Epidemiology and Impact of Frailty in Patients with Atrial Fibrillation in Europe

Running Title: Frailty in European AF Patients

Marco Proietti[a,b,c] MD PhD*, Giulio Francesco Romiti[a,d] MD*, Marco Vitolo[a,e,f] MD, Stephanie L Harrison[a] PhD, Deirdre A Lane[a,g] PhD, Laurent Fauchier[h] MD PhD, Francisco Marin[i] MD PhD, Michael Näbauer[l] MD, Tatjana S Potpara[m,n] MD PhD, Gheorghe-Andrei Dan[o] MD, Aldo P Maggioni[p] MD, Matteo Cesari[b,c] MD PhD, Giuseppe Boriani[d] MD PhD†, Gregory YH Lip[a,g] MD†
on behalf of the ESC-EHRA EORP-AF General Long-Term Registry Investigators[q]

[a]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; [b]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [c]Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy; [d]Department of Translational and Precision Medicine, Sapienza – University of Rome, Italy; [e]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [f]Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy; [g]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [h]Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, Tours, France; [i]Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, IMIB-Arrixaca, University of Murcia, CIBER-CV, Murcia, Spain; [l]Department of Cardiology, Ludwig-Maximilians-University, Munich, Germany; [m]School of Medicine, University of Belgrade, Belgrade, Serbia; [n]Intensive Arrhythmia Care, Cardiology Clinic, Clinical Center of Serbia, Belgrade, Serbia; [o]University of Medicine, 'Carol Davila', Colentina University Hospital, Bucharest, Romania; [p]ANMCO Research Center, Heart Care Foundation, Florence, Italy; [q]Listed in Appendix.

*these two authors equally contributed to the paper
†joint senior authors

Total Word Count: 3263

Corresponding Author:
Prof. Gregory YH Lip
E-mail: gregory.lip@liverpool.ac.uk

COMPETING INTERESTS

DL has received investigator-initiated educational grants from Bristol-Myers Squibb (BMS), has been a speaker for Boehringer Ingelheim, and BMS/Pfizer and has consulted for BMS, Boehringer Ingelheim, and Daiichi-Sankyo; **LF** has been consultant or speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Novartis; **TSP** is consultant for Bayer and Pfizer, with no fees received personally; **GB** received small speaker's fees from Medtronic, Boston, Boehringer Ingelheim and Bayer; **GYHL** has been consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are directly received personally. All the disclosures happened outside the submitted work. All other authors have nothing to declare**.**

FUNDING

Since the start of EORP, the following companies have supported the programme: Abbott Vascular Int. (2011-2021), Amgen Cardiovascular (2009-2018), AstraZeneca (2014-2021), Bayer (2009-2018), Boehringer Ingelheim (2009-2019), Boston Scientific (2009-2012), The Bristol Myers Squibb and Pfizer Alliance (2011-2016), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2011-2017), Edwards (2016-2019), Gedeon Richter Plc. (2014-2017), Menarini Int. Op. (2009-2012), MSD-Merck & Co. (2011-2014), Novartis Pharma AG (2014-2020), ResMed (2014-2016), Sanofi (2009-2011), SERVIER (2010-2021), Vifor (2019-2022).

ACKNOWLEDGEMENTS

EORP Oversight Committee, Executive and Steering Committees (National Coordinators) of the EURObservational Research Programme (EORP) – Atrial Fibrillation General Long-Term (EORP-AFGen LT) Registry of the European Society of Cardiology (ESC). Data collection was conducted by the EORP department by Patti-Ann McNeill as Project Officer, Viviane Missiamenou as Data Manager. Overall activities were coordinated and supervised by Doctor Aldo P. Maggioni (EORP Scientific Coordinator).

Epidemiology and Impact of Frailty in Patients with Atrial Fibrillation in Europe

Running Title: Frailty in European AF Patients

ABSTRACT

Background: Frailty is a medical syndrome characterized by reduced physiological reserve and increased vulnerability to stressors. Data regarding the relationship between frailty and atrial fibrillation (AF) are still inconsistent.

Objectives: We aim to perform a comprehensive evaluation of frailty in a large European cohort of AF patients.

Methods: A 40-item frailty index (FI) was built according to the accumulation of deficits model in the AF patients enrolled in the ESC-EHRA EORP-AF General Long-Term Registry. Association of baseline characteristics, clinical management, quality of life, healthcare resources use, and risk of outcomes with frailty was examined.

Results: Among 10,177 patients [mean age (SD) 69.0 (11.4) years, 4103 (40.3%) females], 6,066 (59.6%) were pre-frail and 2,172 (21.3%) were frail, while only 1,939 (19.1%) were considered robust. Baseline thromboembolic and bleeding risks were independently associated with increasing FI. Frail patients with AF were less likely to be treated with oral anticoagulants (OACs) (odds ratio 0.70, 95% confidence interval 0.55-0.89), especially with non-vitamin K antagonist OACs, and managed with a rhythm control strategy, compared to robust patients. Increasing frailty was associated with a higher risk for all outcomes examined, with a non-linear exponential relationship. The use of OAC was associated with a lower risk of outcomes, except in patients with very/extremely high frailty.

Conclusions: In this large cohort of AF patients, there was a high burden of frailty, influencing clinical management and risk of adverse outcomes. The clinical benefit of OAC is maintained in patients with high frailty, but not in very high/extremely frail ones.

KEY POINTS:

- Data on the relationship between frailty and atrial fibrillation (AF) are scarce. We assessed the epidemiology and impact of frailty, evaluated through a 40-item frailty index (FI), in the contemporary ESC-EHRA EORP-AF General Long-Term Registry.
- Among 10,177 AF patients, 2,172 (21.3%) were frail, and a total of 80% of patients showed a relevant burden of frailty.
- Thromboembolic and bleeding risks were independently associated with increasing FI, and frail patients were also less likely treated with oral anticoagulants (OACs) and with a rhythm control strategy.
- Frailty was associated with a higher risk for all outcomes examined, with a non-linear exponential relationship. OACs reduced the risk of outcomes, except in patients with very/extremely high frailty.

KEYWORDS: atrial fibrillation; frailty; chronicity; oral anticoagulant therapy; outcomes; epidemiology.

INTRODUCTION

Frailty is a medical syndrome characterized by a reduced physiologic function, which increases vulnerability to endogenous and exogenous stressors and the risk of adverse outcomes (including dependency and death)[1]. Frailty may indeed serve as a surrogate for measuring the biological complexity of individuals[2].

In the light of progressive population aging, frailty has rapidly become an emergent public health priority, demanding specific interventions and strategies[3]. While being initially ‘confined’ to geriatric medicine, awareness of frailty has increased in other clinical specialties, including cardiovascular medicine[4–6]. Measuring such a complex phenomenon as frailty poses significant challenges, with several models that have been proposed to identify and evaluate frailty[7]. Among these, the Frailty Index (FI), proposed by Rockwood and Mitnitski, was designed to capture the accumulation of health deficits over time, to provide an alternative to chronological age[8].

It is well recognised that atrial fibrillation (AF) is closely related to increasing age, multimorbidity, and clinical complexity[9–11]. Notwithstanding this, the evidence regarding frailty evaluation in the context of AF is still limited[12].

We aimed to report the epidemiology of frailty in a large European cohort of AF patients, and describe its impact on the clinical management and outcomes of these patients.

METHODS

The European Society of Cardiology (ESC) – European Heart Rhythm Association (EHRA) EURObservational Research Programme (EORP) Atrial Fibrillation General Long-Term Registry is a prospective multicentre observational registry held by the ESC and endorsed by the EHRA. The study enrolled consecutive AF patients presenting in 250 cardiology practices in 27 participating countries, both in- and outpatient settings. A detailed description of the study design, baseline characteristics, and 1-year follow-up results have been provided elsewhere[13–15].

All participants were adults ≥18 years, had AF electrocardiographically documented within 12 months before enrolment, and provided written informed consent. Enrolment was undertaken from October 2013 to September 2016, with planned 1-year and 2-year follow-up. The institutional review boards approved the study protocol at each participating center, according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

Evaluation of Frailty

Frailty was assessed according to a 40-item frailty index (FI) (Supplemental Table 1), built on the cumulative deficits model, as proposed by Rockwood and Mitnitski[8,16] and according to the standardization principles described by Searle and colleagues[17]. FI was computed based on a multidimensional evaluation, including patients' vital signs, comorbidities, symptoms, biomarkers, and functions. For each patients, the FI was calculated as the ratio of the total deficits, and the total number of deficits included in the index (i.e., 40). According to the usual standards, a FI

ranging from 0.10 to <0.25 defined the presence of pre-frailty, while a FI ≥0.25 denoted the presence of frailty[18].

Details regarding definitions of baseline variables, evaluation of healthcare resources use, quality of life and outcomes, and the statistical analysis are reported in the Supplemental Methods.

RESULTS

Among the original 11,096 patients enrolled in the ESC-EHRA EORP-AF General Long-Term Registry, a total of 10,177 (91.7%) had available data to evaluate the FI at baseline. Mean age (SD) was 69.0 (11.4) years, 4,103 (40.3%) were women. At baseline, median [IQR] CHA_2DS_2-VASc and HAS-BLED scores were 3 [2-4] and 1 [1-2], respectively; EHRA score was ≥2 in 5,606 (55.1%) patients.

At baseline, mean (SD) FI was 0.18 (0.09), with a median [IQR] of 0.17 [0.11-0.23]. Accordingly, 6,066 (59.6%) were pre-frail, and 2,172 (21.3%) were frail. The distribution of the overall cohort according to FI is shown in Figure 1.

Baseline characteristics according to FI categories are reported in Table 1. For higher levels of the FI, AF patients were more likely to be older and women, present low socioeconomic status, live alone, and have sedentary behaviour. The prevalence of cardiovascular risk factors, comorbidities, and polypharmacy was higher among pre-frail and frail subjects.

Baseline Characteristics associated with Frailty

A multivariable multinomial logistic model showed that female sex, being enrolled in Eastern Europe and in-hospital and polypharmacy were associated with both pre-frailty and frailty, while low socioeconomic status was associated with frailty (Supplemental Table 2). Reporting regular/intense exercise, paroxysmal AF and being enrolled in Southern Europe were inversely associated with pre-frailty and frailty (Supplemental Table 2).

Relationship between Frailty Index and AF Scores

Both CHA_2DS_2-VASc and HAS-BLED scores increased with FI (Table 1 and Supplemental Figure 1) (both p<0.001). A linear regression model, adjusted for AF type and EHRA score, showed that both CHA_2DS_2-VASc and HAS-BLED scores were independently associated with FI (Beta 0.025, 95% CI 0.025-0.026, t=68.608, p<0.001 and Beta 0.031, 95% CI 0.029-0.032, t=46.211, p<0.001, respectively), with no evidence of collinearity (VIF=1.064, maximum condition index=9.625, and VIF=1.029, maximum condition index=9.555, respectively). The two scores were independently associated with increasing FI also in a multivariable model containing both (data not shown).

AF Management according to Frailty

The use of antithrombotic therapies and clinical management according to frailty is reported in Supplemental Table 3. The highest prevalence of oral anticoagulants (OAC) prescription was observed among pre-frail patients (87.6%), followed by frail (83.0%) and robust patients (80.6%) (p<0.001). Multivariable logistic regression analysis showed that, differently than frail patients (odds ratio [OR] 0.70, 95% CI 0.55-0.89, p=0.004), pre-frail patients were more likely to receive OAC than robust patients (OR 1.21, 95% CI 1.01-1.44, p=0.036).

