients included.

Multimorbidity was evaluated as the cumulative addition of 12 conditions as retrieved from the original database. On the basis of the median number of comorbidities, the cohort was divided into 'low multimorbidity' and 'high multimorbidity' groups.

Prescription of OAC was evaluated at baseline. Stroke, any thromboembolic event (TE), bleeding events, CV death, all-cause death, any AF rehospitalization, any CV rehospitalization were considered as outcomes.

3.1.3 The REPOSI Study

The REPOSI study is a multicentre collaborative observational registry jointly held by the Italian Society of Internal Medicine (SIMI), the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation and the IRCCS Mario Negri Institute of Pharmacological Research, is based upon the participation of a representative network of internal medicine and geriatric wards in Italy. Full details about register design and specific aims have been reported[74]. Briefly, REPOSI was held for three non-consecutive years (2008, 2010, 2012) and then annually from 2014 onwards. In each of these years, consecutive patients acutely admitted to the participating wards and being older than 65 years were enlisted in the register over a period of 4 weeks on a quarterly basis (*i.e.* February, June, September and December). All diagnoses made at hospital admission were coded according to the International Classification of Diseases – 9th Edition (ICD-9) system. Medication use at admission and discharge was assessed according to the Anatomic Therapeutic Chemical (ATC) Classification System.

Multimorbidity was evaluated according to the CIRS-IC index, an established tool to evaluate multimorbidity in elderly patients[75]. All patients with a diagnosis of AF, with data about CIRS-IC and available follow-up data were included in this analysis. Out of the 7003 patients enrolled in the registry so far, a total of 1102 patients were considered for this analysis. The analysis was performed according to CIRS-IC tertiles.

The Short Blessed Test (SBT) was used as a tool to evaluate cognitive functions[76]. The Geriatric Depression Scale (GDS) was considered as a tool to evaluate depression in the elderly[77]. Patient functional status was assessed with the Barthel

index[78]. CV death, all-cause death and rehospitalization were the outcomes considered.

3.1.4 The Lombardy Region Administrative Health Databases

This study used linkable administrative health databases of the Lombardy Region which include the demographic data of all residents and detailed information on hospital admissions and drug prescriptions. To date, with a population of more than 10 million inhabitants, Lombardy is the largest Italian region, comprising highly populated urban areas, as well as industrial and rural ones.

All databases are linked anonymously using unique encrypted patient codes, in accordance with the Italian privacy regulations. By virtue of a specific agreement between the Mario Negri Institute and the Lombardy Region, for the use of the anonymous administrative data derived from these databases it was not necessary to obtain approval from any ethics committee. Data were available for fifteen consecutive years, from 2000 to 2014. For any hospital admission, all discharge diagnoses have been coded according to International Classification of Disease 9th revision [ICD-9]. Moreover, the hospital discharge database records the date of hospital admission, date of discharge or death and procedures performed during admission. The drug prescription database contains the drug name and its Anatomical Therapeutic Chemical classification code, quantity and dispensation date after the discharge at home, but not during the index hospitalization. All data about subjects ≥40 years old (>6 million inhabitants) were available and included in this analysis.

Data from 2000 to 2001 were used to build the clinical history of patients and to calculate baseline CCI. Year 2002 was used as index year to evaluate AF diagnosis. All discharge diagnoses were searched for codes 427.31 and 427.32, and all subjects with these codes irrespective of position, were assigned to the group of patients with prevalent AF. A random sample of non-AF patients ten times greater than those with AF was taken as a control group.

According to the diagnoses reported at discharge and coded as per ICD-9, all patients were evaluated for presence of concomitant conditions. In its original definition, CCI comprised 19 diagnosis to which different weights have been assigned and summed to obtain the final calculation of CCI[70]. For this study, the CCI was calculated according to a validated method applied to the administrative databases[79]. All AF patients were grouped according to CCI as patients with low multimorbidity (CCI 0-3) and a high multimorbidity (CCI ≥4).

OAC prescription at beginning and end of observation was evaluated according to both continuous and categorical CCI. Stroke, major bleeding and all-cause death were considered as outcomes and evaluated according to time-dependent continuous CCI.

3.1.5 The FANTASIIA Study

The FANTASIIA registry is an observational, prospective, national and multicentre study of clinical and demographic characteristics of Spanish AF patients. In brief, the main objective was to assess the incidence of thromboembolic and bleeding events in an unselected population of patients with AF, specifically the type of oral anticoagulant (VKA or NOACs) used and quality of anticoagulation with VKAs.

Between June 2013 and March 2014, all outpatients with confirmed diagnosis of paroxysmal, persistent or permanent AF, were prospectively enrolled. All patients included in the registry had been receiving OAC (VKA or NOACs) for at least 6 months before enrolment. A total of 2178 patients were enrolled and followed for 2 years. At baseline each investigator directly calculated CCI for each patient. Study cohort was divided on the basis of CCI quartiles.

Quality of anticoagulation was evaluated according to TTR. Stroke, major bleeding, CV death and all-cause death were considered as outcomes.

3.2 Statistical Methods

All continuous variables were expressed as mean (SD) or median (IQR) according to variables characteristics. Differences between groups were assessed according to t-test or One-Way ANOVA, and Mann-Whitney U test or Kruskal-Wallis ANOVA test according to the type of variable and the number of groups considered. Categorical variables were expressed as counts and percentages. Differences between groups were assessed with chi-square test.

Differences throughout follow-up points of continuous variable were evaluated according to repeated measures ANOVA F test.

Differences in cumulative risk of studies outcomes between groups were evaluated according to Kaplan-Meier curves. All linear and logistic regression analyses were performed as univariate and multivariate adjusted analyses according to biological plausibility and scientific evidence. Similarly, Cox regression analyses were performed as univariate and multivariate adjusted analyses according to biological

plausibility and scientific evidence. A two-sided value of p ≤ 0.05 was considered statistically significant. All the analyses were performed with SPSS 25.0 (IBM, NY, USA), Stata 13.0 (Stata Corp LP, College Station, TX, USA) or SAS software 9.4 (SAS Institute).

4. RESULTS

4.1 The AFFIRM Study

4.1.1 General Characteristics of the Population

All the 4060 patients originally enrolled entered the study. Distribution of the number of concomitant comorbidities are reported in Figure 9. Among them, 11.1% had no comorbidities, 33.4% had one comorbidity and 55.5% had 2 or more comorbidities. According to quartiles, 1809 patients were in Q1 (0-1 comorbidity), 1108 were in Q2 (2 comorbidities), 615 were in Q3 (3 comorbidities) and 528 were in Q4 (≥4 comorbidities) (Table 3). General characteristics according the four quartiles are reported in Table 3. No differences were noted in terms of age and sex distribution, while smoking habit was progressively more prevalent according to the increasing quartiles. Also, patients were more likely symptomatic with increasing quartiles.

Polypharmacy (≥5 drugs assumed contemporarily) was progressively more prevalent from Q1 to Q4, as well as the use of aspirin and the use of warfarin as OAC treatment (Table 3). Median CHA_2DS_2-VASc was progressively higher in the four quartiles, as well as the proportion of patients with high thromboembolic risk (CHA_2DS_2-VASc≥2). Conversely, TTR was found to be progressively lower as the quartiles increased.

4.1.2 Relationship between Multimorbidity and TTR

A multivariable adjusted logistic regression analysis found that an inverse association between the increasing quartiles and the prevalence of TTR >70% was found (Table 4). Conversely, a progressively stronger direct association between increasing comorbidities quartiles and TTR ≤65% (bad control) and TTR ≤60% (very bad control) was confirmed. Similar evidence was retrieved considering the number of comorbidities as a continuous variable (Table 4).

4.1.3 Follow-Up Analysis

During follow-up observation, a significant increasing rate of all the outcomes considered, except for stroke, across the quartiles (Table 5).

Kaplan-Meier curves documented across the quartiles an increased cumulative risk of stroke (p=0.037) [Figure 10], major bleeding (p<0.001) [Figure 11], CV death (p<0.001) [Figure 12] and All-Cause death (p<0.001) [Figure 13]. Similar data were found for first hospitalization (chi-square: 181.027, p<0.001) and first CV hospitalization (chi-square: 73.122, p<0.001).

Adjusted Cox regression analysis showed that while stroke was not independently predicted by the burden of comorbidities, the highest quartile was associated with major bleeding occurrence (compared to Q1, Q2: HR 1.16, 95% CI 0.79-1.70; Q3: HR 1.52, 95% CI 0.99-2.33; Q4: HR 1.99, 95% CI 1.31-3.04). A progressively higher risk across the quartiles was found for CV death occurrence (compared to Q1, Q2: HR 2.56, 95% CI 1.60-4.10; Q3: HR 3.49, 95% CI 2.13-5.71; Q4: HR 8.70, 95% CI 5.60-13.54). It was also associated with an increased risk of all-cause death

(compared to Q1, Q2: HR 2.14, 95% CI 1.56-2.94; Q3: HR 2.47, 95% CI 1.75-3.50; Q4: HR 5.53, 95% CI 4.06-7.52).

The progressively increasing burden of comorbidity was also found associated with first hospitalization (compared to Q1, Q2: HR 1.32, 95% CI 1.18-1.48; Q3: HR 1.47, 95% CI 1.29-1.68; Q4: HR 1.95, 95% CI 1.70-2.24) and first CV hospitalization (compared to Q1, Q2: HR 1.32, 95% CI 1.14-1.53; Q3: HR 1.38, 95% CI 1.15-1.65; Q4: HR 2.04, 95% CI 1.71-2.43).

4.1.4 Quality of Life Evaluation

A pool of 795 patients also entered the quality of life substudy. The SF-36 physical health and SF-36 mental health scores and the Ferrans & Powers Cardiac III Quality of Life Index were examined at 6 pre-specified follow-up points. Given the low number of subjects, the cohort was divided into two groups: i) low comorbidity: 0-3 comorbidities; ii) high comorbidity: ≥4 comorbidities.

As reported in Figure 14, patients with high comorbidity (black solid line) had a steadily lower score for the SF-36 physical health score (F: 11.308, p=0.001) [Figure 14, Upper Panel], while there was no difference in terms of the SF-36 mental health score (F: 1.234, p=0.269) [Figure 14, Middle Panel]. Further, patients with high comorbidity has a steadily lower score for the Cardiac III Quality of Life Index (F: 7.374, p=0.008) [Figure 14, Lower Panel].

4.2 The EORP-AF General Pilot Study

The original study enrolled 3119 patients. Of these 2119 (67.9%) qualified for the 3 years follow-up analysis. All the patients that had complete data about all the 12

chronic comorbidities considered were included in this analysis, with a final cohort of 1629 AF patients.

4.2.1 General Characteristics of the Population

Among the patients included, the median [IQR] number of comorbidities was 3 [2-5]. Only 47 (2.9%) had no comorbidities, 178 (10.9%) had only one comorbidity, while the remaining 86.2% had ≥2 comorbidities. According to median value, we defined the low multimorbidity (840, 51.6%) and the high multimorbidity (789, 48.4%) (Table 6). Patients with high multimorbidity were older, more likely obese and with a more likely permanent AF.

At baseline, both median [IQR] CHA_2DS_2-VASc and HAS-BLED were higher in patients with high multimorbidity. As well as the proportion of high thromboembolic risk (CHA_2DS_2-VASc≥2) and high bleeding risk (HAS-BLED≥3) (Table 6).

Patients with high multimorbidity were more likely treated with antiplatelet drugs and aspirin. While there was no difference in terms of the overall OAC use, patients with high multimorbidity were more likely treated with VKA, while those with low multimorbidity were more treated with NOACs (Table 6). Looking at the patterns of antithrombotic drugs, patients with high multimorbidity were more likely treated with duel antithrombotic therapy (antiplatelet drugs plus OAC) (Table 6). At univariate logistic regression analysis, the presence of high multimorbidity was not associated to any difference in OAC prescription (OR: 1.13, 95% CI: 0.88-1.45), so no multivariate analysis was performed.

After a 3 years follow-up observation, patients with high multimorbidity had a higher rate of any TE, CV death, all-cause death and of the composite outcome of any TE/bleeding/CV death (Table 7). Also, while the rate of any AF rehospitalization was lower in patients with high multimorbidity, the rate of any CV rehospitalization was conversely higher in those patients (Table 7).

An adjusted logistic regression analysis found that high multimorbidity was significantly associated with the risk of any TE (OR: 1.88, 95% CI: 1.09-3.25), CV death (OR: 2.48, 95% CI: 1.59-3.87), all-cause death (OR: 2.77, 95% CI: 2.08-3.69), any TE/bleeding/CV death (OR: 2.14, 95% CI: 1.56-2.92) and any CV rehospitalization (OR: 2.00, 95% CI: 1.54-2.61). Conversely high multimorbidity was inversely associated with any AF rehospitalization (OR: 0.66, 95% CI: 0.51-0.86).

Kaplan-Meier curves were drafted for CV death [Figure 15] and all-cause death [Figure 16], with high multimorbidity showing a significantly higher cumulative risk for both events (both p<0.0001).

Cox fully multivariate adjusted analysis confirmed that high multimorbidity was significantly independently associated with CV death (HR: 2.38, 95% CI: 1.52-3.73) and all-cause death (HR: 2.57, 95% CI: 1.93-3.42) occurrence.

4.3 The REPOSI Study

4.3.1 General Characteristics of the Population

According to baseline CIRS-IC, the 1102 patients included in the cohort were divided in three tertiles: i) T1= 362 patients; ii) T2= 412 patients; iii) T3= 328 patients (Table

8). No differences in age and sex proportion were found. Progressively higher values of GDS and SBT according to the increasing tertiles were found; conversely Barthel index was progressively lower. An increasing prevalence of caregiver presence was found across the tertiles, as well as the smoking habit. Accordingly, several of the comorbidities considered at baseline were found progressively more prevalent across the tertiles (Table 8). Furthermore, an increasing rate of polypharmacy was found across the three groups.

CHA_2DS_2-VASc score was progressively higher across the tertiles. No difference in terms of any antithrombotic therapy (Table 8).

4.3.2 Cognitive and Functional Status

According to the CIRS-IC tertiles [Figure 17] it was found a progressively higher rate of dementia according to SBT (p=0.002), as well as a higher rate of depression according to GDS (p=0.014). Furthermore, an increasing proportion of patients moderately and highly dependent according to Barthel index, was found across the tertiles (p<0.001).

4.3.3 Follow-Up Analysis

During follow-up a progressively higher rate of CV death (4.4% vs. 6.8% vs. 10.7%, p=0.006), all-cause death (10.5% vs. 16.3% vs. 24.1%, p<0.001) across the tertiles, while the rate of rehospitalization was higher in the T3 (23.8% vs. 18.0% in T1 and 15.8% in T2, p=0.019). A multivariate adjusted logistic regression analysis found an increasing direct association between increasing tertiles and risk of all-cause death (compared to T1, T2: OR 1.55, 95% CI 1.01-2.39 and T3: OR 2.61, 95% CI 1.70-4.01), conversely only the highest tertile was found directly associated with risk of CV

death (compared to T1, T2: OR 1.48, 95% CI 0.78-2.79 and T3: OR 2.61, 95% CI 1.70-4.01) and with risk of rehospitalization (compared to T1, T2: OR 0.88, 95% CI 0.60-1.29 and T3: OR 1.45, 95% CI 1.00-2.11).

Continuous CIRS-IC was directly associated with increased risk of CV death (OR: 1.26, 95% CI: 1.12-1.41), all-cause death (OR: 1.26, 95% CI: 1.16-1.37) and rehospitalization (OR: 1.11, 95% CI: 1.03-1.20).