The use of vitamin K antagonists (VKAs) progressively increased with frailty, while the opposite was observed for non-vitamin K antagonist OACs (NOACs) (p<0.001; Supplemental Table 3). Multivariable logistic regression analysis (Table 2) showed that VKAs, compared to no OAC use, were more likely prescribed in pre-frail patients and less likely prescribed in frail patients. Moreover, frail patients were less likely to

receive a NOAC than robust ones. Among patients prescribed OAC, a multivariable logistic regression analysis showed that both pre-frail and frail patients were less likely to be prescribed a NOAC than a VKA (OR 0.83, 95% CI 0.72-0.97, p=0.019 and OR 0.69, 95% CI 0.56-0.84, p<0.001, respectively).

The clinical management strategy at discharge is described in Supplemental Table 3. Frail patients were more likely managed according to a rate control strategy rather than a rhythm control strategy (p<0.001) (Supplemental Table 3). After multivariable adjustments (Table 2), both pre-frailty and frailty were independently associated with the use of a rate control strategy, and no difference was observed regarding the rhythm control strategy. Excluding those patients managed exclusively with an observation strategy, both pre-frailty and frailty were associated with lower odds of receiving rhythm control strategy than rate control (OR 0.75, 95% CI 0.63-0.89, p<0.001 and OR 0.69, 95% CI 0.55-0.86, p=0.001, respectively).

Relationship between Quality of Life and FI

At baseline, median [IQR] health utility score values decreased significantly according to frailty levels (0.95 [0.89-1.00], 0.87 [0.75-0.95], 0.71 [0.54-0.84] for robust, pre-frail and frail patients, respectively; p<0.001); similar findings were observed for the visual analogue scale (VAS) values (80 [70-90], 70 [55-80], 60 [50-75] for the robust, pre-frail and frail patients, respectively; p<0.001). Linear multivariable regression models, adjusted for AF type, OAC use, and CHA_2DS_2-VASc and EHRA scores, showed that FI (for each 0.10 increase) was inversely and independently associated with both the health utility score (Beta -0.127, 95% CI -0.133/-0.121, t=-42.865, p<0.001), and VAS (Beta -7.108, 95% CI -7.799/-6.416, t=-

20.147, p<0.001), with no evidence of collinearity (VIF=1.918, maximum condition index=12.619 and VIF=1.918, maximum condition index=12.620, respectively).

Impact of Frailty on Health-Resources Use

Increasing frailty was broadly associated with higher use of healthcare resources (Supplemental Table 4). After adjustment for potential confounders, increasing frailty was significantly associated with greater use of both Internal Medicine/General Practioner visits and Emergency Room admissions during follow-up. Similar results were also reported for hospitalisation events (both for cardiovascular and non-cardiovascular causes; Supplemental Table 4).

Relationship between Frailty and Major Adverse Events

Among the patients included in the analysis, follow-up data were available for 9,613 (95.5%) participants. During a mean (SD) follow-up of 1.84 (0.51) years, the rate of all major adverse events increased across frailty levels (all p<0.001; Table 3). Kaplan-Meier curves showed increasing cumulative risk across the level of frailty for all the outcomes [Supplemental Figures 2-6]. Cox multivariable adjusted analysis confirmed this finding (for both frailty levels and each 0.10 increase of FI) (Table 3).

The analysis of the interaction between frailty and age on the risk of all-cause mortality and major adverse cardiovascular events [MACEs] is reported in Supplemental Table 5. Regression curves describing the association between FI, age strata and risk of outcomes are reported in Supplemental Figures 7 and 8. The risk of all-cause death increased progressively with FI across the age strata, but the difference in risk magnitude was lower with increasing age and FI [Supplemental

Figure 7]; conversely, while the risk of MACEs increased progressively with FI up until FI=0.40 across all age classes, the magnitude of risk increase for higher FI values appeared higher in younger patients [Supplemental Figure 8].

Spline Curves Analysis and Impact of OAC

Multivariable adjusted restricted cubic splines of the association between FI and the risk of outcomes are reported in Supplemental Figure 9, Panels A-E, with FI=0.10 as a reference, and showed a non-linear relationship between FI and risk of the examined outcomes was observed.

When stratifying the analysis according to OAC use, all-cause death was significantly lower in patients treated with OAC reporting a FI between 0.05 and 0.36. In patients with a higher FI (around 3% of the cohort), no difference was found in the risk of all-cause death between OAC users and non-users [Figure 2 Panel A]. Patients with a FI between 0.03 and 0.44 (equal to more than 98% percentile of the cohort distribution) treated with OAC showed a significantly lower risk of MACEs than those not treated with OAC [Figure 2 Panel B]. Similar data were found for the occurrence of cardiovascular death and non-cardiovascular death [Supplemental Figures 10-11]. No difference was found across the spectrum of FI regarding major bleeding [Supplemental Figure 12].

Predictive Performance of Frailty Index among AF Patients

FI had a modest-to-good predictive value for all the major adverse outcomes examined (Supplemental Table 6), with the highest c-index found for the occurrence

of cardiovascular death (0.715, 95% CI 0.688-0.741) and the lowest for major bleeding occurrence (0.611, 95% CI 0.575-0.648).

DISCUSSION

In a large and representative cohort of contemporary AF patients, frailty was found in about one out of five persons, whereas the prevalence of pre-frailty was around 60%. Frailty and pre-frailty were associated with greater deprivation, both on health and social aspects, and increasing FI was independently associated with higher thromboembolic and bleeding risks estimates, as reflected by CHA_2DS_2-VASc and HAS-BLED scores. Frailty also impacted the clinical management of AF patients (including OAC prescription) and also had a detrimental effect on quality of life and healthcare resources use. Finally, frailty and pre-frailty were associated with a proportionally higher risk for all major adverse outcomes examined, and FI was non-linearly associated with an increased risk of adverse events. OAC reduced the risks of outcomes, except in patients with very high/extreme frailty, without any significant increase in the risk of major bleeding across the spectrum of FI (Central Illustration).

Recently, the concept of frailty has gained significant attention, even beyond geriatric medicine, where it was initially conceived[3–6]. Given the high burden of multimorbidity, the impact on quality of life, perceived health and the risk for major adverse outcomes, AF appears to be significantly burdened by frailty[9,10]. However, the relationship between AF and frailty has been investigated in a limited number of studies and cohorts, providing so far only inconsistent evidence[12,19,20].

Our study assesses and describes the epidemiology of frailty in a cohort of contemporary European AF patients, and represents the first large validation of the FI tool in this clinical and geographical setting. Our results show that more than 80% of European AF patients present with some degree of frailty. Previous estimates of

frailty prevalence among AF patients showed considerable variability, ranging from 1% to over 80%[12,19,20]. A sub-analysis of the ENGAGE-AF TIMI 48 trial reported a similar prevalence of frailty and prefrailty, although in the context of a randomised controlled trial[21]. Finally, a recent meta-analysis showed how prevalence of frailty among AF patients is up to 40%, reaching 75% when considering also pre-frailty[22]; these findings are consistent with our results.

Our analysis also shows how several factors associated with a more deprived or susceptible personal and health status (i.e., low socioeconomic status, hospitalised patients, increased polypharmacy) were incrementally associated with pre-frailty and frailty. Moreover, the significant associations between frailty and age, female sex, and physical activity were expected[23–25]. Consistency with previous evidence further strengthens our results and confirms the estimates of frailty in the present cohort[23–25]. Also, paroxysmal AF was inversely associated with frailty, confirming that more permanent AF is associated with a greater burden of comorbidities[26]. Thromboembolic and bleeding risks contribute to the burden of frailty, further underlining the relationship between AF and frailty.

We also found that frailty was inversely associated with OAC prescriptions and lower likelihood of receiving a rhythm control strategy. Furthermore, frail individuals were less likely to be prescribed with both VKAs and NOACs, while VKAs were more likely prescribed in pre-frail patients. Finally, considering only patients prescribed with OAC, we found NOACs less likely prescribed than VKAs in both pre-frail and frail patients.

Thus far, data about the relationship between frailty and OAC prescription have been controversial[12]. Our data reinforce previous evidence on the OAC undertreatment of frail AF patients[22], reflecting the substantial absence of specific evidence and, in turn, of guidelines' recommendations related to the prescription and management of OAC in frail patients[9]. Nevertheless, the available evidence suggests that frailty very likely represents an obstacle to OAC prescription due to physicians' concerns about the risk of major bleeding[12,27]. Moreover, lower NOACs prescription among frail patients may reflect the limited data on the effectiveness and safety of NOACs in this patient group[28–30].

Similarly, limited data are available regarding the relationship between frailty and rate/rhythm control. In a cohort of patients age ≥65 years old, rate control was more prescribed than rhythm control, although with no differences between frail and non-frail patients[31], while a survey performed by the EHRA, showed that 40% of cardiologists reported rate control as a unique approach in frail patients, while 57% believed that both approaches could be used[27]. In this context, our data prove that AF patients are less managed with rhythm control according to the burden of frailty, which entails conservative management.

Our study also shows how frailty impacts the impact quality of life, healthcare resource use and risk of major adverse events in AF patients. While the relationship between frailty, quality of life and higher use of healthcare resources has already been described[32–34], our study is the first to analyse these relationships in AF patients, and we found a detrimental effect of frailty on both. Furthermore, we demonstrated a significant association between increasing frailty and the risk of all

major adverse events. The evidence of an association between FI and higher risk of death has been already reported in the general population[35], as well as among AF patients[19]. However, previous studies may have not been able to achieve the same granularity of analysis[36,37]. For example, Wilkinson et al. found a significant association with all-cause mortality, but did not show any association with cerebrovascular events and only a partial association with bleeding outcomes[36]. Conversely, Gugganig et al. demonstrated a significant association with adverse outcomes (i.e., all-cause death, stroke, bleeding), but did not explore the causes of death, the overall risk of cardiovascular events, or the relevant outcome of major bleeding[37]. Furthermore, they did not show a similar 'exposure-effect' relationship as we did in our analysis[37]. While a recent meta-analysis confirmed that frailty increases the risk of outcomes in AF patients[22], the granularity of our data allowed us to expand the understanding of this association, describing an 'exposure-effect' between the burden of frailty and risk of outcomes. The results of the predictive analysis reinforce these results, showing that FI has a good-to-moderate predictive ability for all the outcomes considered (in line with all the AF scores used in clinical practice)[38].

We also showed how age (i.e., chronological aging) and frailty (i.e., biological aging) are independently able to influence the risk of outcomes. The observed interaction between age and FI suggests that the impact of frailty is even more prominent than age in determining the occurrence of events. The relative impact of FI is particularly important in younger subjects regarding the all-cause death and MACEs, consistently with a clinically relevant role of frailty already observed in younger adults[39]. Nevertheless, our data demonstrate that, although age plays a role as

determinant of frailty, chronological and biological aging should be distinguished because only partially overlapping[40,41].

The spline curves analysis suggests that FI is non-linearly associated with the risk of outcomes, and that OAC reduces the risk even up to high levels of FI, with no difference only in those with very or extremely high FI. These results underline how the use of OAC allows a significant reduction of risk only in patients that have a significant residual capacity. Our data are also reassuring about the positive benefit/risk ratio even in AF patients with moderate to high levels of frailty, since the use of OAC did not increase the risk of bleeding at any level of frailty. These data seem to support a recent EHRA consensus on the use of NOACs in AF patients[42], introducing that in some patients with extreme frailty, the OAC prescription may not be safe. Also, the authors suggested for the first time the use of an objective tool to measure frailty, the Clinical Frailty Scale[42].

Taken together, our data emphasise the need for a routine evaluation of frailty in AF patients. A formal assessment of frailty - through the means of geriatric comprehensive assessment, followed by a personalised intervention - can reduce the burden of frailty, leading to improvement in clinical outcomes[43–46]. More data are needed to elucidate which patients would benefit the most from receiving a formal frailty assessment. Combining the evaluation of frailty with an integrated care management approach, recommended as the ‘Atrial fibrillation Better Care’ pathway[47,48], could significantly reduce all the primary AF-related adverse outcomes.

Limitations

The main limitation of the current study relates to the observational nature of the registry itself. Consequently, the study was not specifically powered to determine differences between the subgroups examined. The absence of a central events adjudication with an investigator-based reporting of the adverse outcomes represents another limitation, which entails caution in interpreting the current results. Third, since not all the patients included in the analysis had follow-up available represents another limitation. Moreover, since our project is derived from an AF registry we could not evaluate whether frailty could have a specific, stronger impact on AF patients compared to non-AF subjects. Lastly, in the process of building the FI, the absence of specific tools to measure physical and other types of physiological performance, which are instead evaluated by the EQ-5D-5L, represents another limitation which could limit the generalizability of results, particularly in relation to older subjects.

CONCLUSIONS

In this large European cohort of unselected AF patients, we found a highly significant burden of frailty, influencing significantly all the main aspects related to the management of AF, comprising OAC prescription and clinical management. A higher burden of frailty (i.e., biological age) was associated with a higher risk for all the major adverse events independently and more prominently than chronological age. The clinical benefit of using OAC was maintained even in patients with high frailty, but not in those with very high/extreme frailty. More data are still needed on the optimal management of this topical issue in AF patients.

REFERENCES

1. Morley JE, Vellas B, van Kan GA *et al.* Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013;**14**:392–7.

2. Amblàs-Novellas J, Espaulella J, Rexach L *et al.* Frailty, severity, progression and shared decision-making: A pragmatic framework for the challenge of clinical complexity at the end of life. *Eur Geriatr Med* 2015;**6**:189–94.

3. Cesari M, Prince M, Thiyagarajan JA *et al.* Frailty: An Emerging Public Health Priority. *J Am Med Dir Assoc* 2016;**17**:188–92.

4. Ida S, Kaneko R, Imataka K *et al.* Relationship between frailty and mortality, hospitalization, and cardiovascular diseases in diabetes: A systematic review and meta-analysis. *Cardiovasc Diabetol* 2019;**18**:81.

5. Aprahamian I, Sassaki E, dos Santos MF *et al.* Hypertension and frailty in older adults. *J Clin Hypertens* 2018;**20**:186–92.

6. Yang X, Lupón J, Vidán MT *et al.* Impact of frailty on mortality and hospitalization in chronic heart failure: A systematic review and meta-analysis. *J Am Heart Assoc* 2018;**7**, DOI: 10.1161/JAHA.117.008251.

7. Proietti M, Cesari M. Frailty: What Is It? *Adv Exp Med Biol* 2020;**1216**:1–7.

8. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001;**1**:323–36.

9. Hindricks G, Potpara T, Dagres N *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.

10. Proietti M, Marzona I, Vannini T *et al.* Long-Term Relationship Between Atrial Fibrillation, Multimorbidity and Oral Anticoagulant Drug Use. *Mayo Clin Proc* 2019;**94**:2427–36.

11. Proietti M, Vitolo M, Harrison SL *et al.* Impact of clinical phenotypes on management and outcomes in European atrial fibrillation patients: a report from the ESC-EHRA EURObservational Research Programme in AF (EORP-AF) General Long-Term Registry. *BMC Med* 2021;**19**:256.

12. Wilkinson C, Todd O, Clegg A *et al.* Management of atrial fibrillation for older people with frailty: A systematic review and meta-analysis. *Age Ageing* 2019;**48**:196–204.

13. Boriani G, Proietti M, Laroche C *et al.* Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: A report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace* 2018;**20**:747–57.

14. Boriani G, Proietti M, Laroche C *et al.* Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation: The EORP-AF General Long-Term Registry. *Europace* 2019;**21**:1013–22.

15. Vitolo M, Proietti M, Harrison S *et al.* The Euro Heart Survey and EURObservational Research Programme (EORP) in atrial fibrillation registries: contribution to epidemiology, clinical management and therapy of atrial fibrillation patients over the last 20 years. *Intern Emerg Med* 2020;**15**:1183–92.

16. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *Journals Gerontol - Ser A Biol Sci Med Sci* 2007;**62**:722–7.

17. Searle SD, Mitnitski A, Gahbauer EA *et al.* A standard procedure for creating a frailty index. *BMC Geriatr* 2008;**8**:24.

18. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. *Eur J Intern Med* 2016;**31**:3–10.

19. Proietti M, Cesari M. Describing the relationship between atrial fibrillation and

frailty: Clinical implications and open research questions. *Exp Gerontol* 2021;**152**:111455.

20. Villani ER, Tummolo AM, Palmer K *et al.* Frailty and atrial fibrillation: A systematic review. *Eur J Intern Med* 2018;**56**:33–8.

21. Wilkinson C, Wu J, Searle SD *et al.* Clinical outcomes in patients with atrial fibrillation and frailty: insights from the ENGAGE AF-TIMI 48 trial. *BMC Med* 2020;**18**:401.

22. Proietti M, Romiti GF, Raparelli V *et al.* Frailty Prevalence and Impact on Outcomes in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis of 1,187,000 Patients. *Ageing Res Rev* 2022:101652.

23. Feng Z, Lugtenberg M, Franse C *et al.* Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: A systematic review of longitudinal studies. Ginsberg SD (ed.). *PLoS One* 2017;**12**:e0178383.

24. O'Connell ML, Coppinger T, McCarthy AL. The role of nutrition and physical activity in frailty: A review. *Clin Nutr ESPEN* 2020;**35**:1–11.

25. Tolley APL, Ramsey KA, Rojer AGM *et al.* Objectively measured physical activity is associated with frailty in community-dwelling older adults: A systematic review. *J Clin Epidemiol* 2021;**137**:218–30.

26. Boriani G, Vitolo M, Diemberger I *et al.* Optimizing indices of atrial fibrillation susceptibility and burden to evaluate atrial fibrillation severity, risk and outcomes. *Cardiovasc Res* 2021;**117**:1–21.

27. Fumagalli S, Potpara TS, Bjerregaard Larsen T *et al.* Frailty syndrome: An emerging clinical problem in the everyday management of clinical arrhythmias. the results of the European Heart Rhythm Association survey. *Europace* 2017;**19**:1896–

902.

28. Grymonprez M, Steurbaut S, De Backer TL *et al.* Effectiveness and Safety of Oral Anticoagulants in Older Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Front Pharmacol* 2020;**11**, DOI: 10.3389/fphar.2020.583311.

29. Kim DH, Pawar A, Gagne JJ *et al.* Frailty and Clinical Outcomes of Direct Oral Anticoagulants Versus Warfarin in Older Adults With Atrial Fibrillation. *Ann Intern Med* 2021;**174**:1214–23.

30. Proietti M, Camera M, Gallieni M *et al.* Use and Prescription of Direct Oral Anticoagulants in Older and Frail Patients with Atrial Fibrillation: A Multidisciplinary Consensus Document. *J Pers Med* 2022;**12**:469.

31. Nguyen TN, Cumming RG, Hilmer SN. Atrial fibrillation in older inpatients: are there any differences in clinical characteristics and pharmacological treatment between the frail and the non-frail? *Intern Med J* 2016;**46**:86–95.

32. Roe L, Normand C, Wren MA *et al.* The impact of frailty on healthcare utilisation in Ireland: Evidence from the Irish longitudinal study on ageing. *BMC Geriatr* 2017;**17**:203.

33. Han L, Clegg A, Doran T *et al.* The impact of frailty on healthcare resource use: A longitudinal analysis using the Clinical Practice Research Datalink in England. *Age Ageing* 2019;**48**:662–8.

34. Crocker TF, Brown L, Clegg A *et al.* Quality of life is substantially worse for community-dwelling older people living with frailty: systematic review and meta-analysis. *Qual Life Res* 2019;**28**:2041–56.

35. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: A systematic review and meta-analysis. *Age Ageing* 2018;**47**:193–200.

36. Wilkinson C, Clegg A, Todd O *et al.* Atrial fibrillation and oral anticoagulation in

older people with frailty: a nationwide primary care electronic health records cohort study. *Age Ageing* 2021;**50**:772–9.

37. Gugganig R, Aeschbacher S, Leong DP *et al.* Frailty to predict unplanned hospitalization, stroke, bleeding, and death in atrial fibrillation. *Eur Hear J - Qual Care Clin Outcomes* 2021;**7**:42–51.

38. Borre ED, Goode A, Raitz G *et al.* Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thromb Haemost* 2018;**118**:2171–87.

39. Hanlon P, Nicholl BI, Jani BD *et al.* Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Heal* 2018;**3**:e323–32.

40. Fedarko NS. The Biology of Aging and Frailty. *Clin Geriatr Med* 2011;**27**:27–37.

41. Takeda C, Angioni D, Setphan E *et al.* Age-Related Frailty: A Clinical Model for Geroscience? *J Nutr Heal Aging* 2020;**24**:1140–3.

42. Steffel J, Collins R, Antz M *et al.* 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *EP Eur* 2021;**23**:1612–76.

43. Cesari M, Vellas B, Hsu FC *et al.* A physical activity intervention to treat the frailty syndrome in older persons - Results from the LIFE-P study. *Journals Gerontol - Ser A Biol Sci Med Sci* 2015;**70**:216–22.

44. Gené Huguet L, Navarro González M, Kostov B *et al.* Pre Frail 80: Multifactorial Intervention to Prevent Progression of Pre-Frailty to Frailty in the Elderly. *J Nutr Heal Aging* 2018;**22**:1266–74.

45. Rezaei-Shahsavarloo Z, Atashzadeh-Shoorideh F, Gobbens RJJ *et al.* The impact of interventions on management of frailty in hospitalized frail older adults: a

systematic review and meta-analysis. *BMC Geriatr* 2020;**20**:526.