4.4 The Lombardy Region Administrative Health Databases

4.4.1 General Characteristics of the Population

In 2002, a total of 24,040 AF patients were retrieved, as well as 240,400 non-AF patients. At baseline (Table 9), AF patients had a significantly higher mean (±SD) CCI than non-AF subjects (1.8±2.1 vs. 0.2±0.9, p<0.001). Patients with AF were significantly older and more likely male, and more likely affected by comorbidities compared to non-AF subjects. Accordingly, AF patients had a significantly higher mean CHA_2DS_2-VASc score compared to non-AF subjects.

Within the overall AF patient cohort, 4295 patients (17.9%) had high multimorbidity (CCI ≥4), while 19,745 (82.1%) had low multimorbidity (CCI 0-3) (Table 9). Mean (±SD) CCI for the high multimorbidity group was 5.5±1.8, while for the low multimorbidity group, 1.1±1.1 (p<0.001). Patients with high multimorbidity were older and more likely male than those with low multimorbidity (both p<0.001). In patients with high multimorbidity all conditions considered were more prevalent, except for hypertension which was more prevalent in the low multimorbidity group (p<0.001). Patients with high multimorbidity had a higher thromboembolic risk than the low multimorbidity group. At baseline, patients with high multimorbidity were significantly

less prescribed with OAC than those with low multimorbidity (30.0% vs. 42.3%, p<0.001) ([Table 9](#)).

4.4.2 Trends in CCI and Relationship with AF

A mixed linear effect logistic model was compiled to analyse the relationship between AF and CCI. Overall, CCI progressively increased over time both in non-AF and AF patients, being increasingly and steadily higher in AF patients compared to non-AF ones (p<0.001) [[Figure 18](#)]. After adjustment for years of observation, age, sex and an interaction term between AF and years of observation, AF was associated with a progressively higher CCI (beta coefficient: 1.69, 95% confidence interval [CI]: 1.67-1.70), F= 99943.8, p<0.001). Further, the interaction term between AF and years of observation was also independently associated to the progressively higher CCI (p<0.001). Subgroup analysis for age classes, showed that this relationship was consistently statistically significant for patients <65 years, 65-74 years and ≥75 years (all p<0.001).

4.4.3 CCI and OAC Prescription

After adjustment for age and sex, CCI as a continuous variable was inversely associated with OAC prescription (odds ratio [OR]: 0.91, 95% CI: 0.89-0.92). The high multimorbidity category (CCI ≥4) was inversely associated with OAC prescription (OR: 0.65, 95% CI: 0.60-0.70).

At the end of follow-up, even though CCI as a continuous variable was inversely associated with OAC prescription (OR: 0.98, 95% CI: 0.98-0.99), the high multimorbidity category was not significantly associated (OR: 0.98, 95% CI: 0.93-1.04). Examining separately VKA and NOACs prescription, while there was no

difference in VKA prescription, both continuous (OR: 0.86, 95% CI: 0.81-0.90) and categorical (OR: 0.48, 95% CI: 0.37-0.63) CCI were inversely associated with prescription of NOACs.

4.4.4 Survival and Regression Analysis

At follow-up, all the outcomes showed higher cumulative incidence in the high multimorbidity group (all p<0.001). Kaplan-Meier analysis shows that risk for stroke, major bleeding and all-cause death was consistently higher in high multimorbidity group compared to the low multimorbidity group [Figure 19].

Cox regression analysis, using CCI as a continuous time-dependent variable to take account of the temporal increase and adjusted for age, sex and use of OAC, CCI was significantly associated with an increased risk for stroke (HR: 1.04, 95% CI: 1.02-1.06 per increasing point), major bleeding (HR: 1.03, 95% CI: 1.01-1.06 per increasing point) and all-cause death (HR: 1.10, 95% CI: 1.09-1.11 per increasing point).

4.5 The FANTASIIA Study

4.5.1 General Characteristics of the Population

According to availability of baseline CCI, among 2178 patients enrolled 1956 (89.8%) were available for the analysis. According to CCI patients were divided in quartiles: i) Q1= 676 patients; ii) Q2= 683 patients; iii) Q3= 345 patients; iv) Q4= 252 patients (Table 10). At baseline, a progressively lower proportion of female AF patients were found across the quartiles, with patients in Q3 and Q4 being more likely on permanent AF. Both CHA_2DS_2-VASc and HAS-BLED scores were progressively higher across the quartiles (both p<0.001) (Table 10). No differences were found in terms of OAC used, while antiplatelet drugs were progressively more prescribe

across the quartiles (Table 10).

Mean (±SD) TTR was progressively lower according to increasing quartiles (63.1±24.5 vs. 62.0±25.3 vs. 62.2±25.7 vs. 54.7±24.2, p<0.001). Multivariate adjusted linear regression analysis found that CCI Q4 was inversely associated with TTR (unstandardized beta: -6.97, 95% CI: -11.59 / -2.36). Also, proportion of patients with TTR >70% was progressively lower from Q1 to Q4 (43.4% vs. 42.3% vs, 41.8% vs. 30.2%, p=0.010). Logistic regression analysis confirmed that only Q4 was inversely associated to TTR >70% (compared to Q1, Q2: OR 1.01, 95% CI 0.78-1.31, Q3: OR 1.02, 95% CI 0.74-1.41, Q4: OR 0.64, 95% CI 0.43-0.94).

4.5.2 Follow-Up Analysis

During the 2 years follow-up (Table 11) while no difference was found in terms of stroke rate (p=0.104), an increasing rate for major bleeding (p=0.003), CV death (p<0.001) and all-cause death (p<0.001) was found. Kaplan-Meier curves showed a progressively lower survival probability for major bleeding, CV death and all-cause death (all p<0.001) [Figure 20].

Multivariate adjusted Cox regression found a direct association for Q4 with risk of major bleeding and CV death, while an increasing direct association with risk of all-cause death was found across the quartiles (compared to Q1, Q2: HR 1.52, 95% CI 1.05-2.20, Q3: HR 1.91, 95% CI 1.25-2.89, Q4: HR 2.30, 95% CI 1.47-3.61) (Table 11). A direct association in risk of major bleeding, CV death and all-cause death was found for continuous CCI (Table 11).

5. DISCUSSION

5.1 General Overview of Results

Data coming from the studies' results above described, provided evidence the in AF patients, burden of multimorbidity has a direct impact on OAC prescription, quality of anticoagulation control, performance status, quality of life and, more importantly, on major adverse outcomes. Indeed, increasing multimorbidity were found inversely associated with OAC prescription, as well as with TTR. Further, in two of the studies reported, a higher multimorbidity were found to be characterized by an increased rate of depression, dementia and dependency in daily activities and by an impaired physical health and quality of life. Taking together all the evidence provided it was found that an increased burden of multimorbidity is directly associated with all the major adverse outcomes described (stroke, any TE, major bleeding, CV death, all-cause death, rehospitalization). Finally, it was also provided evidence of a direct relationship between AF and progressively increasing burden of multimorbidity, independent by other context variables.

5.2 Study Results in the Context of Current Knowledge

The independent relationship between various single diseases and AF has been largely demonstrated. Indeed, as described above in the introduction several conditions contribute independently to incident AF occurrence and it has been suggested that tight control of concomitant risk factors and comorbidities could significantly reduce the burden of AF[7,80]. Furthermore, several diseases are independently prevalent in AF patients[81,82]. The data presented allow to establish a strong relationship and a direct link between AF and burden of multimorbidity, making AF as a proxy of a worse clinical status and a clinical model of multimorbidity.

The various designs of the studies presented, contributed to make evidence gathered solid. Obtaining data from randomized controlled trials, observational studies and population-based cohorts allowed us to acquire data that were both methodologically sound and representative of real life, both in general AF population and specific subgroup of elderly patients. Moreover, the use of validated tools to evaluate multimorbidity as CCI and CIRS-IC further reinforced the results.

The influence of multimorbidity on OAC prescription, as we showed, represents a concerning trend, in particular if we consider the associated increased thromboembolic risk. In the study by Vanbeselaere and colleagues, there was a possible inverse relationship between increasing CCI and reduced OAC prescription[83]. This thesis extends previous knowledge, showing how this inverse relationship appears consistent in general AF population and over long-term observation periods. Moreover, we showed that if physicians appear to be more confident in prescribing VKA, the prescription of NOACs is significantly reduced in patients with increased multimorbidity. Our results substantiate previous observations that seem to suggest that AF patients prescribed with NOACs are relatively healthier and have less prevalent comorbidities[81,84].

Notwithstanding the strong results we described, so far data about AF and multimorbidity, in particular about validated tools as CCI or CIRS-IC have been scarce. In a Belgian study derived from a primary care registry, a modified version of the CCI was found higher in AF elderly (≥60 years) patients than in non-AF ones, also being associated with AF diagnosis[83]. The data presented in this thesis extended this previous evidence, confirming how the burden of multimorbidity is significant in AF patients, irrespective of age and of what may be the single medical

conditions. A recent study derived from the UK Biobank, in a cohort of patients with self-reported AF which examined the presence of multimorbidity as the additive presence of various conditions, only 19.6% of patients reported no comorbidities and 11.1% of patients reported 4 or more comorbidities[85]. Very recently, a subgroup analysis derived from the ARISTOTLE study appeared to confirm the association between multimorbidity and all the relevant outcomes in AF patients[86].

In the recent years, the increased risk of CV-related and all-cause death in AF cohorts has shifted the main focus of prevention of adverse events from stroke to mortality[33,36,37,87–89]. Our data show that the increased and increasing multimorbidity burden is strongly associated with an increased risk of all the adverse events, stroke, major bleeding and all-cause death. The Framingham Heart Study previously showed that AF patients with comorbidities have a consistently increased risk for cardiovascular events and all-cause death compared to those without[90]. An analysis from the "Outcomes Registry for Better Informed Treatment of Atrial Fibrillation" study showed that when AF patients were clustered according to the more frequent clinical characteristics, those in the 'low-comorbidity' cluster had the lowest risk major cardiovascular and neurological adverse events than all the other identified clusters, variously affected by risk factors and other comorbidities[82].

This thesis also extends previous knowledge about the usefulness of CCI in AF patients. Thus far CCI have been already validated in patients with acute coronary syndrome[91] and stroke[92] and other cardiovascular conditions[71]. Hence this thesis provided solid and large evaluation of CCI in AF cohorts.

5.3 New Approaches to Manage Multimorbidity and Clinical Complexity

On the basis of the showed increased burden of multimorbidity in AF patients, new approaches are required to manage these patients appropriately. In recent years there has been an increasing need of new approaches to manage AF patients, considering them in a more comprehensive, integrated and holistic way. A systematic review and meta-analysis by Gallagher and colleagues showed how an integrated care approach can significantly reduce hospitalization and mortality in AF patients[93]. Various expert opinions and international consensus statements have proposed new integrated models to properly manage AF patients, with the ultimate objective to reduce the risk of adverse events[94,95]. The "Atrial Fibrillation Better Care" pathway has recently been proposed as a possible model to integrate the various main aspects related to AF patients' management, in order to streamline and facilitate the integrated care and the holistic evaluation of these patients[96] and to be associated with a significant lower risk of major adverse events[97].

The strong association and relationship described between AF and multimorbidity requires the systematic adoption of a new approach that evaluate multimorbidity at baseline in all patients with AF. The recent ESC guidelines proposed a step-by-step approach in treating and managing new patients with AF[19]. On the basis of the results described, a modified version of this approach is proposed, taking ultimately account of the multimorbidity evaluation, to eventually identify a significant burden and adopt specific approaches to manage the associated risk, at the ABC pathway [Figure 21].

In the context of an increasing multimorbidity in the general population[98], paired with the increasing costs associated with its presence and the claim to reduce the use of

hospitalization and multiple referrals[99], a more prominent role of specialist in internal medicine has been claimed to provide a patient-centred healthcare that would be able to manage patients with an holistic approach[100]. On this perspective, to face the burden of multimorbidity in AF patients, possibly a prominent role of specialist in internal medicine is due. Indeed, while heart team and cardiologist would provide specific care that would address the initial specialist management, specialist in internal medicine would be able to address all the aspects associated with clinical management of cardiovascular and non-cardiovascular comorbidities.

Hence, on the basis of the multidisciplinary approach suggested by the 6th AFNET/EHRA Consensus Conference, a modified version is proposed, with the introduction of specialist in internal medicine in the Integrated AF Clinic. In this specific context, the specialist in internal medicine would be able to manage primary and secondary cardiac and vascular prevention, diabetes mellitus, COPD, chronic kidney disease and several other conditions usually part of the clinical skills of the specialist in internal medicine [Figure 22].

The proposal of integrating the internal medicine specialist in the clinical management of the patient with AF need to be intended as speculative and hypotheses generating. The evidence relating AF and multimorbidity appears to be solid and stemming from several studies with different designs. Notwithstanding to provide specific recommendations more data are still needed. Future studies that will specifically and prospectively address the evaluation of multimorbidity in AF, the impact of integrated management approaches and the role of the specialist in internal medicine will better elucidate the clinical utility of the approaches proposed.

6. CONCLUSIONS

This thesis demonstrated that in AF patients exist a significant burden of multimorbidity, with a specific impact in determining treatments, performance and quality of life of patients. Also, and more importantly, the increased burden of multimorbidity is associated with an increased risk of all major adverse outcomes. In order to address this increased burden of multimorbidity, specific integrated management strategies to provide holistic treatment is needed. The assessment of multimorbidity would then be introduced in the systematic evaluation of AF patients. In the management of these patients a more prominent role of specialist in internal medicine, able to provide multiple skills to manage different conditions, is due to better implement the advocated integrated management.

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TABLES

[Table 1](): Association between main risk factors and risk of incident Atrial Fibrillation

Clinical Factor	Years	Type of Studies	Studies (N)	Patients (N)	Follow-Up	Increase in Risk*
Modifiable Lifestyle Risk Factors						
Alcohol Consumption	1985-2014	Prospective Cohort Observational Cohort Case-Control	17	245,903	2.5->50 years	HR 1.08 per 1 drink/day HR 1.08 per 10 g alcohol/day
Physical Activity	2008-2015	Prospective Cohort Retrospective Cohort Longitudinal Cohort	12	649,457	5.4-30 years	Leisure Exercise reduces risk Endurance Training increases risk
Psychological Distress	2004-2012	Prospective Observational RCT	5	83,442	7-10 years	Anger and Hostility: HR 1.1-1.3 Tension: HR 1.28 Anxiety: HR 1.16 Panic Disorder: HR 1.73 High Job Strain: HR 1.23
Smoking Habit	1997-2015	Prospective Cohort Hospital Based Internet Based	15	349,130	5-25.2 years	Former Smoker: HR 1.32-1.67 Current Smoker: HR 1.44-2.05 ≤300 cig-years: HR 1.60 >300 to ≤675 cig-years: HR 2.10
Cardiovascular Risk Factors						
Diabetes Mellitus	1994-2014	Prospective Cohort Population Based RCT	12	1,771551	3-38 years	HR 1.14 (NS) -1.40 HR 1.13 per HbA1c 1% increase Higher risk was found for longer diabetes history HR 1.49 for incident diabetes

Hypertension	1994-2015	Prospective Cohort Community Based RCT	9	76,475	2-38 years	SBP >140 mmHg progressively increases risk DBP >90 mmHg progressively increases risk HR 1.11-1.16 per 10 mmHg SBP increase HR 1.17 per 10 mmHg DBP increase
Obesity	1996-2015	Prospective Cohort Community Based Population Based Case-Control	10	152,122	4.7-34.3 years	Overweight: HR 1.18-1.22 Obese: HR 1.40-1.65 HR 1.45 per 5 kg/m^2 increase
OSAS	2007-2015	Prospective Cohort	2	10,383	4.7-11.9 years	HR 1.55-2.18

Legend: Reproduced from Boriani and Proietti Heart 2017 doi:10.1136/heartjnl-2017-311546[8]; AF= Atrial Fibrillation; cig= cigarette;

DBP= Diastolic Blood Pressure; HR= Hazard Ratio; NS= Not Significant; OSAS= Obstructive Sleep Apnoea Syndrome; SBP=

Systolic Blood Pressure; RCT= Randomized Controlled Trials; *All HR reported are statistically significant, except where reported.