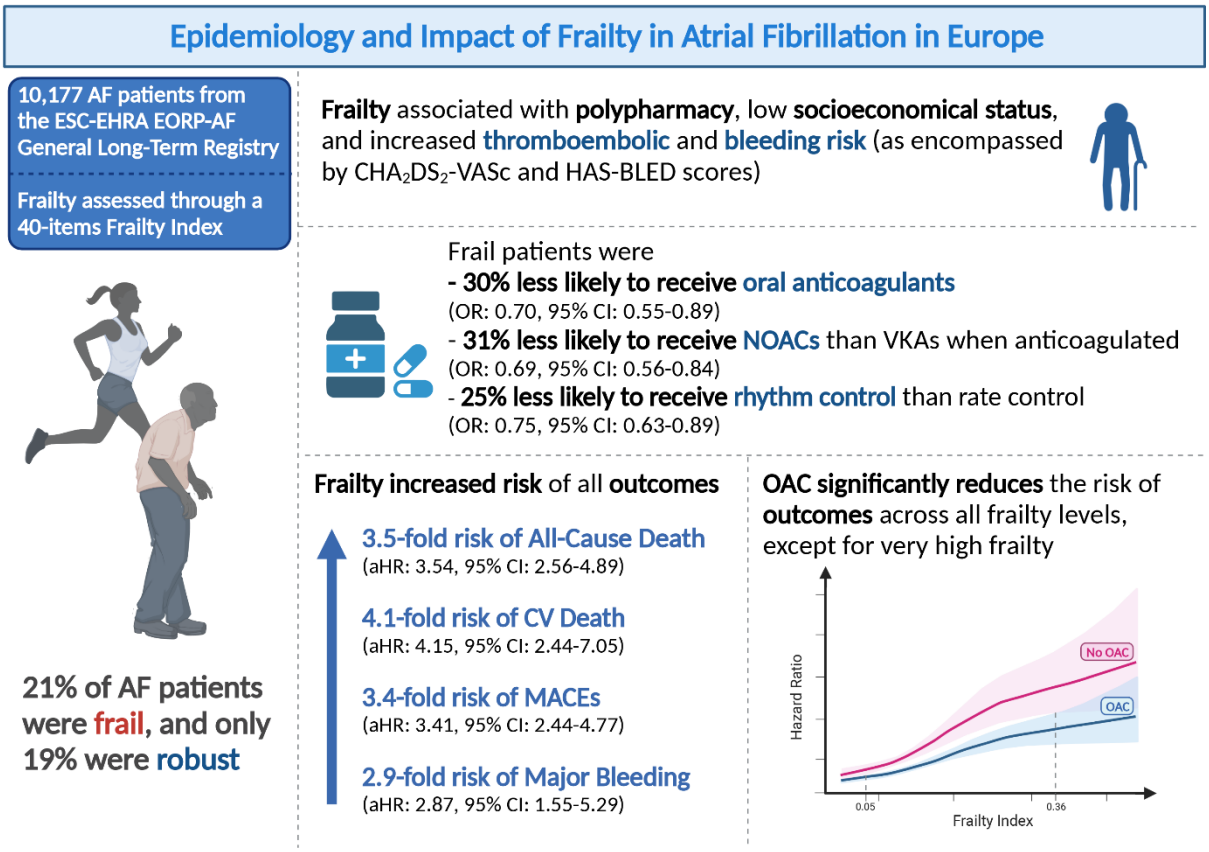
46. Ellis G, Gardner M, Tsiachristas A *et al.* Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2017;**2017**, DOI: 10.1002/14651858.CD006211.pub3.

47. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol* 2017;**14**:627–8.

48. Romiti GF, Pastori D, Rivera-Caravaca JM *et al.* Adherence to the "Atrial Fibrillation Better Care" Pathway in Patients with Atrial Fibrillation: Impact on Clinical Outcomes-A Systematic Review and Meta-Analysis of 285,000 Patients. *Thromb Haemost* 2022;**122**:406–14.

FIGURE LEGENDS

Central Illustration: Epidemiology and Impact of Frailty in Atrial Fibrillation in Europe (Created with Biorender.com)



Legend: AF= Atrial Fibrillation; CI= Confidence Interval; CV= Cardiovascular; EHRA= European Heart Rhythm Association; EORP= EURObservational Research Programme; ESC= European Society of Cardiology; aHR= adjusted Hazard Ratio; MACEs= Major Adverse Cardiovascular Events; NOACs= Non-Vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulant; OR= Odds Ratio; VKAs= Vitamin K Antagonists; created with Biorender.com.

Figure 1: Distribution of Frailty Index in the ESC-EHRA EORP-AF General Long-Term Registry Cohort

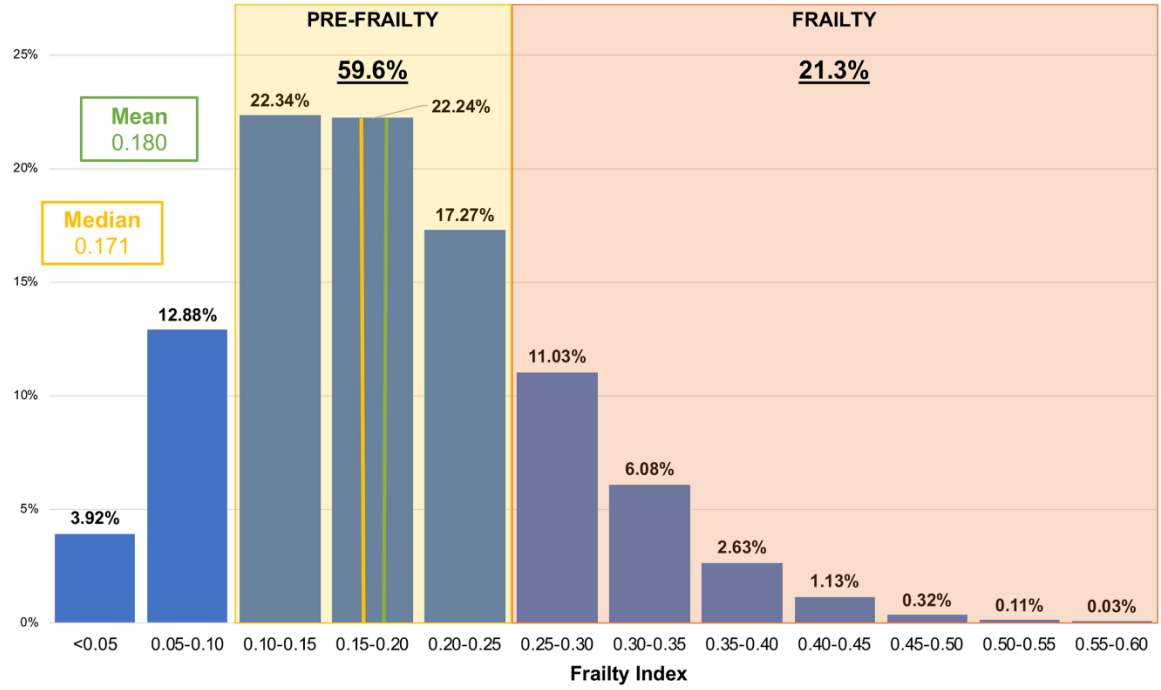
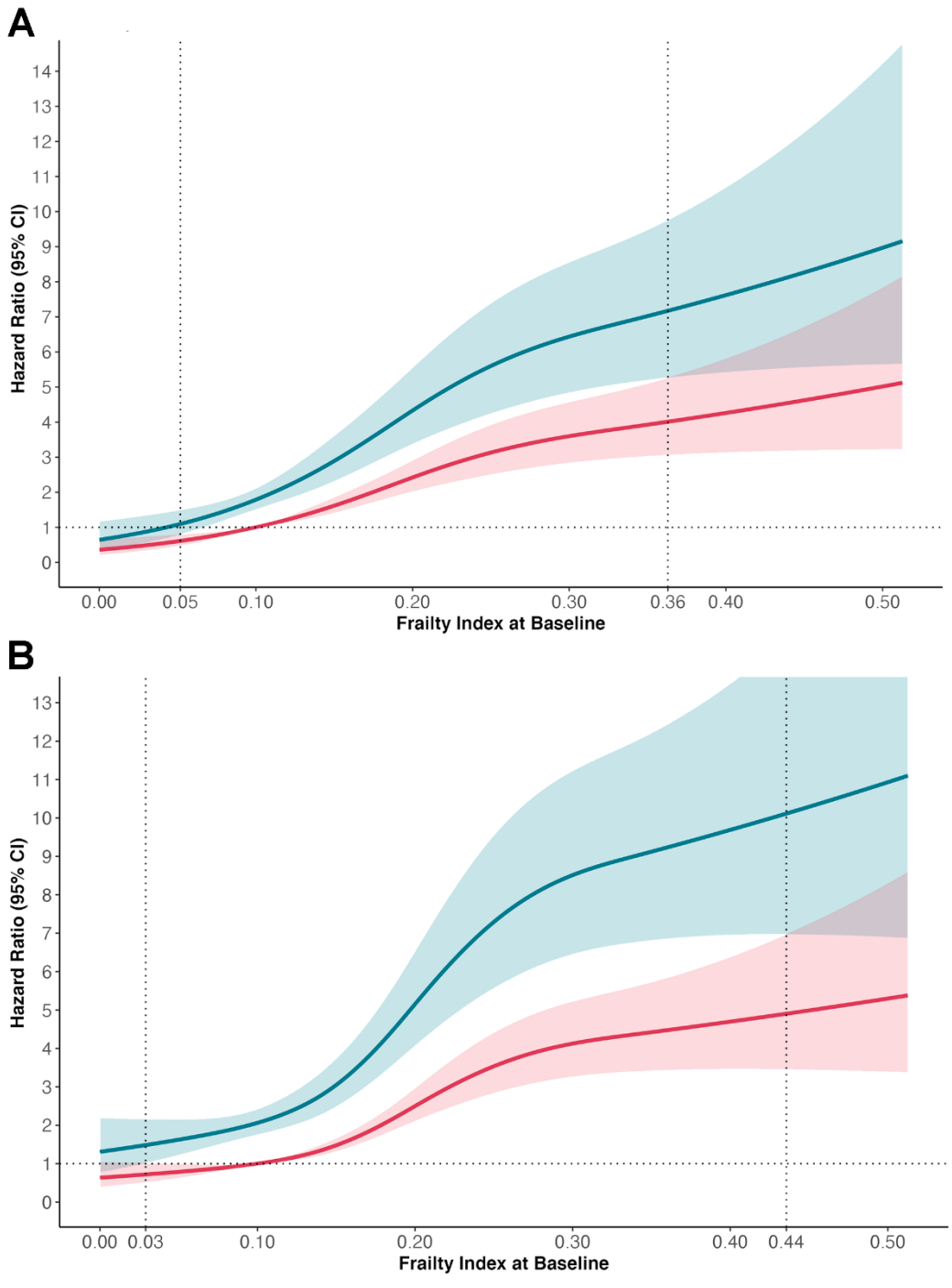


Figure 2: Association between Frailty Index and Risk of All-Cause Death and MACEs according to OAC Use



Legend: Panel A: All-Cause Death; Panel B: MACEs. Red Line) OAC prescribed; Blue Line) OAC not prescribed; CI= Confidence Interval; MACEs= Major Adverse Cardiovascular Events; OAC= Oral Anticoagulant.

1 **Table 1: Baseline Characteristics according to Frailty Classes**

N= 10177	**Robust N= 1939**	**Pre-Frail N= 6066**	**Frail N= 2172**	**p**
Socio-Demographic Characteristics				
Age, *years* median [IQR]	65 [56-74]	71 [63-77]	73 [66-79]	<0.001
Female, n (%)	603 (31.1)	2426 (40.0)	1074 (49.4)	<0.001
European Region, n (%)				<0.001
Northern Europe	368 (19.0)	819 (13.5)	209 (9.6)	
Western Europe	647 (33.4)	2152 (35.5)	489 (22.5)	
Eastern Europe	172 (8.9)	894 (14.7)	618 (28.5)	
Southern Europe	752 (38.8)	2201 (36.3)	856 (39.4)	
Low Socioeconomic Status, n (%) *8079*	721 (47.2)	2410 (51.4)	1202 (64.6)	<0.001
Domestic Status, n (%) *8653*				<0.001
Living Alone	240 (14.2)	885 (17.3)	359 (19.4)	
Living with Partner/Family	1449 (85.8)	4231 (82.7)	1489 (80.6)	
Physical Activity, n (%) *8862*				<0.001
None/Occasional	1014 (60.2)	3905 (75.1)	1728 (87.4)	
Regula**r/**Intense	671 (39.8)	1296 (24.9)	248 (12.6)	
Clinical Characteristics and Comorbidities				
Site of Inclusion, n (%)				<0.001
Outpatient Facility	1188 (61.3)	3038 (50.1)	665 (30.6)	
Hospital	751 (38.7)	3028 (49.9)	1507 (69.4)	
Reason for Admission, n (%)				<0.001
Other than AF	390 (20.1)	2002 (33.0)	1041 (47.9)	
AF	1548 (79.9)	4064 (67.0)	1131 (52.1)	

BMI, *kg/m²* median [IQR]	26.2 [24.0-28.9]	27.7 [24.9-31.2]	28.9 [25.5-32-7]	<0.001
SBP, *mmHg* median [IQR]	125 [119-134]	130 [120-143]	140 [120-150]	<0.001
DBP, *mmHg* median [IQR]	80 [70-80]	80 [70-88]	80 [70-90]	<0.001
AF Classification, n (%)				<0.001
First Detected	346 (17.8)	957 (15.8)	325 (15.0)	
Paroxysmal	632 (32.6)	1528 (25.2)	504 (23.2)	
Persistent	413 (21.3)	1191 (19.6)	397 (18.3)	
LT Persistent	64 (3.3)	258 (4.3)	114 (5.3)	
Permanent	441 (22.7)	2025 (33.4)	811 (37.4)	
Unknown	43 (2.2)	105 (1.7)	19 (0,9)	
Heart Failure, n (%)	157 (8.1)	2143 (35.3)	1586 (73.0)	<0.001
Coronary Artery Disease, n (%)	154 (7.9)	1669 (27.5)	1025 (47.2)	<0.001
Hypertension, n (%)	650 (33.5)	3877 (63.9)	1742 (80.2)	<0.001
Diabetes Mellitus, n (%)	95 (4.9)	1293 (21.3)	949 (43.7)	<0.001
Lipid Disorder, n (%)	322 (16.6)	2485 (41.0)	1247 (57.4)	<0.001
Previous TE Events, n (%)	92 (4.7)	674 (11.1)	409 (18.8)	<0.001
Previous Hemorrhagic Events, n (%)	28 (1.4)	291 (4.8)	219 (10.1)	<0.001
PAD, n (%)	15 (0.8)	402 (6.6)	386 (17.8)	<0.001
CKD, n (%)	37 (1.9)	520 (8.6)	664 (30.7)	<0.001
COPD, n (%)	34 (1.8)	466 (7.7)	402 (18.5)	<0.001
Anaemia, n (%)	2 (0.1)	198 (3.3)	336 (15.5)	<0.001
Predisposition to Bleeding, n (%)	9 (0.5)	81 (1.3)	114 (5.3)	<0.001
Dementia, n (%)	2 (0.1)	41 (0.7)	72 (3.3)	<0.001
Malignancy, n (%)	67 (3.5)	452 (7.5)	242 (11.1)	<0.001
CHA_2DS_2-VASc, median [IQR]	2 [1-3]	3 [2-4]	4 [3-5]	<0.001
High TE Risk, n (%)	868 (44.8)	4722 (77.9)	2051 (94.5)	<0.001

HAS-BLED, Median [IQR]	1 [0-2]	1 [1-2]	2 [1-3]	<0.001
High Bleeding Risk, n (%)	70 (3.6)	925 (15.2)	766 (35.3)	<0.001
Polypharmacy, n (%)	433 (22.5)	3320 (55.2)	1673 (78.0)	<0.001

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; CKD= Chronic Kidney Disease; COPD= Chronic Obstructive Pulmonary Disease; DBP= Diastolic Blood Pressure; IQR= Interquartile Range; PAD= Peripheral Arterial Disease; SBP= Systolic Blood Pressure; TE= ThromboEmbolic.

Table 2: AF Management according to Frailty Classes

OAC Prescription	**OR***	**95% CI**	**p**
VKAs *(n= 5038) vs. No OAC (n= 1496)*			
Frailty Classes			
Robust	Ref.	Ref.	Ref.
Pre-Frail	1.24	1.02-1.51	0.027
Frail	0.73	0.56-0.94	0.016
NOACs *(n= 3638) vs. No OAC*			
Frailty Classes			
Robust	Ref.	Ref.	Ref.
Pre-Frail	1.09	0.90-1.33	0.370
Frail	0.54	0.41-0.70	<0.001
Clinical Management Strategy	**OR†**	**95% CI**	**p**
Rate Control *(n= 4603) vs. Observation (n= 1508)*			
Frailty Classes			
Robust	Ref.	Ref.	Ref.
Pre-Frail	1.23	1.00-1.51	0.045
Frail	1.33	1.00-1.78	0.052
Rhythm Control *(n= 4039) vs. Observation*			
Frailty Classes			
Robust	Ref.	Ref.	Ref.
Pre-Frail	0.98	0.80-1.21	0.864
Frail	0.99	0.73-1.33	0.933

Legend: *adjusted for CHA_2DS_2-VASc score, European region, low socioeconomic status, domestic status, physical activity, site of inclusion, reason for admission, type of AF and polypharmacy; †adjusted for EHRA score, European region, low socioeconomic status, domestic status, physical activity, site of inclusion, reason for admission, type of AF and polypharmacy; AF= Atrial Fibrillation; CI= Confidence Interval; NOACs= Non-vitamin K Antagonist Oral Anticoagulant; OAC= Oral Anticoagulant; OR= Odds Ratio; VKAs= Vitamin K Antagonists.

Table 3: Rate of Adverse Clinical Events and Relationship with Frailty

	Robust	Pre-Frail	Frail	FI (*Each 0.10*)	p
All-Cause Death	56 (3.0)	491 (8.6)	362 (17.9)	-	<0.001
*HR [95% CI]**	-	2.13 [1.60-2.84]	3.54 [2.56-4.89]	1.59 [1.45-1.75]	
CV Death	20 (1.1)	163 (2.8)	161 (8.0)	-	<0.001
*HR [95% CI]**	-	1.92 [1.19-3.11]	4.15 [2.44-7.05]	1.89 [1.63-2.20]	
Non-CV Death	36 (1.9)	328 (5.7)	201 (10.0)	-	<0.001
*HR [95% CI]**	-	2.25 [1.57-3.22]	3.17 [2.10-4.76]	1.42 [1.26-1.60]	
MACEs	69 (3.8)	484 (8.6)	357 (17.8)	-	<0.001
*HR [95% CI]**	-	1.80 [1.35-2.40]	3.41 [2.44-4.77]	1.69 [1.52-1.88]	
Major Bleeding	16 (0.9)	125 (2.2)	65 (3.9)	-	<0.001
HR [95% CI]†	-	2.25 [1.32-3.85]	2.87 [1.55-5.29]	1.32 [1.09-1.59]	

Legend: *adjusted for type of AF, CHA_2DS_2-VASc score, EHRA score, use of OAC; †adjusted for type of AF, HAS-BLED score, EHRA score, use of OAC.

Epidemiology and Impact of Frailty in Patients with Atrial Fibrillation in Europe: A Secondary Analysis from the ESC-EHRA EORP-AF General Long-Term Registry

Supplemental Materials

Supplemental Methods

Symptomatic status was defined according to EHRA score(1). Thromboembolic risk was defined according to CHA_2DS_2-VASc score(1). Bleeding risk was defined according to HAS-BLED score(1). Both CHA_2DS_2-VASc and HAS-BLED scores were computed according to the original schemes. High thromboembolic risk was defined as CHA_2DS_2-VASc ≥2 in males and ≥3 in females. High bleeding risk was defined for HAS-BLED ≥3. Polypharmacy was defined as the concomitant use of ≥5 drugs(2). AF was classified according to the current European guidelines as: i) first detected AF; ii) paroxysmal AF; iii) persistent AF; iv) long-standing persistent AF; v) permanent AF(1).

Evaluation of Quality of Life

Quality of life was evaluated at baseline and 1-year follow-up using the EQ-5D-5L questionnaire, a generic, extensively validated, easy to use instrument 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 consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 5 possible levels for each dimension (no problems, slight problems, moderate problems, severe problems and extreme problems), generating 5^5= 3125 unique health states. According to a previous report, using the United Kingdom trade-off value set we translated each of the levels into a single numeric value, with lowest values corresponding to better health(3). Furthermore, combining the single values we translated the 5-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 (=11111) corresponded to an HUS of 1.0 (perfect health). A 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).

Evaluation of Health-Care Resources Use

We examined the differential use of health-care resources according to the use of early rhythm control. In patients enrolled during hospitalization, we evaluated the overall length of stay. Further, we analysed the occurrence and number of cardiology and internal medicine/general practitioner visits, as well as the emergency room (ER) admissions during the follow-up observation (at 1 and 2 years of follow-up). Furthermore, we evaluated the occurrence, throughout the entire follow-up time observation, of hospitalisations, defined as follows: i) any hospitalisation; ii) any CV hospitalisation; iii) any non-CV hospitalisation.

Major Adverse Events

According to the eCRF of the study, we considered as clinical outcomes the following major adverse events: i) all-cause death; ii) CV death; iii) non-CV death; iv) major adverse cardiovascular events (MACEs) as the composite of any thromboembolic events, any acute coronary syndrome and CV death; v) major bleeding as the occurrence of any intracranial bleeding and major extracranial bleeding according to each investigator clinical evaluation.

Statistical Analysis

Continuous variables were expressed as mean (SD) or median [IQR] and differences across the groups were evaluated according to One-Way ANOVA and Kruskal-Wallis One-Way ANOVA, respectively according to the number of groups. Categorical variables were expressed as counts and percentages and differences across groups were evaluated according to the chi-square test.

A linear regression model was compiled to study the association between CHA_2DS_2-VASc and HAS-BLED scores and FI, adjusted for chronic AF and EHRA score. Alongside with the regression model we also performed a collinearity diagnostic to evaluate the possible collinearity between the scores and FI. According to differences in distribution of baseline characteristics, a multivariable multinomial logistic regression model was compiled to evaluate the baseline characteristics associated with pre-frailty and frailty.

To examine the association between frailty categories and prescription of OAC and, subsequently, prescription of vitamin K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs), as well as the clinical management established at baseline, we computed a multinomial logistic regression model adjusted for baseline characteristics according to the one included in the previous model. To evaluate the impact of FI on quality of life and use of health care resources a linear regression model and a logistic regression model were computed, respectively, adjusted for type of AF, CHA_2DS_2-VASc score, EHRA score, use of OAC.

Differences in survival according to frailty classes for the major adverse outcomes were analysed with Log-Rank test and Kaplan-Meier curves were drafted accordingly. The association between frailty categories, as well as increasing FI, and the outcomes was evaluated through a Cox regression model, adjusted for type of AF, CHA_2DS_2-VASc score, EHRA score, and the use of OAC. We modelled the association between FI and outcomes with the use of restricted cubic splines, with 4 knots placed at default locations, to account for the non-linearity of the relationship. Finally, we plotted the relationship between FI and Hazard Ratios (HR) of outcomes, with FI=0.1 as reference (i.e., HR=1).

A two-sided $p<0.05$ was considered statistically significant. All analyses were performed using SPSS statistical software version 27.0.1.0 (IBM, NY, USA) for MacOS, and R 4.1.0 (R Core Team, Vienna, Austria) for Windows, with the use of ‘rms’ and ‘survival’ package.