Table 2: CHA$_2$DS$_2$-VASc Score

	Score Item	Scoring
C	Congestive Heart Failure	1
H	Hypertension	1
A$_2$	Age ≥75 Years Old	2
D	Diabetes Mellitus	1
S$_2$	Stroke or TIA	2
V	Vascular Disease	1
A	Age 65-74 Years Old	1
Sc	Sex Category (i.e. female)	1

Legend: TIA= Transient Ischemic Attack.

Table 3: Baseline Characteristics according to Cumulative Comorbidities Quartiles in AFFIRM Study

	Q1 (0-1) N= 1809	Q2 (2) N= 1108	Q3 (3) N= 615	Q4 (≥4) N= 528	p
Age, *years* median [IQR]	71 [65-76]	70 [64-76]	71 [64-76]	71 [65-76]	0.078
Female Sex, n (%)	731 (40.4)	450 (40.6)	229 (37.2)	184 (34.8)	0.065
SBP, *mmHg* median [IQR]	131 [120-148]	135 [120-150]	132 [120-149]	120 [130-150]	<0.001
DBP, *mmHg* median [IQR]	78 [70-84]	78 [70-84]	76 [70-82]	72 [64-81]	<0.001
Smoking Habit, n (%)	156 (8.6)	146 (13.2)	94 (15.3)	100 (18.9)	<0.001
First AF Episode, n (%)	550 (31.6)	376 (35.1)	252 (42.4)	213 (41.8)	<0.001
Symptoms ≥2, n (%)	1048 (58.0)	687 (62.0)	423 (68.9)	404 (76.7)	<0.001
Randomized Treatment, n (%)					0.914
Rate Control	895 (49.5)	563 (50.8)	305 (49.6)	264 (50.0)	
Rhythm Control	914 (50.5)	545 (49.2)	310 (50.4)	264 (50.0)	
Drugs, *n* median [IQR]	3 [2-4]	4 [3-5]	5 [4-6]	6 [5-6]	<0.001
Polypharmacy, n (%)	425 (23.5)	457 (41.2)	345 (56.1)	400 (75.9)	<0.001
CHA$_2$DS$_2$-VASc, median [IQR]	2 [1-3]	3 [2-4]	4 [3-5]	5 [4-6]	<0.001

CHA$_2$DS$_2$-VASc ≥2, n (%)	1295 (71.6)	1026 (92.6)	603 (98.0)	526 (99.6)	<0.001
Aspirin, n (%)	423 (23.4)	287 (25.9)	185 (30.1)	186 (35.2)	<0.001
Warfarin, n (%)	1508 (83.4)	935 (84.4)	530 (86.2)	461 (87.3)	0.097
TTR, % median [IQR]	69.6 [55.7-81.9]	67.8 [50.3-81.4]	64.1 [46.1-80.0]	62.8 [44.3-77.8]	<0.001

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; DBP= Diastolic Blood Pressure; IQR= Interquartile Range; SBP= Systolic

Blood Pressure; TTR= Time in Therapeutic Range.

Table 4: Logistic Regression Analysis for Quality of Anticoagulation Control Indexes

	TTR >70%*			TTR ≤65%*			TTR ≤60%*		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
1st Quartile (ref.)	-	-	-	-	-	-	-	-	-
2nd Quartile	0.87	0.73-1.03	0.103	1.22	1.03-1.45	0.023	1.34	1.12-1.60	0.001
3rd Quartile	0.73	0.59-0.90	0.004	1.55	1.25-1.92	<0.001	1.69	1.36-2.11	<0.001
4th Quartile	0.58	0.46-0.73	<0.001	1.76	1.39-2.22	<0.001	1.91	1.51-2.42	<0.001
Cumulative Comorbidities	0.88	0.83-0.92	<0.001	1.16	1.09-1.22	<0.001	1.18	1.12-1.25	<0.001

Legend: *Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, first atrial fibrillation episode, randomized treatment and polypharmacy; CI= Confidence Interval; OR= Odds Ratio; TTR= Time in Therapeutic Range.

Table 5: Major Clinical Adverse Events according to Cumulative Comorbidities Quartiles

	Q1 (0-1) N= 1809	Q2 (2) N= 1108	Q3 (3) N= 615	Q4 (≥4) N= 528	p
Stroke, n (%)	57 (3.2)	45 (4.1)	31 (5.0)	24 (4.5)	0.136
Major Bleeding, n (%)	92 (5.1)	66 (6.0)	46 (7.5)	53 (10.0)	<0.001
CV Death, n (%)	57 (3.2)	68 (6.1)	78 (12.7)	128 (24.2)	<0.001
All-Cause Death, n (%)	143 (7.9)	147 (13.3)	137 (22.3)	186 (35.2)	<0.001
First Hospitalization, n (%)	968 (54.4)	694 (63.5)	424 (69.9)	389 (76.7)	<0.001
First CV Hospitalization, n (%)	438 (30.3)	330 (37.1)	178 (38.8)	190 (50.5)	<0.001
Multiple Hospitalizations, n (%)	392 (27.1)	298 (33.5)	201 (43.8)	198 (52.7)	<0.001

Legend: CV= Cardiovascular

Table 6: Baseline Characteristics according to Comorbidity in EORP-AF Pilot
Study

	Low Multimorbidity N= 840	High Multimorbidity N= 789	p
Demographics			
Age in years Median (IQR)	68.0 (61.0-75.0)	74.0 (66.0-80.0)	<0.0001
Female gender (%)	356 / 840 (42.4%)	306 / 789 (38.8%)	0.1395
BMI, n (%)			
Underweight	9 / 799 (1.1%)	9 / 775 (1.2%)	0.0254
Normal	245 / 799 (30.7%)	209 / 775 (27.0%)	
Overweight	345 / 799 (43.2%)	310 / 775 (40.0%)	
Obese	200 / 799 (25.0%)	247 / 775 (31.9%)	
Type of AF, n (%)			
First detected	281 / 840 (33.5%)	244 / 789 (30.9%)	<0.0001
Paroxysmal	235 / 840 (28.0%)	162 / 789 (20.5%)	
Long-standing persistent AF	185 / 840 (22.0%)	162 / 789 (20.5%)	
Persistent	27 / 840 (3.2%)	47 / 789 (6.0%)	
Permanent	112 / 840 (13.3%)	174 / 789 (22.1%)	
Current smoker, n (%)	95 / 818 (11.6%)	69 / 778 (8.9%)	0.0711
Alcohol >= 2-3/day, n (%)	74 / 783 (9.5%)	58 / 751 (7.7%)	0.2277
EHRA I Class, n (%)	369 / 840 (43.9%)	376 / 789 (47.7%)	0.1313
Physical activity, n (%)	468 / 769 (60.9%)	388 / 751 (51.7%)	0.0003
HAS-BLED score			
Median (IQR)	1.0 (0.0-2.0)	2.0 (1.0-3.0)	<0.0001
0-2	786 / 840 (93.6%)	583 / 789 (73.9%)	<0.0001
>=3	54 / 840 (6.4%)	206 / 789 (26.1%)	
CHA$_2$DS$_2$-VASc score			
Median (IQR)	2.0 (1.0-3.0)	4.0 (3.0-5.0)	<0.0001

0 or 1	229 / 840 (27.3%)	12 / 789 (1.5%)	<0.0001
>=2	611 / 840 (72.7%)	777 / 789 (98.5%)	
Antithrombotic therapy, n (%)			
At least one	797 / 837 (95.2%)	762 / 789 (96.6%)	0.1689
Any antiplatelet	231 / 838 (27.6%)	376 / 788 (47.7%)	<0.0001
Aspirin	212 / 838 (25.3%)	333 / 788 (42.3%)	<0.0001
Any OAC	666 / 834 (79.9%)	645 / 789 (81.7%)	0.3334
VKA	600 / 834 (71.9%)	621 / 789 (78.7%)	0.0016
NOACs	66 / 838 (7.9%)	26 / 789 (3.3%)	<0.0001
Patterns of Antithrombotic Drugs, n (%)			
No Antiplatelet/No OAC	40 / 834 (4.8%)	27 / 788 (3.4%)	<0.0001
Antiplatelet drugs only	128 / 834 (15.3%)	117 / 788 (14.8%)	
OAC only	566 / 834 (67.9%)	385 / 788 (48.9%)	
Antiplatelet + OAC	100 / 834 (12.0%)	259 / 788 (32.9%)	

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; EHRA= European Heart Rhythm Association; NOACs= Non-Vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulant; VKA= Vitamin K Antagonist.

Table 7: Major Adverse Events at Follow-Up in EORP-AF Pilot

	Low Multimorbidity N= 840	High Multimorbidity N= 789	p
Stroke, n (%)	10 / 767 (1.3%)	13 / 619 (2.1%)	0.2486
Any TE, n (%)	23 / 767 (3.0%)	34 / 619 (5.5%)	0.0201
Bleeding, n (%)	24 / 766 (3.1%)	25 / 618 (4.0%)	0.3613
CV Death, n (%)	30 / 840 (3.6%)	70 / 789 (8.9%)	<0.0001
All-Cause Death, n (%)	82 / 840 (9.8%)	183 / 789 (23.2%)	<0.0001
Any TE/Bleeding/CV death, n (%)	75 / 772 (9.7%)	123 / 653 (18.8%)	<0.0001
Any AF Rehospitalisation, n (%)	207 / 765 (27.1%)	119 / 620 (19.2%)	0.0006
Any CV Rehospitalisation, n (%)	130 / 767 (16.9%)	179 / 619 (28.9%)	<0.0001

Legend: AF= Atrial Fibrillation; CV= Cardiovascular; TE= Thromboembolic Event.

Table 8: Baseline Characteristics according to the Burden of Comorbidity

	Index of Comorbidity T1 N= 362	Index of Comorbidity T2 N= 412	Index of Comorbidity T3 N= 328	p
Age *years*, median [IQR]	81 [76-86]	82 [77-86]	81 [76-86]	0.424
BMI *kg/m²*, median [IQR] *660*	24.7 [22.1-27.7]	25.7 [23.1-28.3]	25.6 [22.7-30.4]	0.323
GDS, median [IQR] *628*	1 [0-2]	1 [0-2]	1 [0-2]	0.010
SBT, median [IQR] *677*	6 [2-12]	8 [4-14]	10 [4-16]	<0.001
Barthel Index, median [IQR] *720*	95 [82-100]	92 [68-100]	86 [62-100]	<0.001
Education *years*, median [IQR] *689*	5 [5-10]	5 [5-10]	5 [5-8]	0.417
Female Sex, n (%)	203 (56.1)	211 (51.2)	157 (47.9)	0.093
Work Type, n (%)				0.221
Low Income	256 (76.0)	312 (82.3)	229 (77.9)	
Middle Income	49 (14.5)	37 (9.8)	34 (11.6)	
High Income	32 (9.5)	30 (7.9)	31 (10.5)	
Marital Status, n (%)				0.477
Single	182 (51.6)	211 (52.9)	164 (51.2)	
Married	139 (39.4)	164 (41.1)	126 (39.4)	
Unmarried	32 (9.1)	24 (6.0)	30 (9.4)	
Living Status, n (%)				0.374

Alone	90 (25.9)	89 (22.6)	64 (20.4)	
Spouse	154 (44.3)	161 (40.9)	136 (43.5)	
Family	78 (22.4)	107 (27.2)	79 (25.2)	
Institution	26 (7.5)	37 (9.4)	34 (10.9)	
Caregiver, n (%)	185 (51.2)	242 (59.2)	206 (63.6)	0.004
Smoking Habit, n (%)	125 (35.6)	166 (40.9)	160 (50.3)	0.001
Use of Alcohol, n (%)	142 (40.6)	180 (44.4)	152 (48.6)	0.118
Hypertension, n (%)	270 (74.6)	352 (85.4)	302 (92.1)	<0.001
Hypercholesterolemia, n (%)	18 (5.0)	26 (6.3)	33 (10.1)	0.026
Heart Failure, n (%)	102 (28.2)	124 (30.1)	117 (35.7)	0.089
Coronary Artery Disease, n (%)	69 (19.1)	79 (19.2)	95 (29.0)	0.002
Previous MI, n (%)	10 (2.8)	16 (3.9)	14 (4.3)	0.539
Peripheral Arterial Disease, n (%)	6 (1.7)	13 (3.2)	17 (5.2)	0.033
Previous Stroke/TIA, n (%)	30 (8.3)	40 (9.7)	39 (11.9)	0.282
Diabetes Mellitus, n (%)	65 (18.0)	118 (28.6)	139 (42.4)	<0.001
CKD, n (%)	55 (15.2)	105 (25.5)	159 (48.5)	<0.001
COPD, n (%)	70 (19.3)	103 (25.0)	118 (36.0)	<0.001
Neoplasm, n (%)	23 (6.4)	46 (11.2)	57 (17.4)	<0.001
Polypharmacy, n (%)	247 (68.8)	314 (76.8)	291 (89.0)	<0.001
CHA$_2$DS$_2$-VASc, median [IQR]	4 [3-4]	4 [3-5]	4 [4-5]	<0.001

Any Antiplatelet, n (%)	108 (29.8)	128 (31.1)	119 (36.3)	0.160
VKA, n (%)	159 (43.9)	167 (40.5)	142 (43.3)	0.596
Any NOAC, n (%)	21 (5.8)	30 (7.3)	18 (5.5)	0.550
Any OAC, n (%)	180 (49.7)	197 (47.8)	160 (48.8)	0.869

Legend: BMI= body mass index; CKD= chronic kidney disease; COPD= chronic obstructive pulmonary disease; GDS= geriatric depression scale; IQR= interquartile range; MI= myocardial infarction; OAC= oral anticoagulant; SBT= short blessed test; TIA= transient ischemic attack.