Supplemental Table 1: Items Included into the Frailty Index

1. Biological Parameters Domain	**DEFINITION**	**DEFICIT VALUE**
Systolic Blood Pressure	≥140 mmHg	1
Diastolic Blood Pressure	≥90 mmHg	1
Heart Rate	≥110 bpm	1
Body Mass Index	<18.5 kg/m^2 25.0-29.9 kg/m^2 ≥30.0 kg/m^2	1 0.5 1
2. Comorbidities Domain		
Hypertension	Present	1
Diabetes Mellitus	Present	1
Lipid Disorder	Present	1
Coronary Artery Disease	Present	1
Heart Failure	Present	1
Valvular Disease	Present	1
Cardiomyopathy	Present	1
Pulmonary Arterial Hypertension	Present	1
Peripheral Artery Disease	Present	1
Previous Thromboembolic Events	Present	1
Previous Hemorrhagic Events	Present	1
Hyperthyroidism	Present	1
Hypothyroidism	Present	1
Chronic Kidney Disease	Present	1
Liver Disease	Present	1
Chronic Obstructive Pulmonary Disease	Present	1
Obstructive Sleep Apnoea Syndrome	Present	1
Dementia	Present	1
History of Anaemia	Present	1
Malignancy	Present	1

3. Symptoms Domain		
Palpitations	Present	1
Syncope	Present	1
Shortness of Breath	Present	1
Chest Pain	Present	1
General not-Well Being	Present	1
Dizziness	Present	1
Fatigue	Present	1
Fear	Present	1
Other Symptoms	Present	1
4. Function/Autonomy Domain *(EQ-5D-5L Questionnaire)*		
Mobility	No Problems Slight Problems Moderate Problems Severe Problems Unable to Walk	0 0.25 0.5 0.75 1
Self-Care	No Problems Slight Problems Moderate Problems Severe Problems Unable to Wash/Dress	0 0.25 0.5 0.75 1
Usual Activities	No Problems Slight Problems Moderate Problems Severe Problems Unable to Usual Activities	0 0.25 0.5 0.75 1
Pain/Discomfort	No Pain/Discomfort Slight Pain/Discomfort Moderate Pain/Discomfort Severe Pain/Discomfort Extreme Pain/Discomfort	0 0.25 0.5 0.75 1

Anxiety/Depression	None Slight Anxious/Depressed Moderate Anxious/Depressed Severely Anxious/Depressed Extremely Anxious/Depressed	0 0.25 0.5 0.75 1
5. Biomarkers Domain		
Creatinine Clearance (CKD-EPI)	<60 mL/min	1
Haemoglobin	<13 mg/dL for males <12 mg/dL for females	1

Supplemental Table 2: Multivariable Multinomial Logistic Regression Analysis for Characteristics associated with Frailty Classes

Pre-Frailty *vs.* Robustness	**OR**	**95% CI**	**p**
Age (*per 10 years*)	1.38	1.30-1.46	<0.001
Female Sex (*vs. Male Sex*)	1.30	1.13-1.50	<0.001
European Region			
Northern Europe *(ref.)*	-	-	-
Western Europe	1.07	0.87-1.31	0.545
Eastern Europe	1.63	1.24-2.15	<0.001
Southern Europe	0.81	0.65-1.00	0.058
Low Socioeconomic Status	1.00	0.84-1.17	0.922
Domestic Status			
Living Alone *(ref.)*	-	-	-
Living with Partner/Family	1.10	0.92-1.33	0.276
Physical Activity			
None/Occasional (*ref.*)	-	-	-
Regular/Intense	0.66	0.57-0.75	<0.001
Site of Inclusion			
Outpatient Facility (*ref.*)	-	-	-
Hospital	1.55	1.35-1.79	<0.001

Reason for Admission			
Other than AF (*ref.*)	-	-	-
AF	0.92	0.78-1.09	0.336
AF Classification			
First Detected AF (*ref.*)	-	-	-
Paroxysmal AF	0.83	0.68-1.00	0.054
Persistent AF	0.95	0.77-1.17	0.643
Long-Standing Persistent AF	1.24	0.87-1.77	0.241
Permanent AF	1.11	0.89-1.37	0.346
Unknown	0.66	0.40-1.10	0.109
Polypharmacy	3.44	2.98-3.98	<0.001
Frailty *vs.* Robustness	**OR**	**95% CI**	**p**
Age (*per 10 years*)	1.62	1.50-1.75	<0.001
Female Sex (*vs. Male Sex*)	1.52	1.27-1.81	<0.001
European Region			
Northern Europe *(ref.)*	-	-	-
Western Europe	0.98	0.74-1.30	0.886
Eastern Europe	2.63	1.88-3.69	<0.001
Southern Europe	0.56	0.42-0.76	<0.001
Low Socioeconomic Status	1.61	1.30-1.99	<0.001

Domestic Status			
Living Alone *(ref.)*	-	-	-
Living with Partner/Family	1.06	0.85-1.33	0.606
Physical Activity			
None/Occasional (*ref.*)	-	-	-
Regular/Intense	0.38	0.31-0.46	<0.001
Site of Inclusion			
Outpatient Facility (*ref.*)	-	-	-
Hospital	2.72	2.27-3.26	<0.001
Reason for Admission			
Other than AF (*ref.*)	-	-	-
AF	0.73	0.60-0.89	0.002
Type of AF			
First Detected AF (*ref.*)	-	-	-
Paroxysmal AF	0.67	0.52-0.86	0.002
Persistent AF	0.96	0.73-1.26	0.752
Long-Standing Persistent AF	1.66	1.08-2.54	0.020
Permanent AF	0.99	0.76-1.29	0.969
Unknown	0.41	0.20-0.85	0.017
Polypharmacy	8.22	6.83-9.88	<0.001

Legend: AF= Atrial Fibrillation; CI= Confidence Interval; OR= Odds Ratio.

Supplemental Table 3: Antithrombotic Therapies and Clinical Management Strategy at Baseline Discharge according to Frailty Classes

	Robust	Pre-Frail	Frail	p
Any Antiplatelet, n (%)	197 (10.2)	1168 (19.3)	667 (30.8)	<0.001
Any OAC, n (%)	1562 (80.6)	5313 (87.6)	1801 (83.0)	<0.001
Baseline OAC, n (%)				<0.001
No OAC	375 (19.4)	751 (12.4)	370 (17.0)	
VKAs	734 (37.9)	3072 (50.7)	1232 (56.7)	
NOACs	828 (42.7)	2241 (37.0)	569 (26.2)	
Clinical Management Strategy, n (%)				<0.001
Rate Control	724 (37.4)	2783 (45.9)	1096 (50.8)	
Rhythm Control	866 (44.7)	2349 (38.8)	824 (38.2)	
Observation	347 (17.9)	925 (15.3)	236 (10.9)	

Legend: OAC= Oral anticoagulant.

Supplemental Table 4: Health-Resources Use during Follow-Up according to Frailty Classes

	Robust	Pre-Frail	Frail	FI *(Each 0.10)*	p
Cardiology Visits 1Y, n (%)	1244 (72.9)	3670 (73.5)	1217 (76.2)	-	0.067
*OR [95% CI]**	-	1.01 [0.88-1.16]	1.11 [0.91-1.36]	1.04 [0.95-1.12]	
IM/GP Visits 1Y, n (%)	527 (39.5)	2026 (51.2)	789 (56.2)	-	<0.001
*OR [95% CI]**	-	1.48 [1.29-1.70]	1.60 [1.32-1.94]	1.30 [1.20-1.40]	
ER Admissions 1Y, n (%)	225 (13.6)	880 (18.3)	402 (25.6)	-	<0.001
*OR [95% CI]**	-	1.21 [1.02-1.43]	1.54 [1.22-1.93]	1.29 [1.18-1.41]	
Cardiology Visits 2Y, n (%)	1003 (65.9)	2984 (68.5)	929 (70.8)	-	0.018
*OR [95% CI]**	-	1.10 [0.95-1.26]	1.19 [0.97-1.46]	1.03 [0.95-1.11]	
IM/GP Visits 2Y, n (%)	520 (41.2)	1792 (49.4)	659 (55.3)	-	<0.001
*OR [95% CI]**	-	1.54 [1.33-1.77]	2.16 [1.76-2.65]	1.34 [1.24-1.46]	
ER Admissions 2Y, n (%)	163 (11.0)	622 (14.9)	266 (20.9)	-	<0.001
*OR [95% CI]**	-	1.25 [1.03-1.53]	1.65 [1.27-2.16]	1.22 [1.10-1.35]	
Any Hospitalisation	553 (30.3)	2142 (38.1)	905 (45.9)	-	<0.001
*OR [95% CI]**	-	1.31 [1.15-1.48]	1.62 [1.36-1.91]	1.22 [1.14-1.30]	
Any CV Hospitalisation	335 (18.4)	1384 (24.6)	615 (31.2)	-	<0.001
*OR [95% CI]**	-	1.44 [1.25-1.67]	1.94 [1.60-2.35]	1.30 [1.21-1.40]	
Any Non-CV Hospitalisation	137 (7.5)	658 (11.7)	290 (14.7)	-	<0.001
*OR [95% CI]**	-	1.42 [1.15-1.74]	1.60 [1.23-2.08]	1.21 [1.10-1.34]	

Legend: *adjusted for type of AF, CHA_2DS_2-VASc score, 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.

Supplemental Table 5: Sensitivity Analysis about Relationship between Frailty Index and Age

	All-Cause Death*			MACEs*		
i) Upper Panel	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
FI (*each 0.10 increase*)	1.64	1.48-1.82	<0.001	1.62	1.44-1.83	<0.001
Age (*per 10 years*)	1.92	1.78-2.08	<0.001	1.29	1.19-1.40	<0.001
ii) Lower Panel	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
FI (*each 0.10 increase*)	4.89	2.69-8.91	<0.001	3.73	2.11-6.57	<0.001
Age (*per 10 years*)	2.64	2.18-3.19	<0.001	1.64	1.37-1.97	<0.001
Age*FI	0.87	0.80-0.94	<0.001	0.89	0.82-0.96	0.003

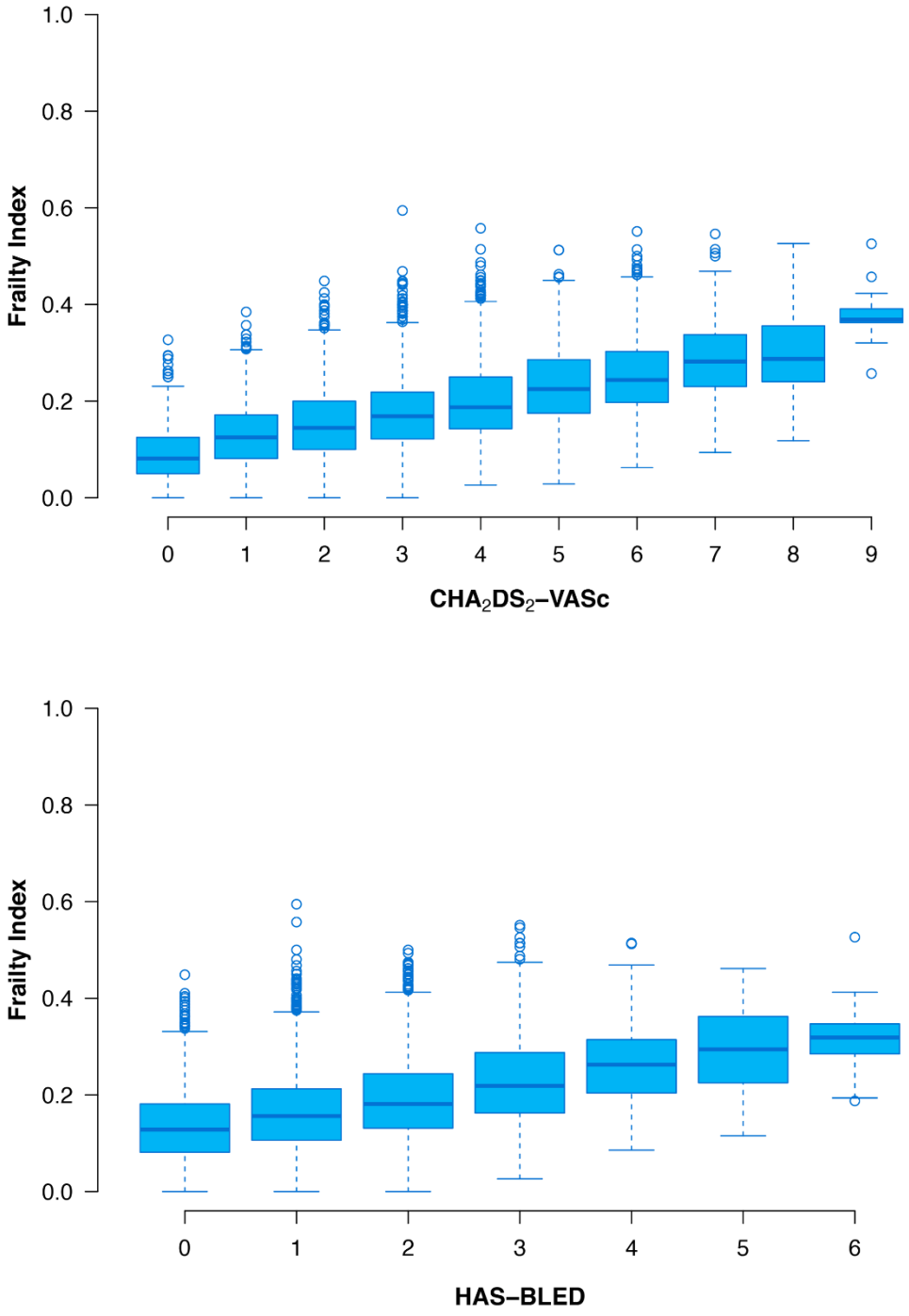
Legend: *adjusted for female sex, heart failure, hypertension, diabetes mellitus, previous thromboembolic events, peripheral arterial disease, type of AF, EHRA score, use of OAC; AF= Atrial Fibrillation; FI= Frailty Index; HR= Hazard Ratio; MACEs= Major Adverse Cardiovascular Events; OAC= Oral Anticoagulant.

Supplemental Table 6: Predictive Performance of Frailty Index for Occurrence of Adverse Clinical Events

	c-index	95% CI	p
All-Cause Death	0.679	0.662-0.697	<0.001
CV Death	0.715	0.688-0.741	<0.001
Non-CV Death	0.643	0.621-0.665	<0.001
MACEs	0.671	0.653-0.689	<0.001
Major Bleeding	0.611	0.575-0.648	<0.001

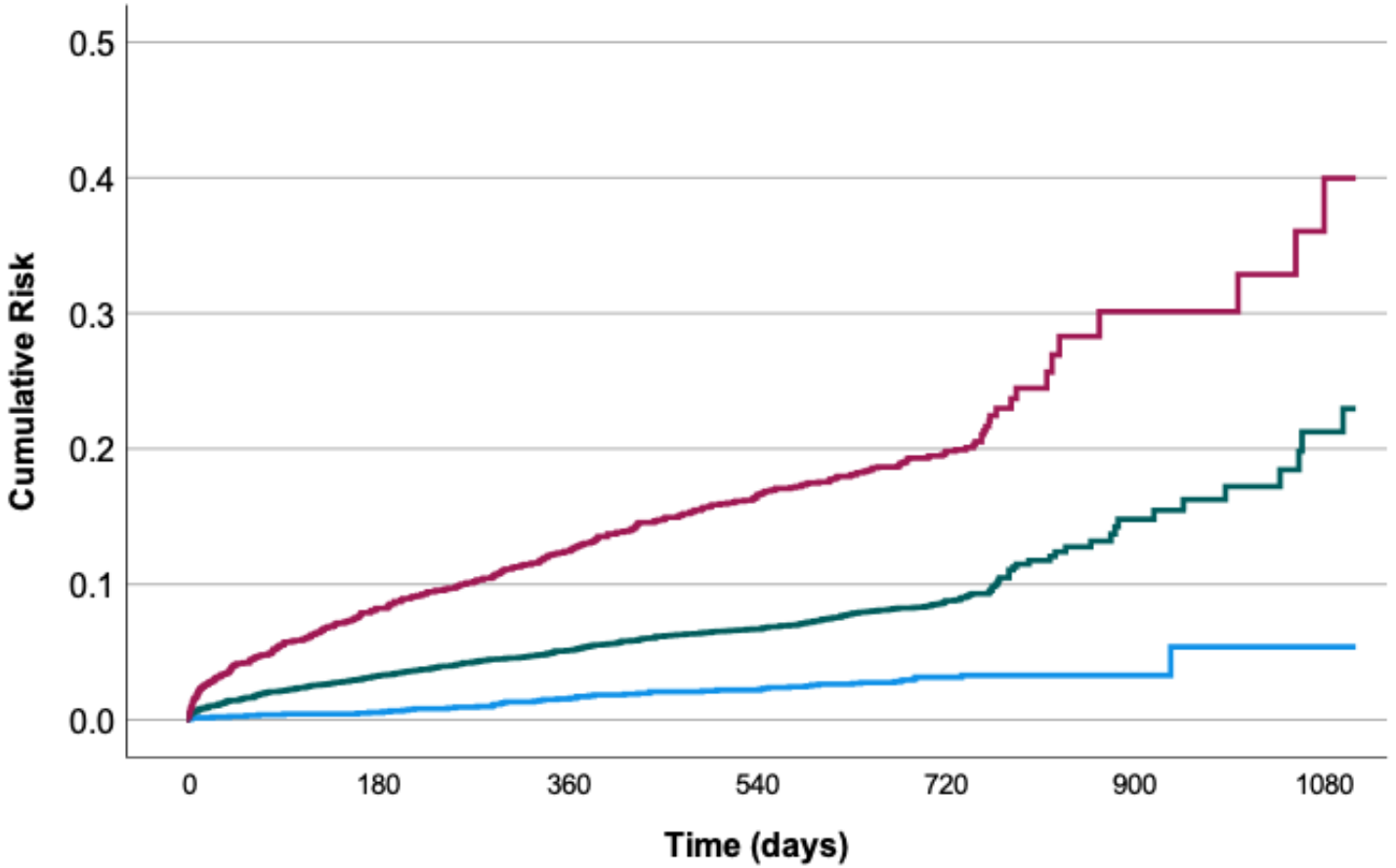
Legend: CI= Confidence Interval; CV= Cardiovascular; MACEs= Major Adverse Cardiovascular Events.

Supplemental Figure 1: Frailty Index Values according to Continuous Scores Points



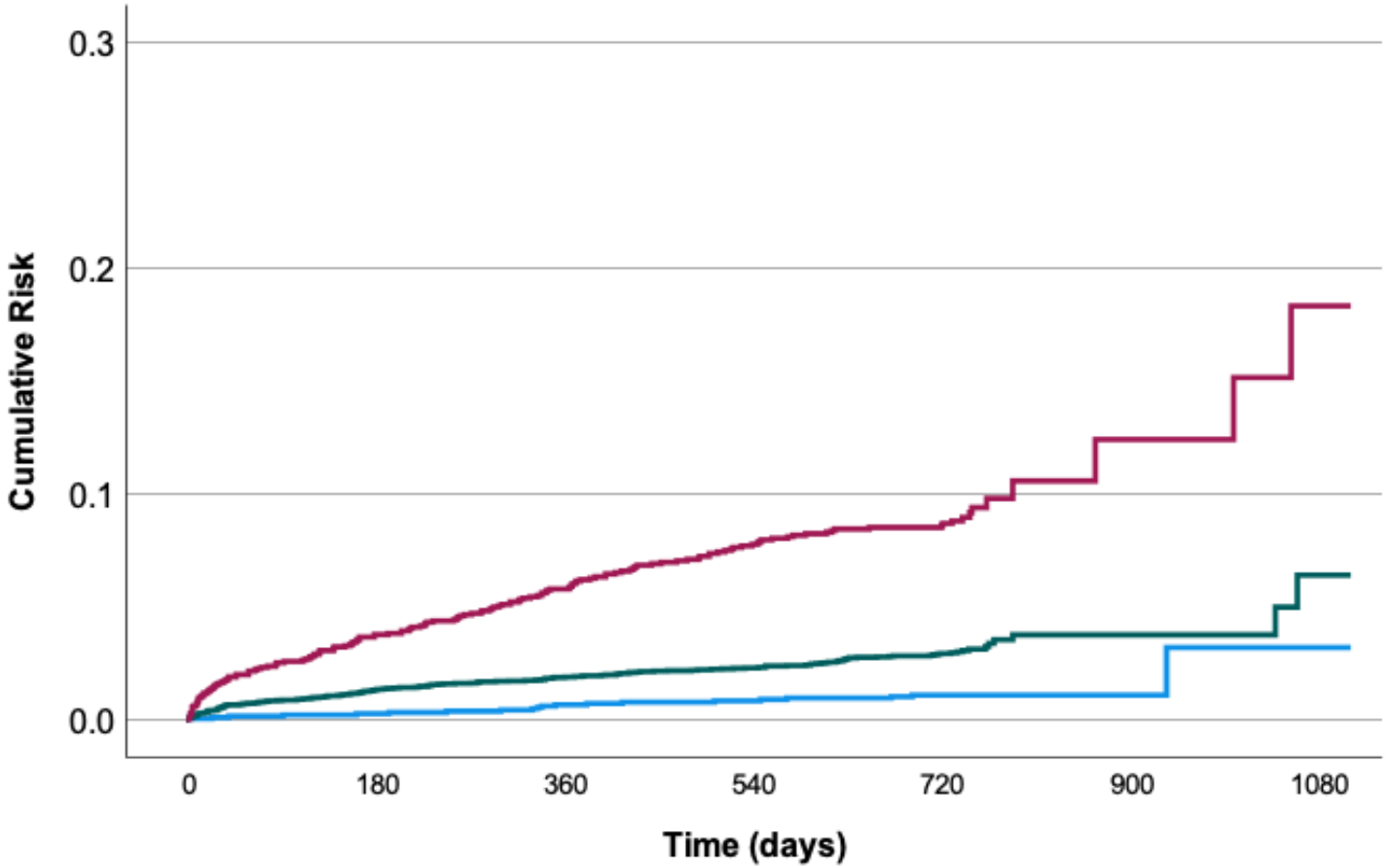
Legend: Boxes represent median and interquartile range, while whiskers stand for 2 standard deviations. For both the scores there is a significant difference across continuous scores points for $p<0.001$.