Table 9: Baseline Characteristics according to Atrial Fibrillation and Charlson Comorbidity Index

	Non-AF	AF	p	AF		
	N= 240400	N= 24040		CCI 0-3	CCI ≥4	p
				N= 19745	N= 4295	
Age, *years* mean±SD	59.7±13.2	76.1±9.8	<0.001	75.7±9.9	77.8±8.8	<0.001
Age classes, n (%)			<0.001			<0.001
<65 years	155310 (64.6)	2964 (12.3)		2651 (13.4)	313 (7.3)	
65-74 years	47525 (19.8)	6702 (27.9)		5611 (28.4)	1091 (25.4)	
≥75 years	37565 (15.6)	14374 (59.8)		11483 (58.2)	2891 (67.3)	
Male, n (%)	11096 (46.2)	12079 (50.2)	<0.001	9841 (49.8)	2238 (52.1)	<0.001
Charlson Comorbidity Index, (mean±SD)	0.2±0.9	1.8±2.1	<0.001	1.1±1.1	5.5±1.8	<0.001
Hypertension, n (%)	79801 (33.2)	18605 (77.4)	<0.001	15452 (78.3)	3153 (73.4)	<0.001
Diabetes Mellitus, n (%)	4316 (1.8)	3555 (14.8)	<0.001	1763 (8.9)	1792 (41.7)	<0.001
Myocardial Infarction, n (%)	1723 (0.7)	1400 (5.8)	<0.001	869 (4.4)	531 (12.4)	<0.001
Congestive Heart Failure, n (%)	2919 (1.2)	7249 (30.1)	<0.001	4882 (24.7)	2367 (55.1)	<0.001
Cerebrovascular Disease, n (%)	3216 (1.3)	3605 (15.0)	<0.001	1625 (8.2)	1980 (46.1)	<0.001
Hemiplegia, n (%)	2282 (0.9)	2830 (11.8)	<0.001	1027 (5.2)	1803 (42.0)	<0.001
Dementia, n (%)	489 (0.2)	400 (1.7)	<0.001	197 (1.0)	203 (4.7)	<0.001
COPD, n (%)	3125 (1.3)	4017 (16.7)	<0.001	2523 (12.8)	1494 (34.8)	<0.001
Connective Tissue Disease, n (%)	560 (0.2)	303 (1.3)	<0.001	228 (1.1)	75 (1.7)	0.002
Ulcer, n (%)	620 (0.3)	440 (1.8)	<0.001	287 (1.4)	153 (3.6)	<0.001
Mild Liver Disease, n (%)	1918 (0.8)	1212 (5.0)	<0.001	669 (3.4)	543 (12.6)	<0.001
Moderate/Severe Liver disease, n (%)	769 (0.3)	334 (1.4)	<0.001	44 (0.2)	290 (6.7)	<0.001

Renal Disease, n (%)	1244 (0.5)	2087 (8.7)	<0.001	788 (4.0)	1299 (30.24)	<0.001
Metastatic Tumor, n (%)	1162 (0.5)	503 (2.1)	<0.001	0 (0.0)	503 (11.7)	<0.001
Leukemia, n (%)	117 (0.1)	86 (0.4)	<0.001	49 (0.2)	37 (0.9)	<0.001
Lymphoma, n (%)	305 (0.1)	190 (0.8)	<0.001	90 (0.5)	100 (2.3)	<0.001
Any Tumor, n (%)	4423 (1.8)	2189 (9.1)	<0.001	1124 (5.7)	1065 (24.8)	<0.001
CHA$_2$DS$_2$-VASc, (mean±SD)	1.4±1.2	3.3±1.4	<0.001	3.2±1.3	4.1±1.5	<0.001
Oral Anticoagulant Drugs, n (%)	4141 (1.7)	9646 (40.1)	<0.001	8358 (42.3)	4295 (30.0)	<0.001

Legend: AF= Atrial Fibrillation; CCI= Charlson Comorbidity Index; COPD= Chronic Obstructive Pulmonary Disease; SD= Standard

Deviation.

Table 10: Baseline Characteristics according to Charlson Comorbidity Index Quartiles

	Q1	Q2	Q3	Q4	p
	N= 676	N= 683	N= 345	N= 252	
Age, *years* (mean±SD)	73.6±9.3	73.2±10.0	74.4±9.6	74.9±8.2	0.118
Female, n (%)	356 (52.7)	293 (42.9)	131 (38.0)	80 (31.7)	<0.001
Type of AF, n (%)					<0.001
Paroxysmal	245 (36.2)	181 (26.5)	82 (23.8)	62 (24.6)	
Persistent	125 (18.5)	125 (18.3)	44 (12.7)	34 (13.5)	
Long-Term Persistent	29 (4.3)	32 (4.7)	16 (4.6)	14 (5.6)	
Permanent	277 (41.0)	345 (50.5)	203 (58.8)	142 (56.3)	
BMI, kg/m^2 (mean±SD)	28.3±4.3	29.1±4.7	29.8±5.6	29.0±5.4	<0.001
GFR, *mL/min* (mean±SD)	71.8±27.1	75.1±34.7	72.5±40.7	61.92±28.1	<0.001
Smoking Habit, n (%)	34 (5.0)	35 (5.1)	17 (4.9)	13 (5.2)	0.999
Excessive Alcohol, n (%)	11 (1.6)	34 (5.0)	15 (4.3)	12 (4.8)	0.006
CHA$_2$DS$_2$-VASc (mean±SD)	2.8±1.1	3.7±1.4	4.5±1.5	5.1±1.6	<0.001

HAS-BLED (mean±SD)	1.7±0.9	1.9±1.0	2.3±1.0	2.7±1.2	<0.001
OAC Drugs, n (%)					0.152
VKA	505 (74.7)	506 (74.1)	270 (78.3)	202 (80.2)	
NOACs	171 (25.3)	177 (25.9)	75 (21.7)	50 (19.8)	
Antiplatelet Drugs, n (%)	43 (6.4)	62 (9.1)	47 (13.6)	55 (21.8)	<0.001

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; GFR= Glomerular Filtration Rate; NOACs= Non-vitamin K Oral

Anticoagulants; OAC= Oral Anticoagulant; SD= Standard Deviation; VKA= Vitamin K Antagonist.

Table 11: Major Adverse Events according to Charlson Comorbidity Index Quartiles

	Q1	Q2	Q3	Q4	Continuous CCI	p
Stroke/TIA, n (%)	8 (1.2)	18 (2.6)	11 (3.2)	8 (3.2)	-	0.104
*HR (95% CI)**	Ref.	1.78 (0.75-4.22)	1.87 (0.68-5.08)	1.80 (0.59-5.53)	1.16 (0.88-1.52)	
Major Bleeding, n (%)	36 (5.3)	47 (6.9)	33 (9.6)	30 (11.9)	-	0.003
*HR (95% CI)**	Ref.	1.18 (0.75-1.86)	1.52 (0.90-2.56)	1.93 (1.10-3.40)	1.19 (1.02-1.38)	
CV Death, n (%)	14 (2.1)	36 (5.3)	27 (7.8)	30 (11.9)	-	<0.001
*HR (95% CI)**	Ref.	1.78 (0.95-3.37)	1.98 (0.98-4.01)	2.72 (1.30-5.69)	1.32 (1.13-1.56)	
All-Cause Death, n (%)	45 (6.7)	86 (12.6)	65 (18.8)	59 (23.4)	-	<0.001
*HR (95% CI)**	Ref.	1.52 (1.05-2.20)	1.91 (1.25-2.89)	2.30 (1.47-3.61)	1.26 (1.13-1.41)	

Legend: *Adjusted for type of AF and CHA_2DS_2-VASc score; CCI= Charlson Comorbidity Index; CV= Cardiovascular; TIA= Transient Ischemic Attack.

FIGURES

Figure 1: Worldwide Prevalence of Atrial Fibrillation

Legend: Data from Global Burden of Disease (http://www.healthdata.org/gbd).
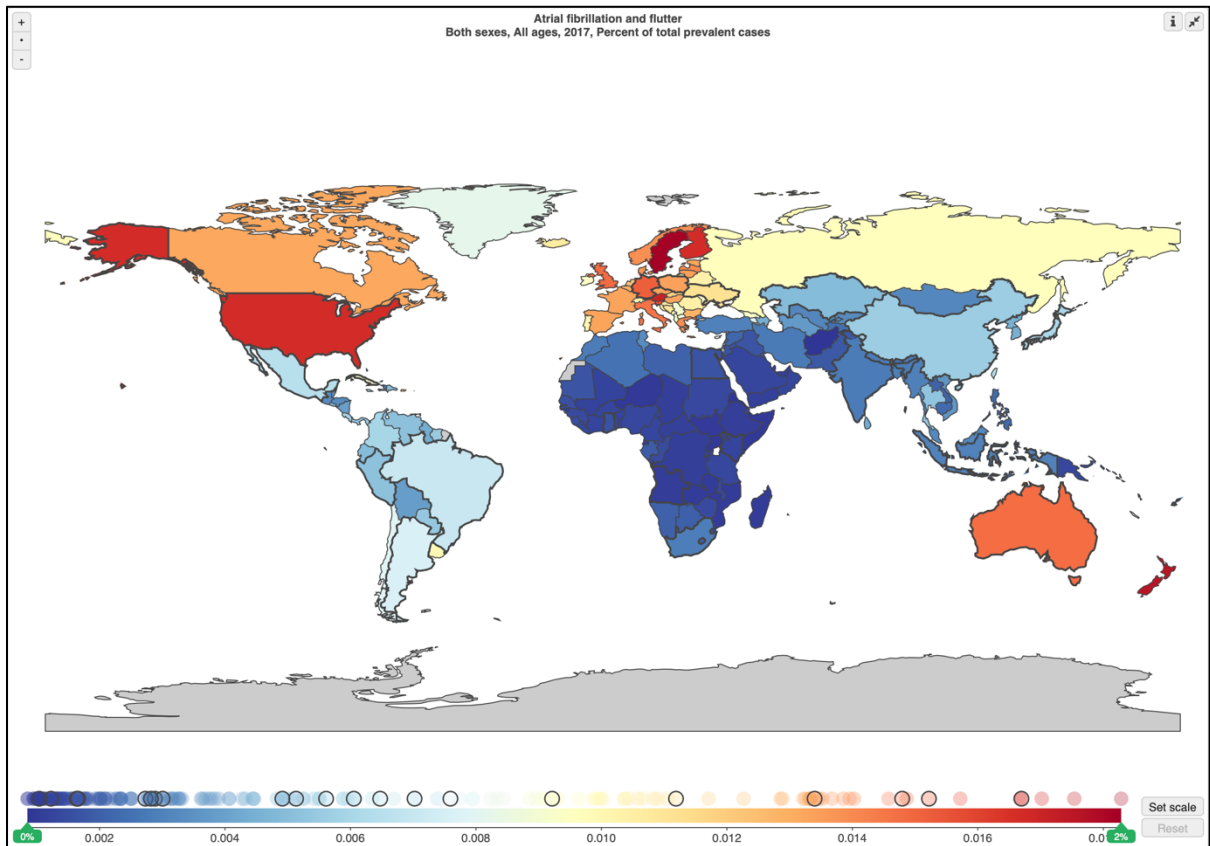
Figure 2: Worldwide Incidence of Atrial Fibrillation

Atrial fibrillation and flutter
Both sexes, All ages, 2017, New cases per 100,000

Legend: Data from Global Burden of Disease (http://www.healthdata.org/gbd).
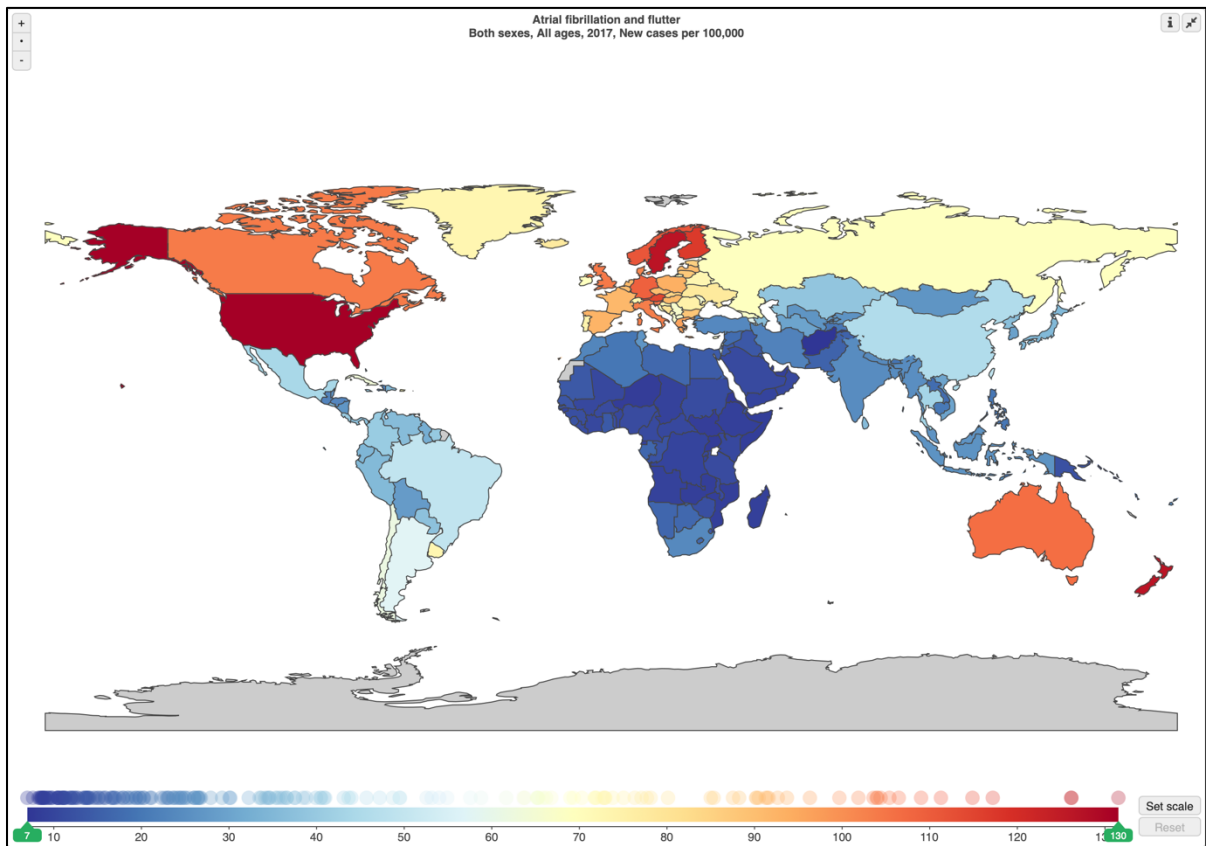
Figure 3: Percental Changes in Worldwide Prevalence of Atrial Fibrillation

Legend: Data from Global Burden of Disease (http://www.healthdata.org/gbd).
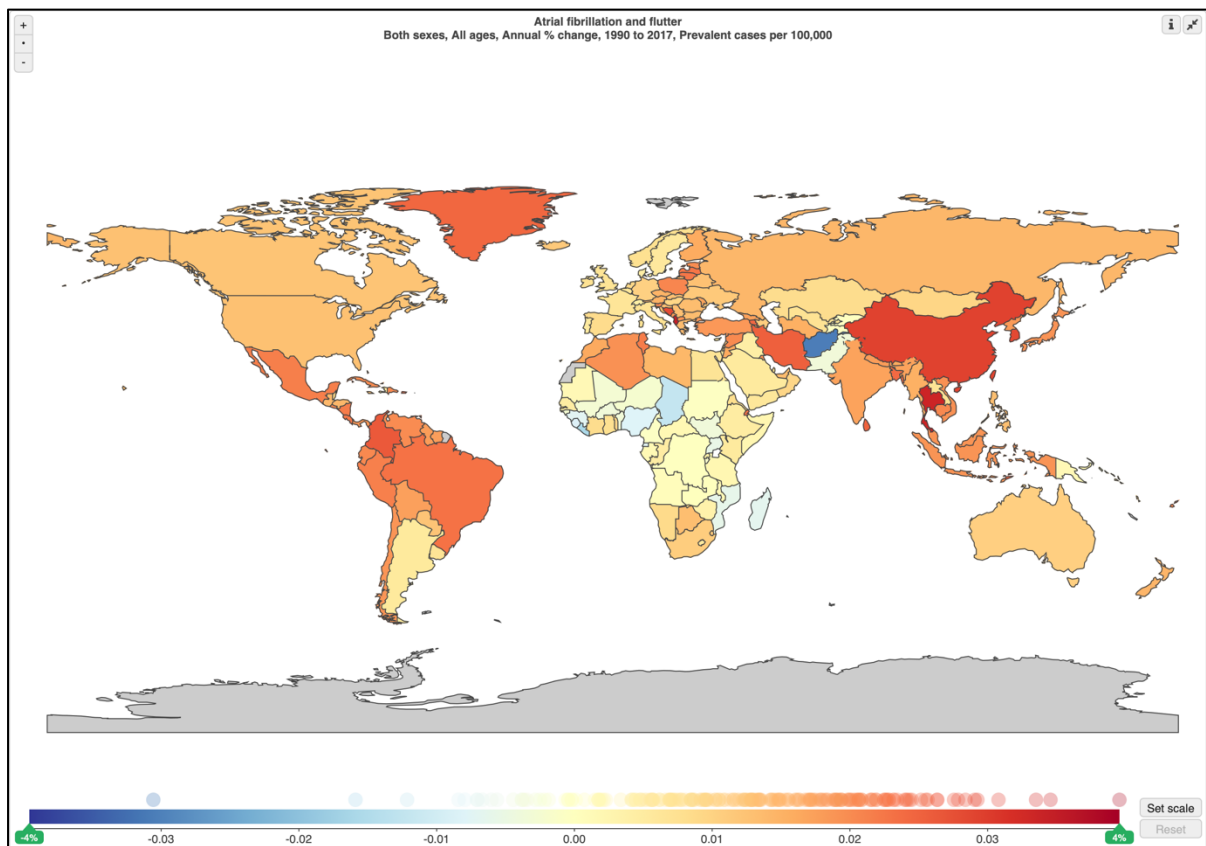
Figure 4: Percental Changes in Worldwide Incidence of Atrial Fibrillation

Atrial fibrillation and flutter
Both sexes, All ages, Annual % change, 1990 to 2017, New cases per 100,000

Legend: Data from Global Burden of Disease (http://www.healthdata.org/gbd).
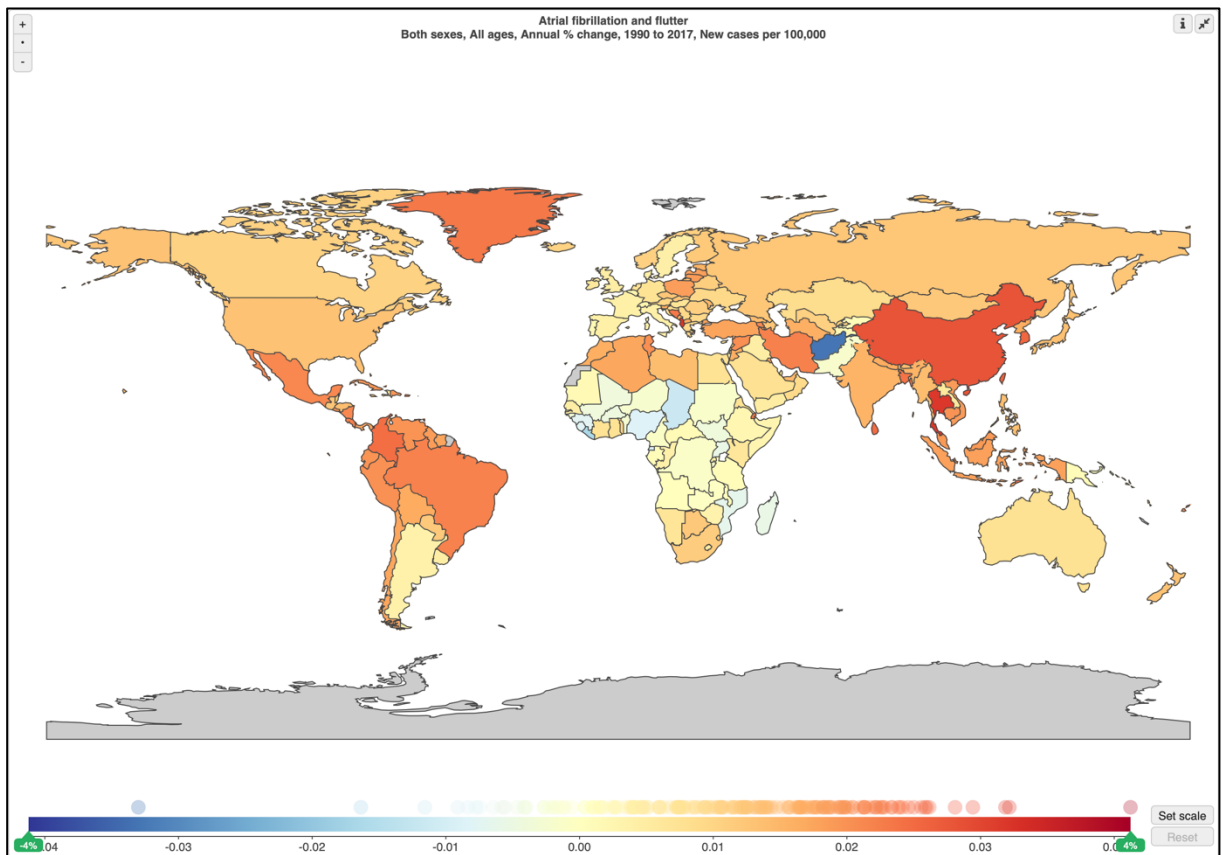
Figure 5: Annual Percental Changes in DALYs Related to Atrial Fibrillation
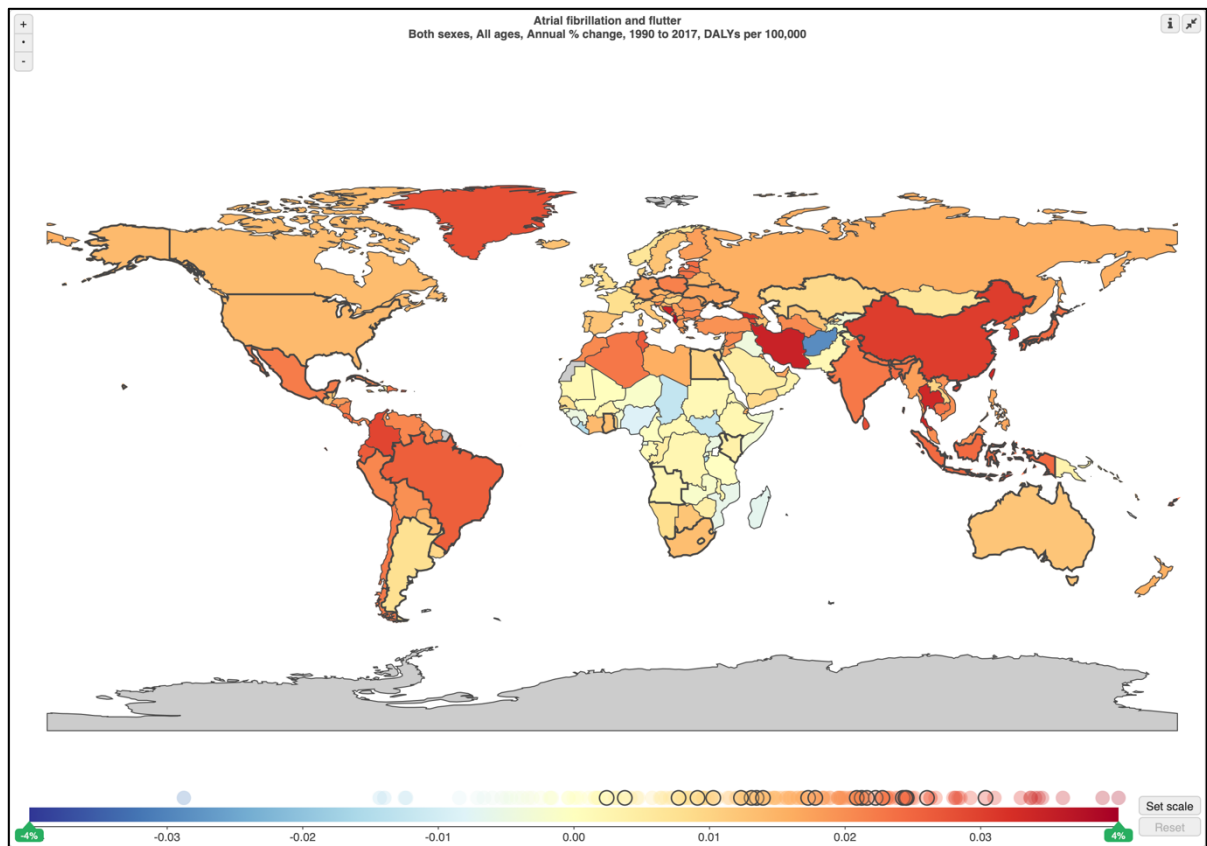
Legend: DALYs= Daily-Adjusted Life Years; Data from Global Burden of Disease

(http://www.healthdata.org/gbd).

Figure 6: Trends in Changes in DALYs Related to Atrial Fibrillation
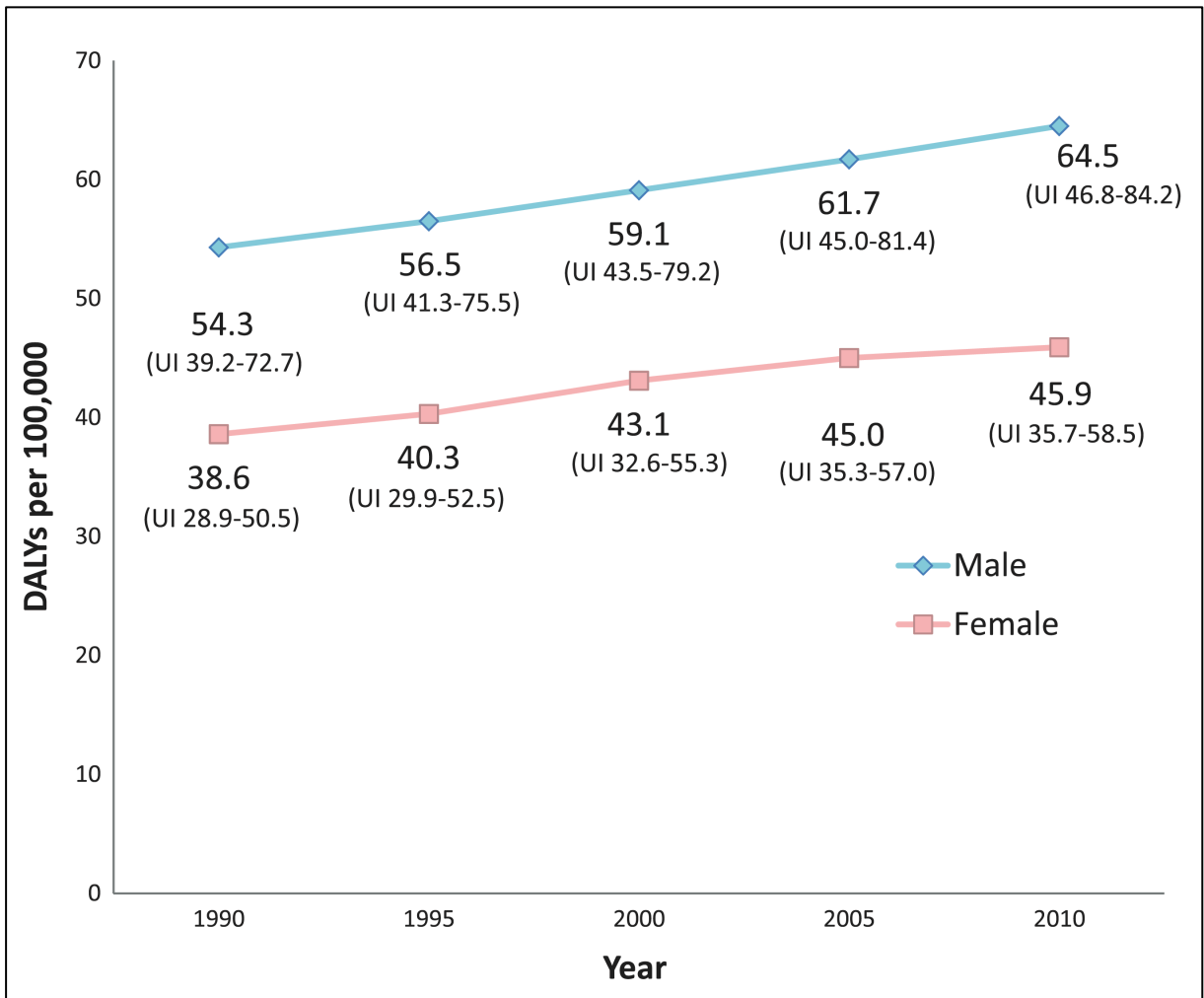
Legend: DALYs= Daily-Adjusted Life Years; Data from Global Burden of Disease

(http://www.healthdata.org/gbd).

Figure 7: Mortality Attributable to Atrial Fibrillation

Legend: Data from Global Burden of Disease (http://www.healthdata.org/gbd).
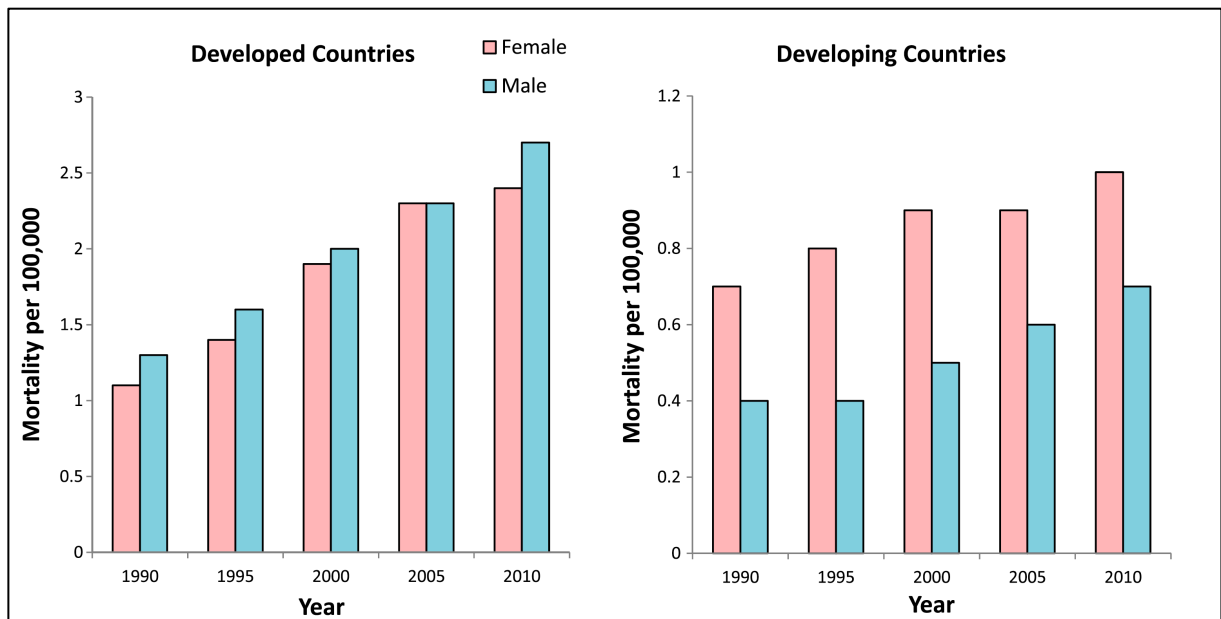
Figure 8: Effect of Various Interventions on Incident AF Occurrence
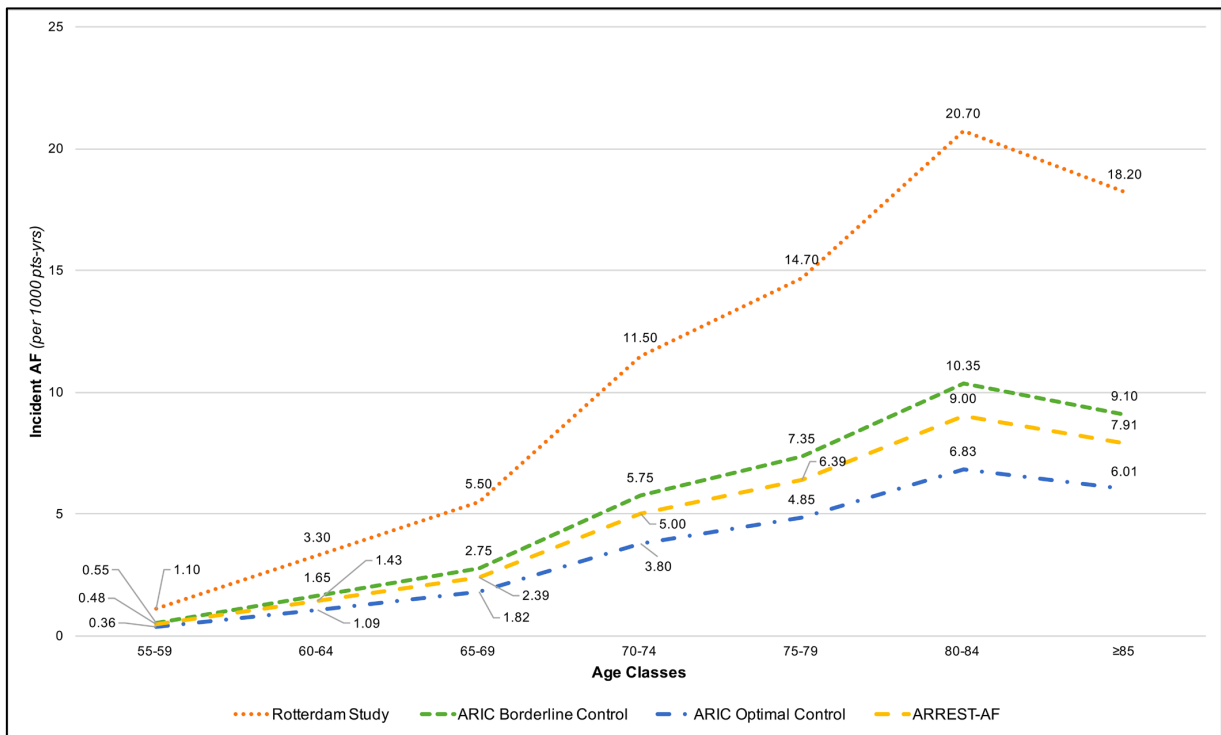
Legend: Expected incidence of atrial fibrillation (AF) without any prevention strategy and implementing the suggested global management of risk factors. Details about risk factors control strategies can be found in Pathak et al for ARREST-AF and Huxley et al for ARIC[11,12].

Figure 9: Distribution of Concomitant Comorbidities in the AFFIRM Study
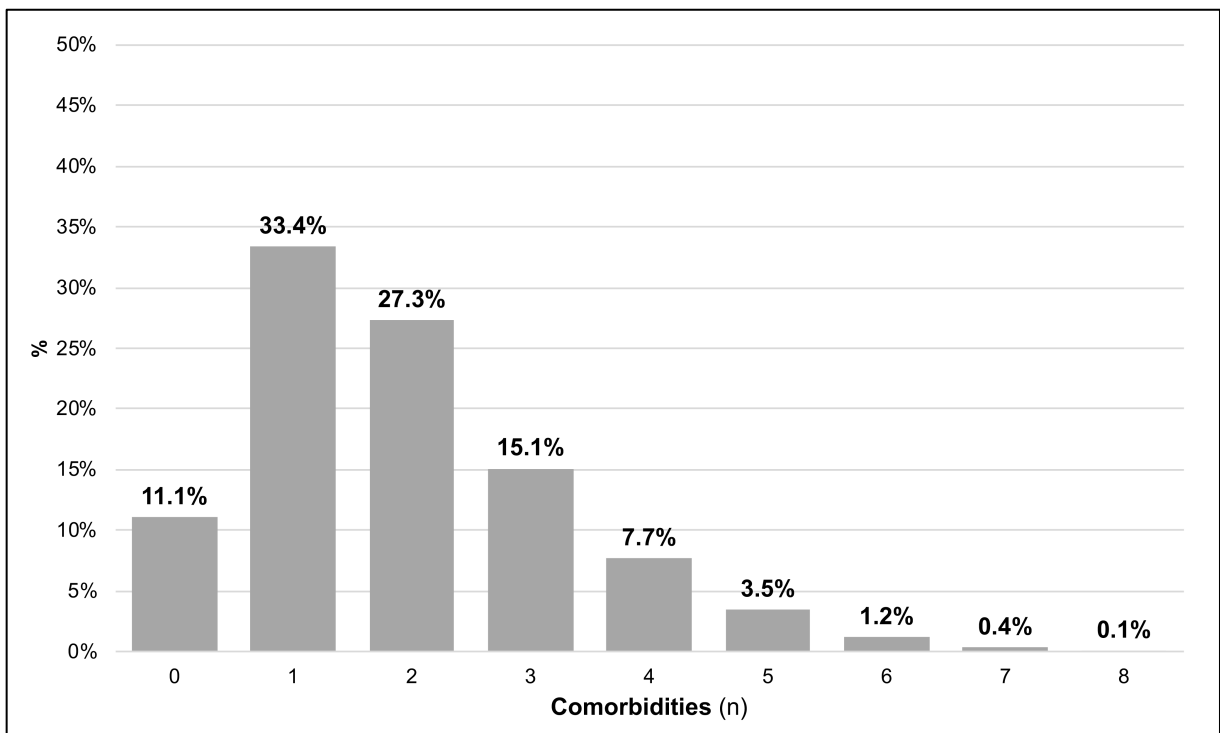
Figure 10: Cumulative Risk of Stroke according to Comorbidities Quartiles in the AFFIRM Study
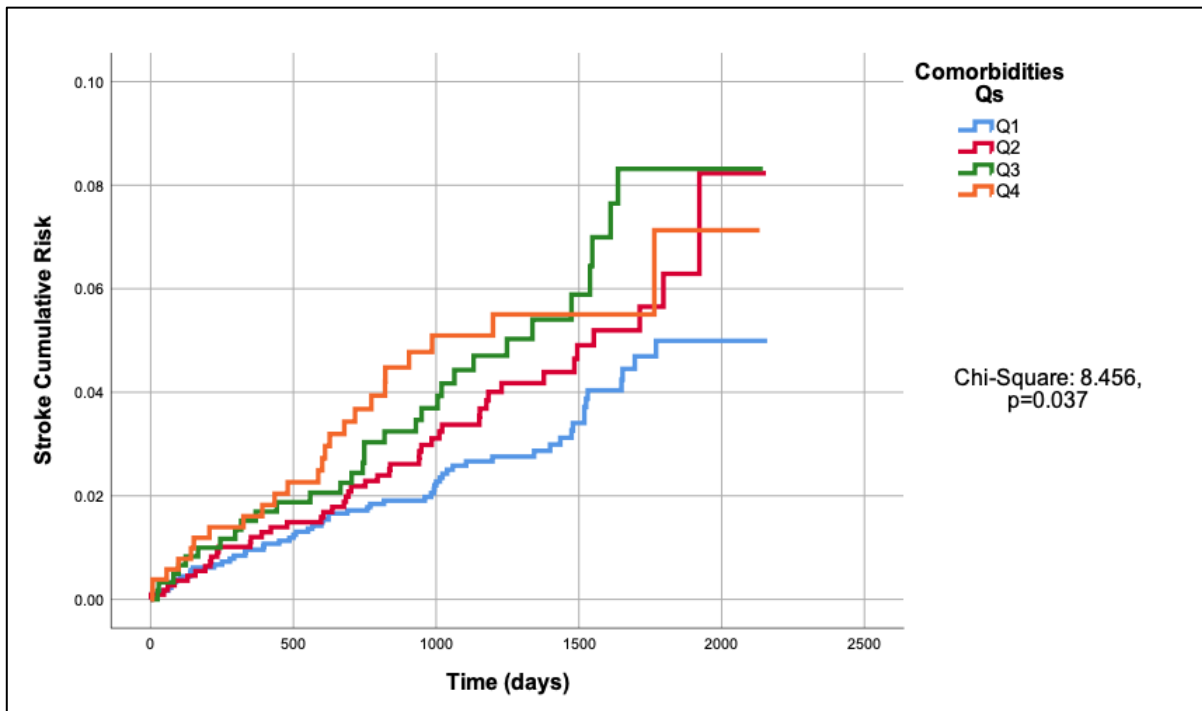
Figure 11: Cumulative Risk of Major Bleeding according to Comorbidities Quartiles in the AFFIRM Study
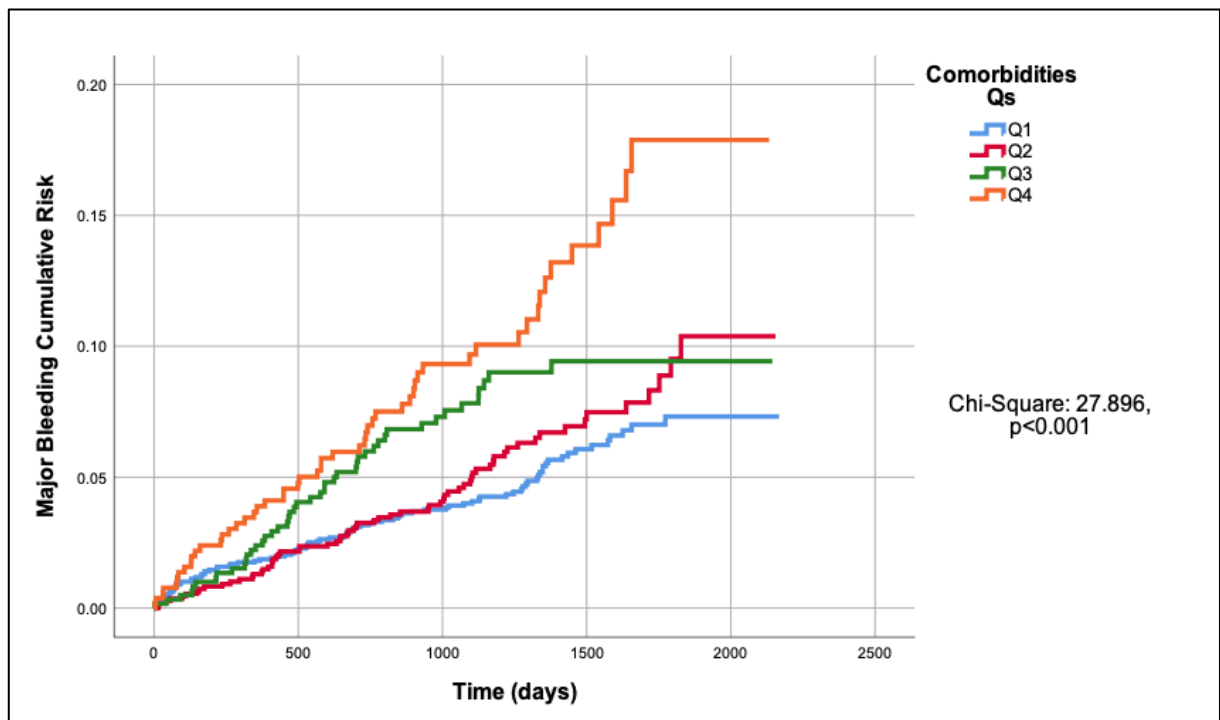
Figure 12: Cumulative Risk of CV Death according to Comorbidities Quartiles in the AFFIRM Study
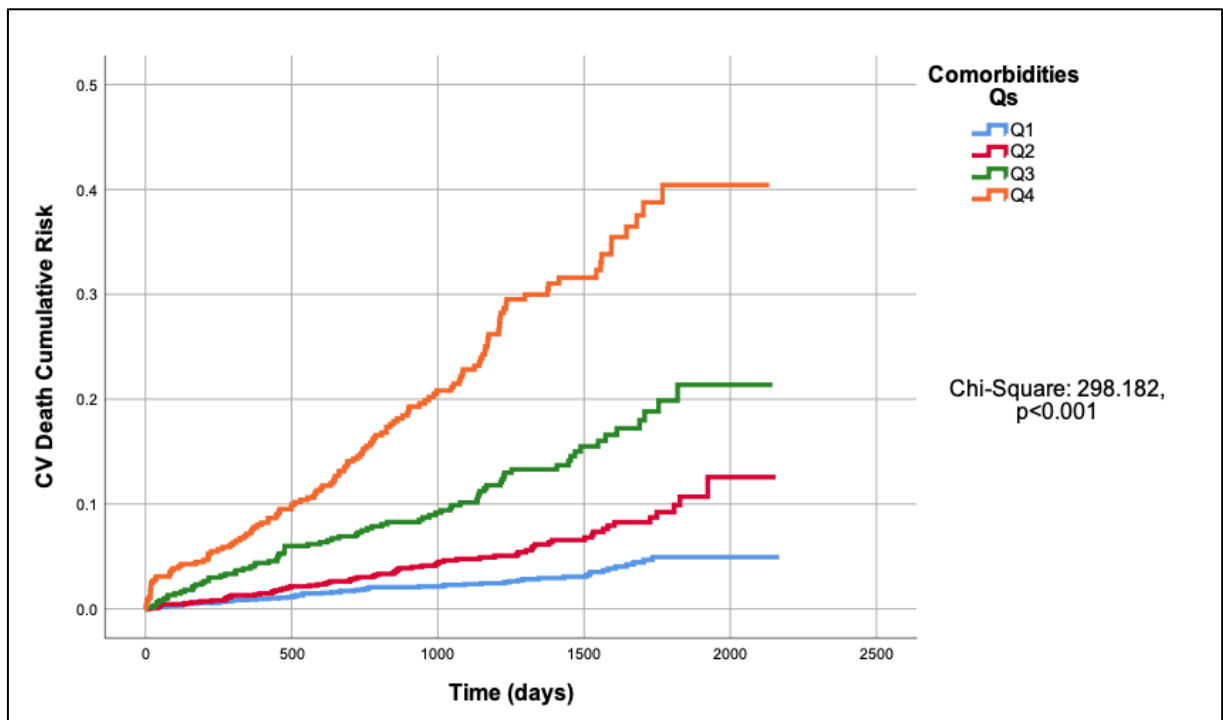
Legend: CV= Cardiovascular.

Figure 13: Cumulative Risk of All-Cause Death according to Comorbidities Quartiles in the AFFIRM Study
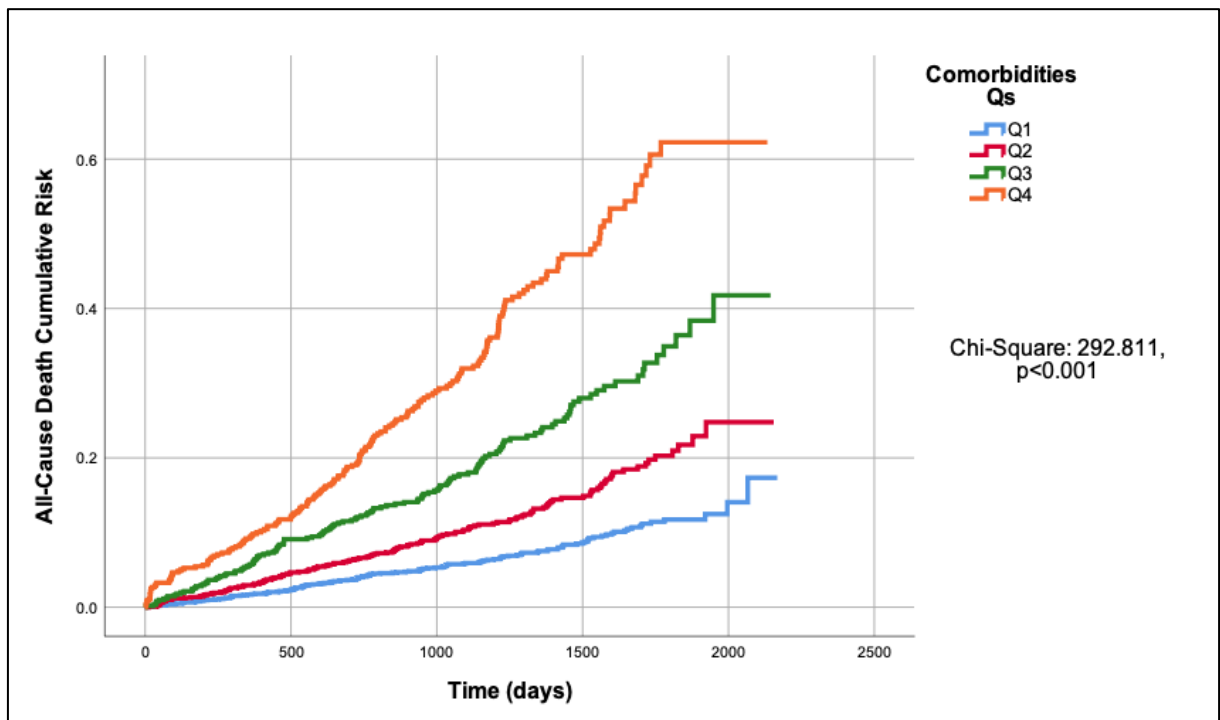
Figure 14: Quality of Life Evaluation in the AFFIRM Study
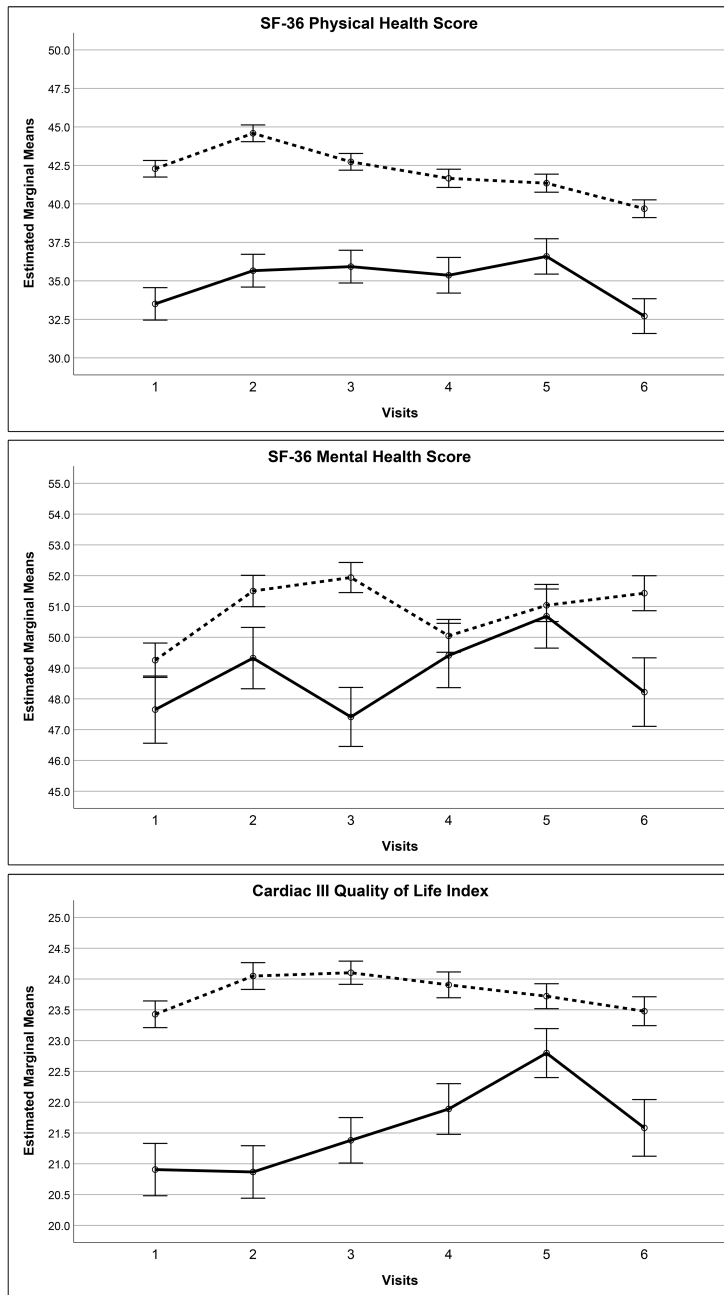
Legend: Black Solid Line= High Comorbidity; Black Dashed Line= Low Comorbidity.

Figure 15: Kaplan-Meier Curve for CV Death in EORP-AF Pilot
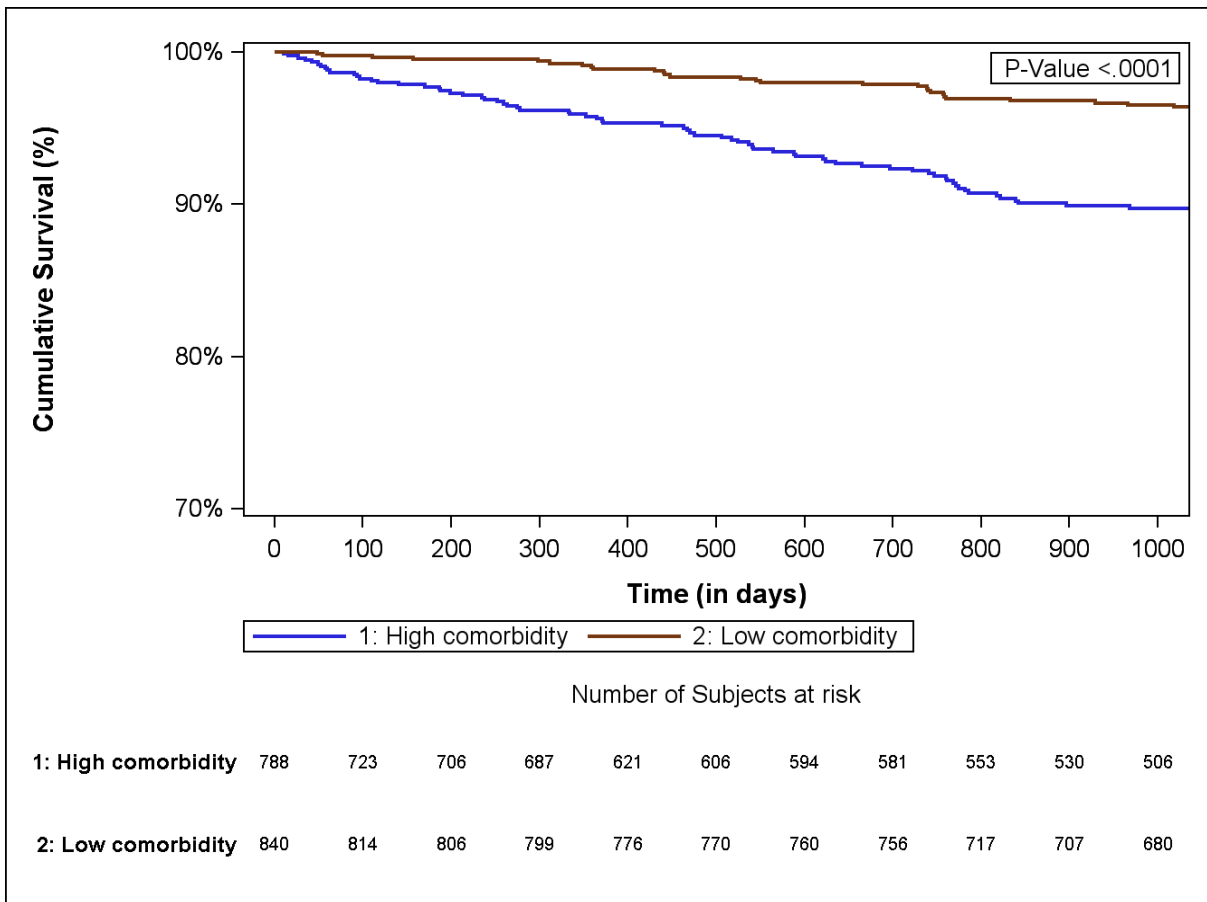
Figure 16: Kaplan-Meier Curve for All-Cause Death in EORP-AF Pilot
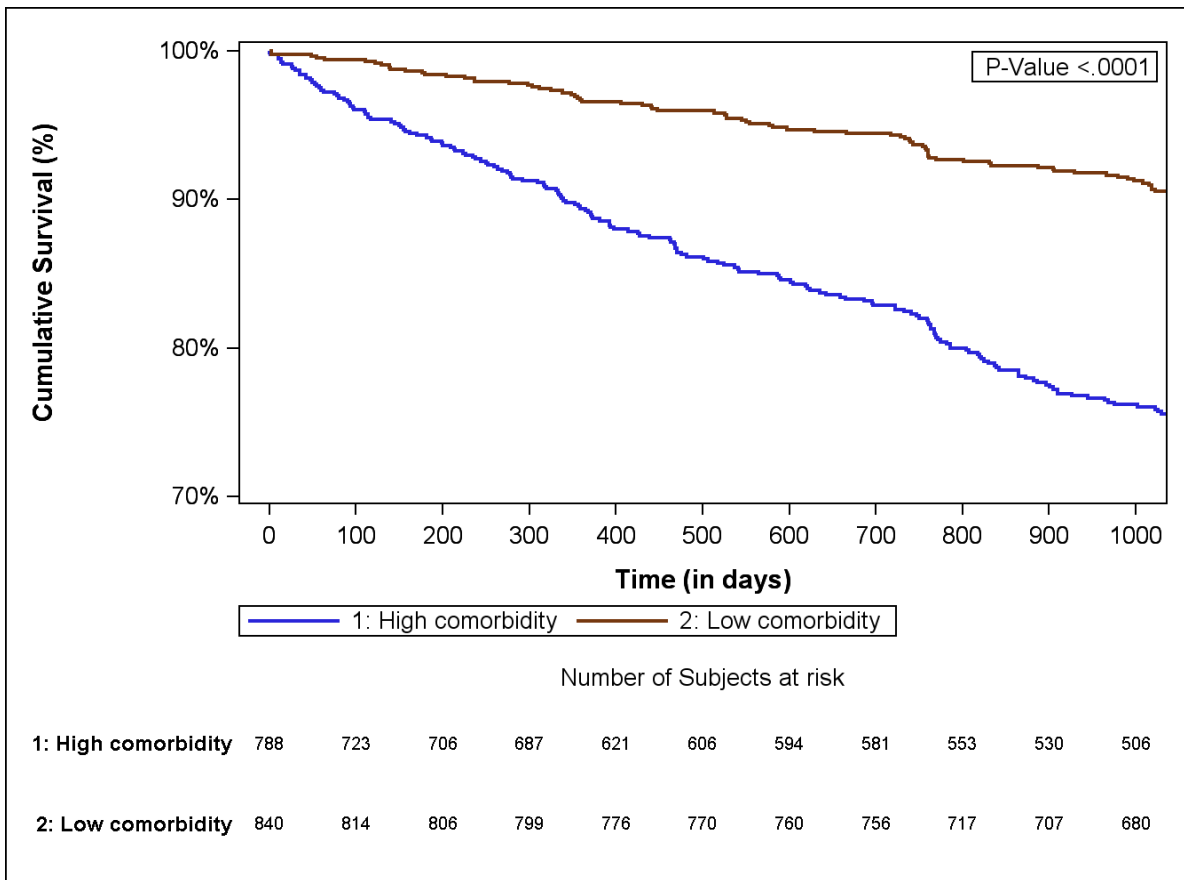
Figure 17: Performance Scales Categories according to the Burden of Comorbidity
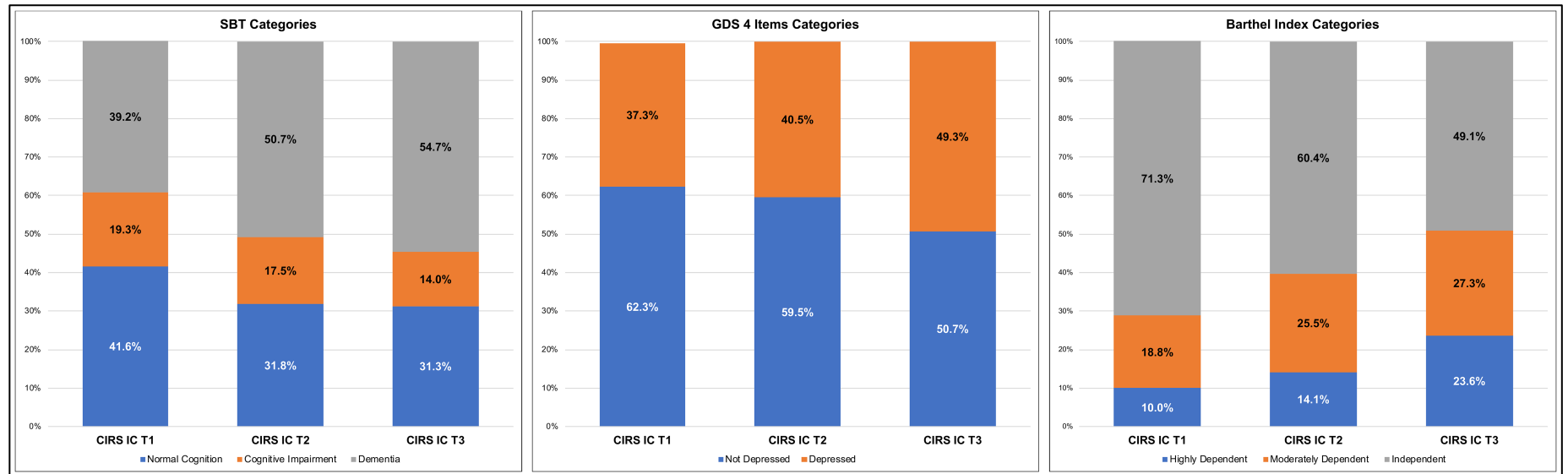
Legend: CIRS IC= Cumulative Illness Rating Scale Index of Comorbidity; GDS= Geriatric Depression Scale; SBT= Short Blessed Test.

Figure 18: Charlson Comorbidity Index Trends according to Atrial Fibrillation Diagnosis across the Follow-Up
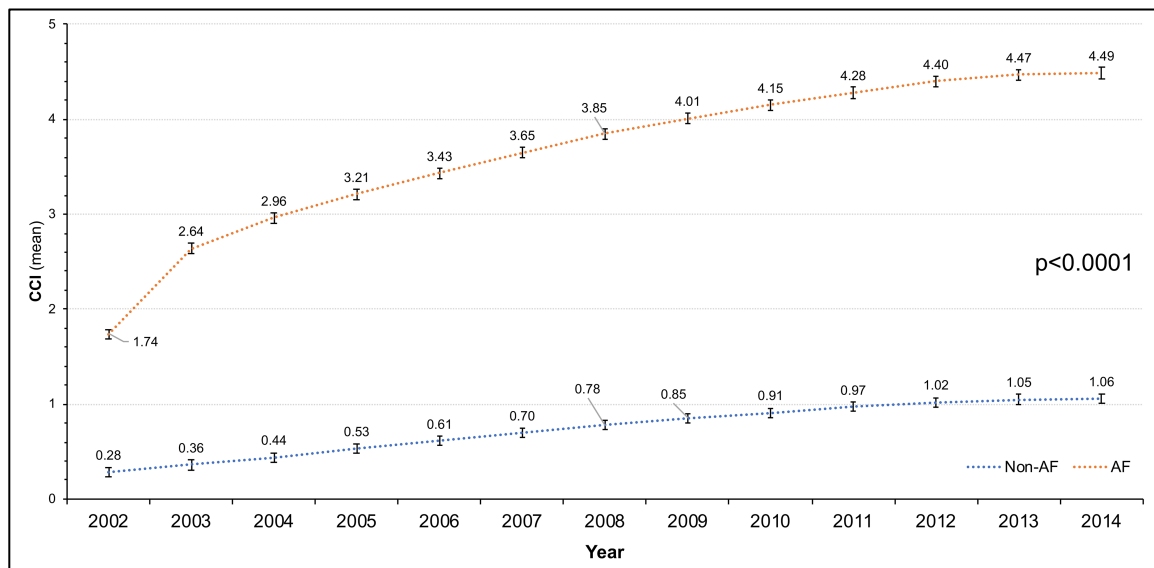
Legend: Whiskers stand for standard deviation of mean; AF= Atrial Fibrillation; CCI= Charlson Comorbidity Index.

Figure 19: Kaplan-Meier Curves for Major Adverse Events according to Charlson Comorbidity Index Classes
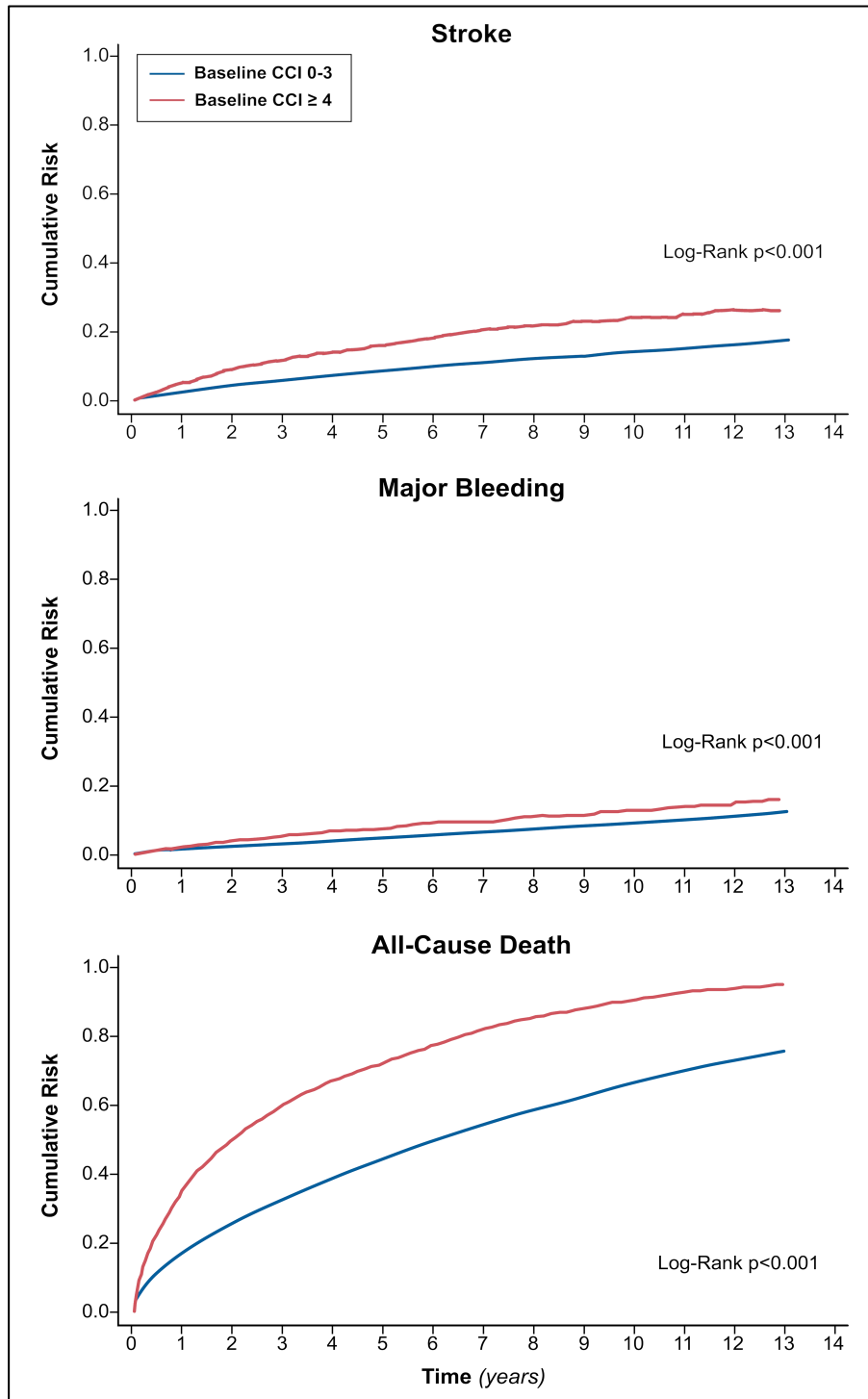
Legend: CCI= Charlson Comorbidity Index.

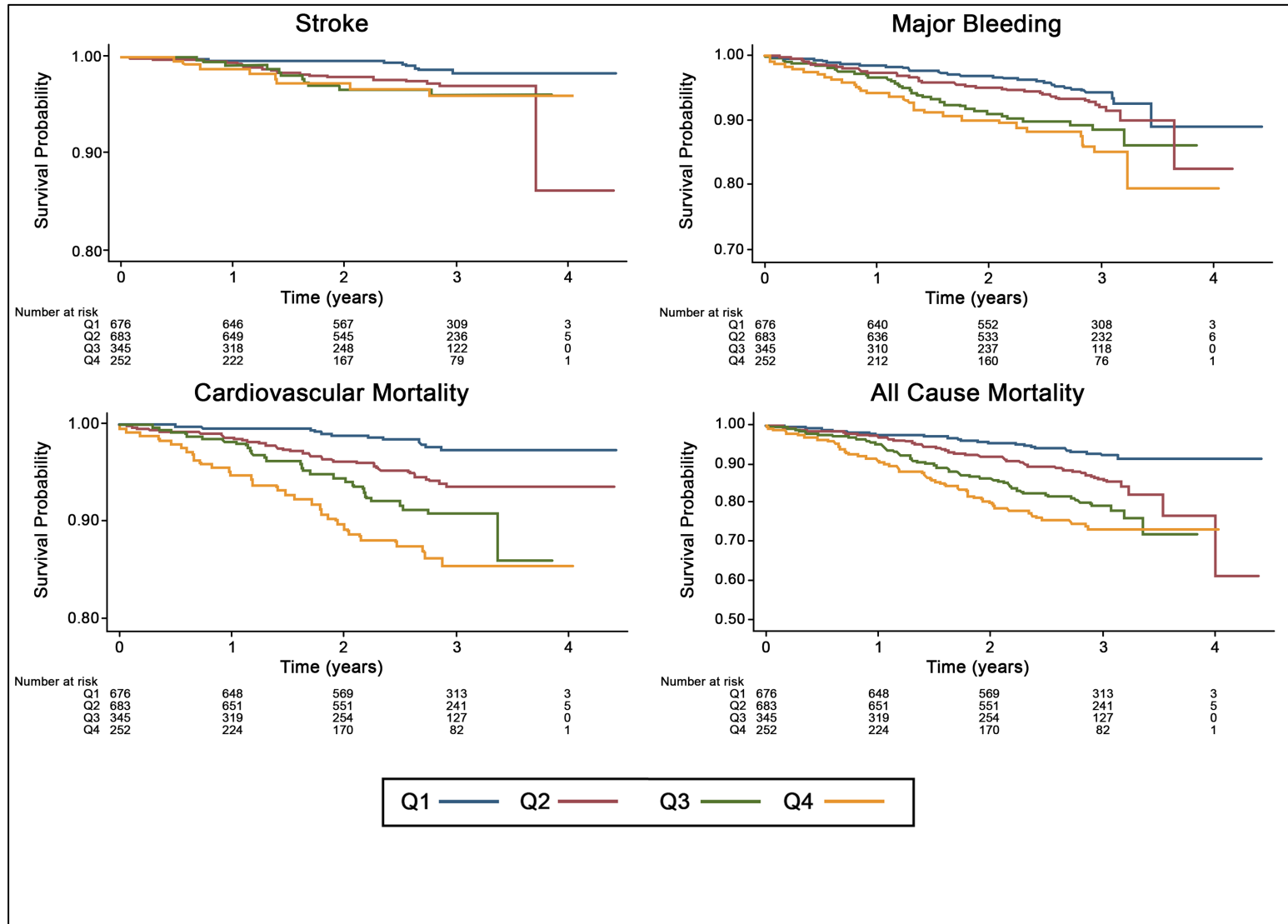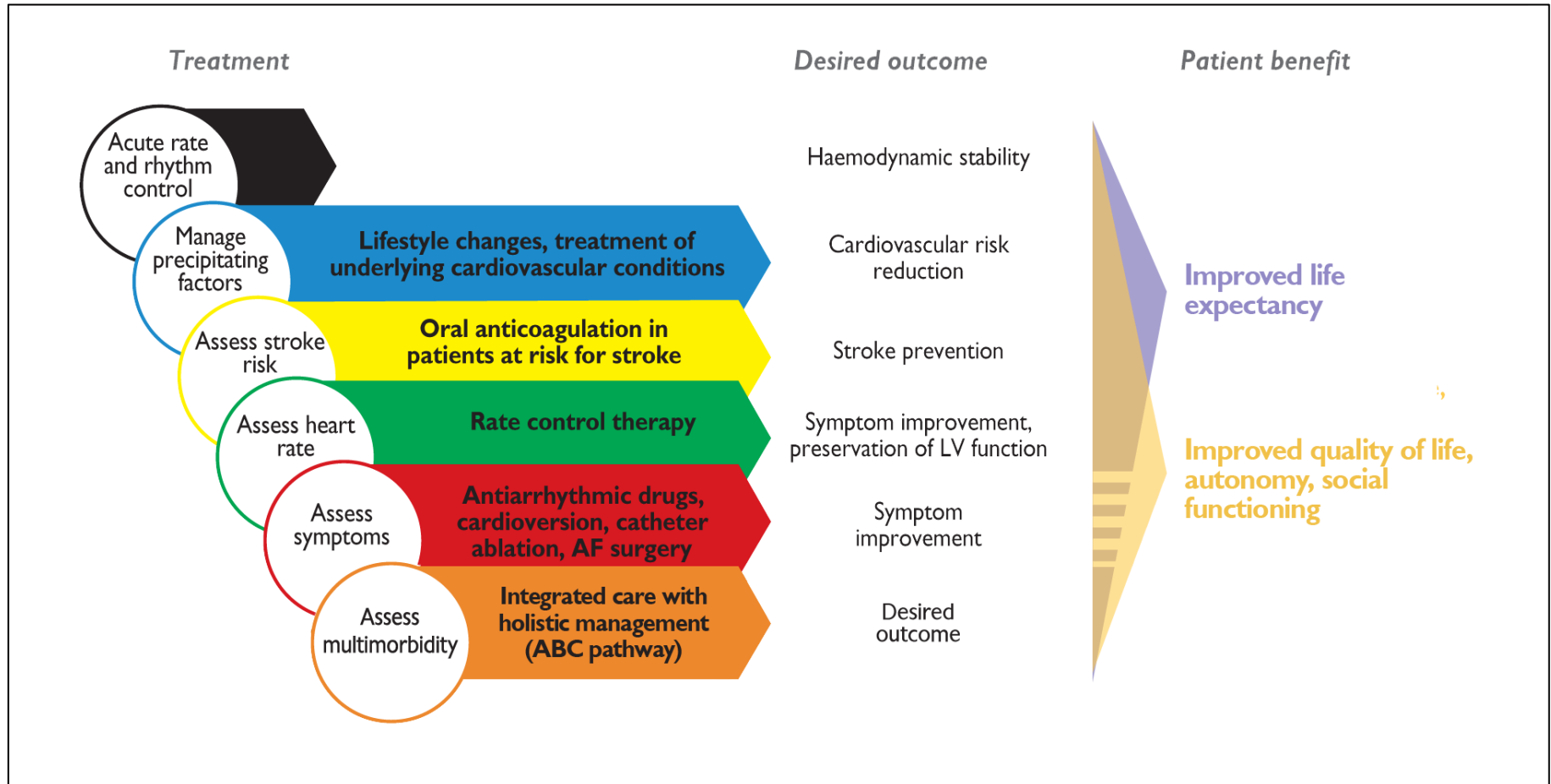Figure 20: Kaplan-Meier Curves for Major Adverse Events according to Charlson Comorbidity Index Quartiles

Figure 21: A New Modified Approach to Treat and Manage AF Patients

Legend: AF= Atrial Fibrillation, LV= Left Ventricular; adapted from Kirchhof et al. 2016[19].

Figure 22: An Alternative Model for the Integrated AF Clinic with Implementation of Specialist in Internal Medicine
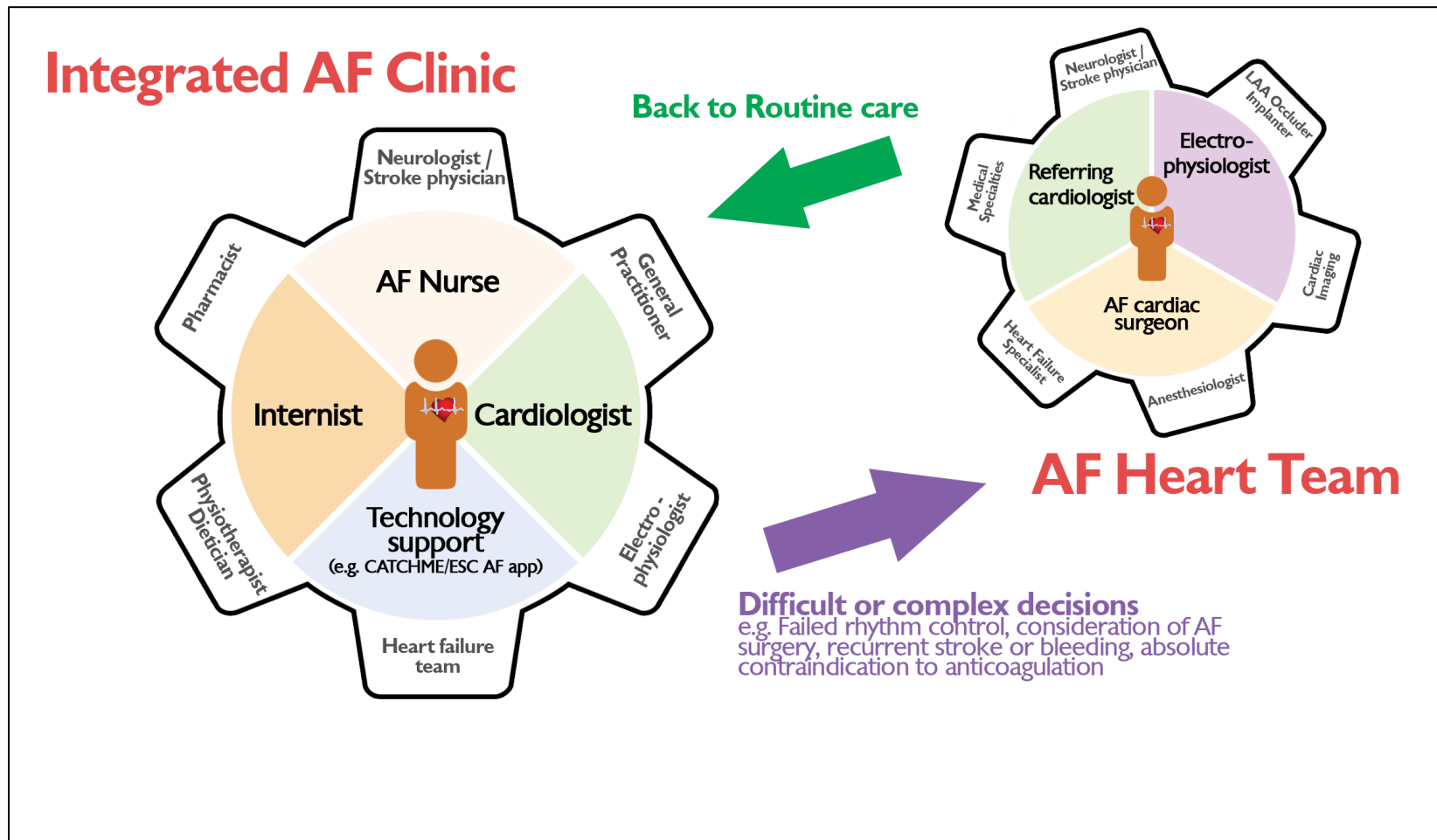
Legend: AF= Atrial Fibrillation; LAA= Left Atrial Appendage.