Supplemental Figure 2: Kaplan-Meier Curves for All-Cause Death Cumulative Risk according to Frailty Classes



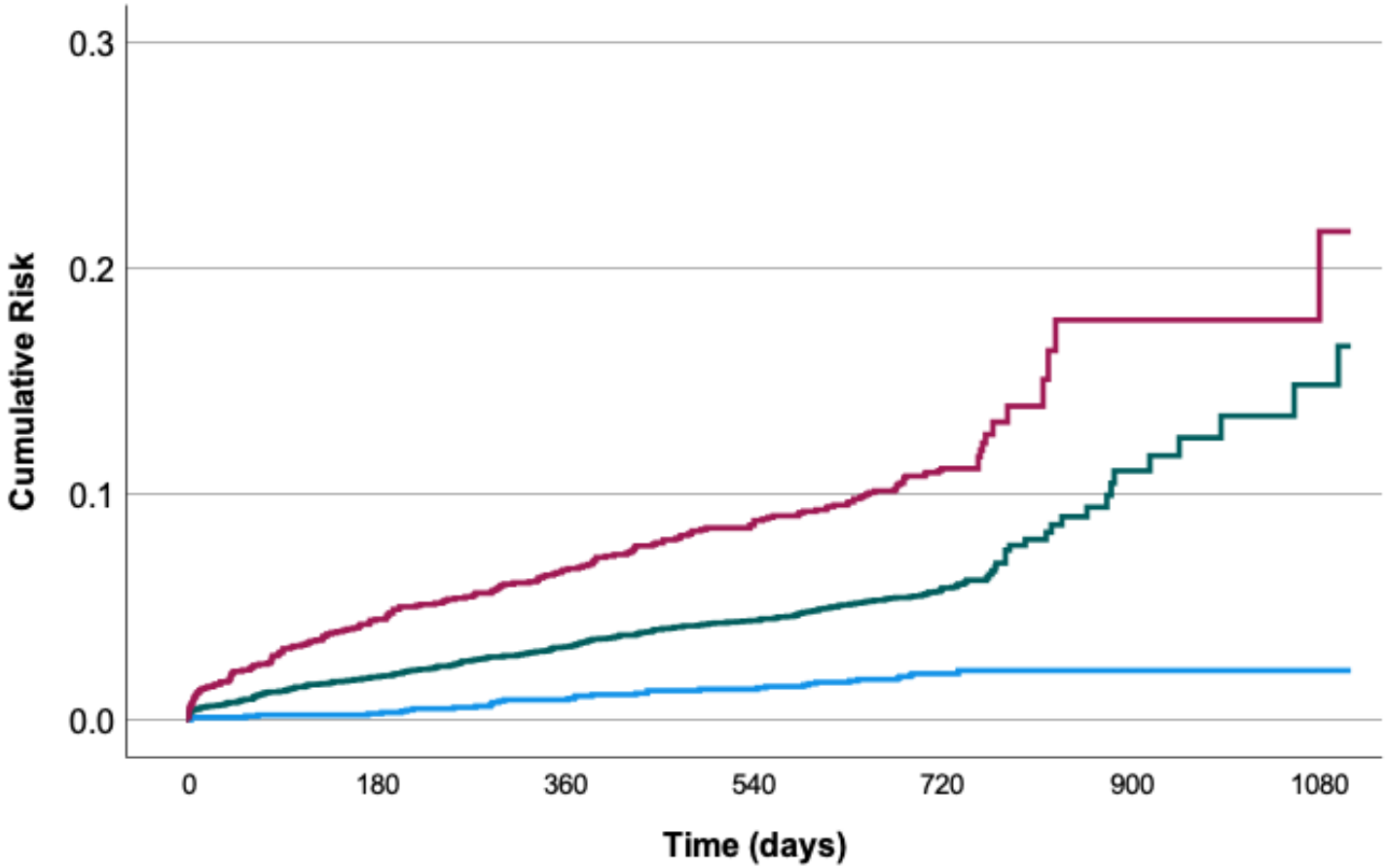
Legend: Log-Rank=279.765, p<0.001; Blue Line= Robust; Green Line= Pre-Frail; Red Line= Frail.

Supplemental Figure 3: Kaplan-Meier Curves for Cardiovascular Death Cumulative Risk according to Frailty Classes



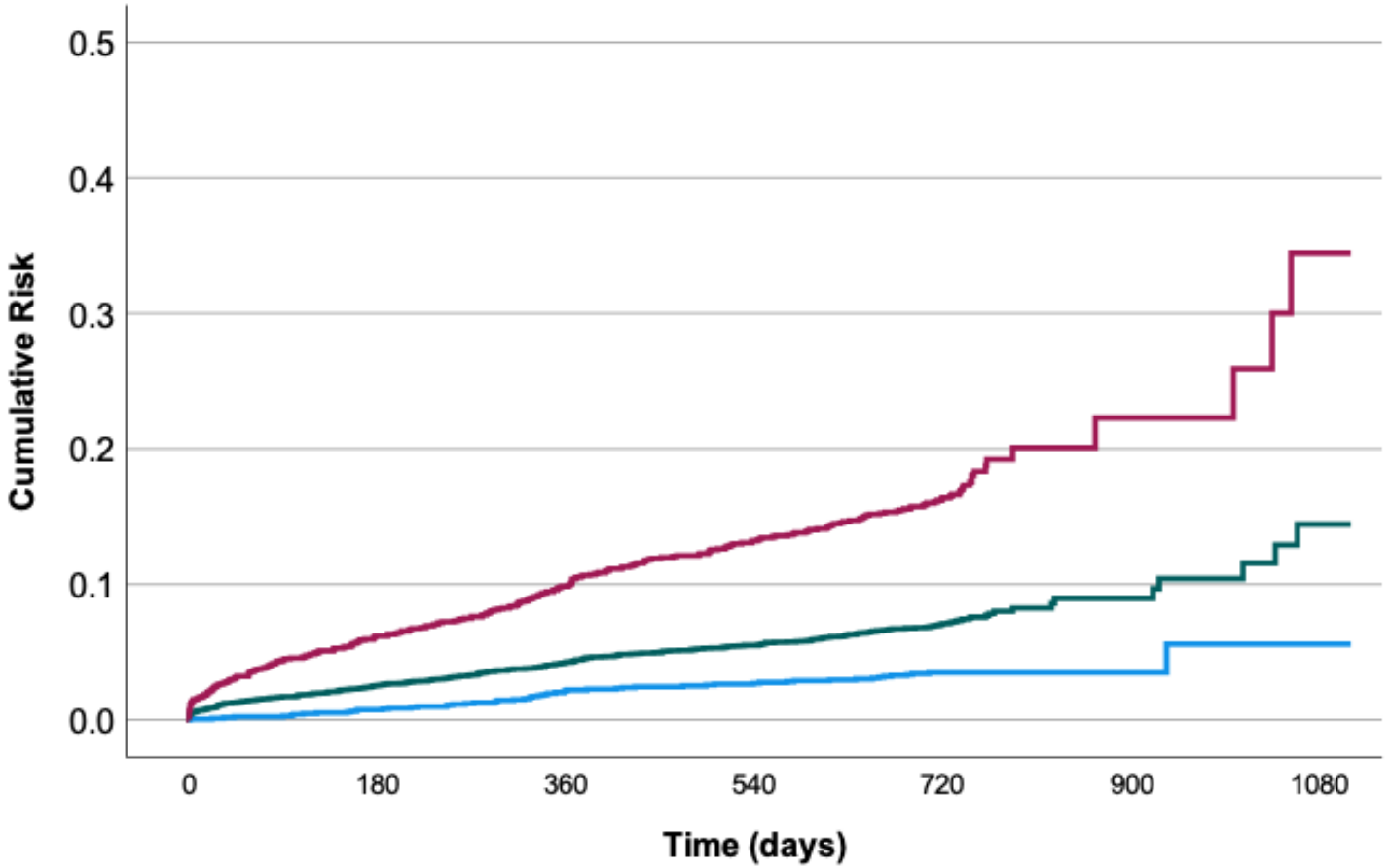
Legend: Log-Rank=169.349, p<0.001; Blue Line= Robust; Green Line= Pre-Frail; Red Line= Frail.

Supplemental Figure 4: Kaplan-Meier Curves for Non-Cardiovascular Death Cumulative Risk according to Frailty Classes



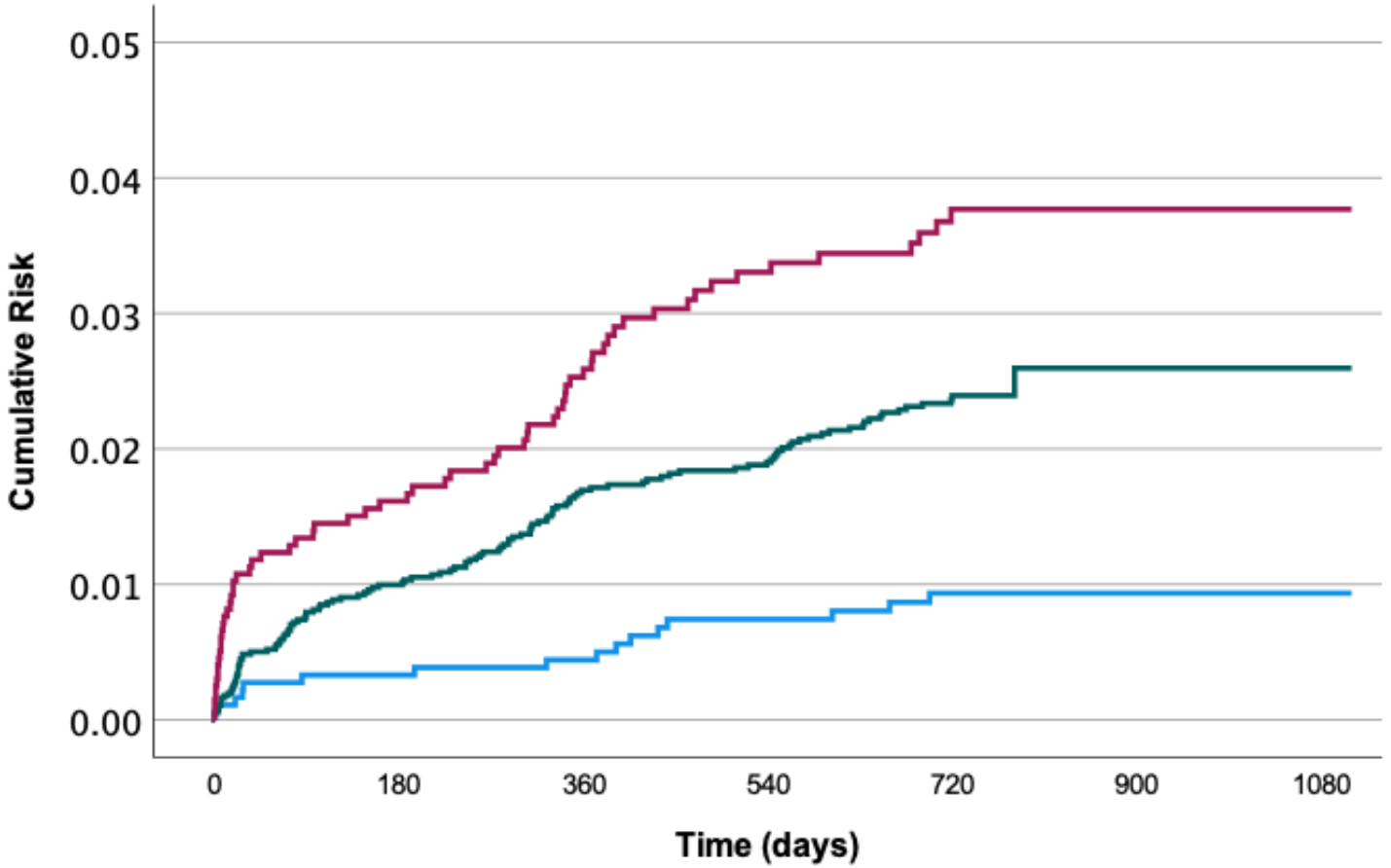
Legend: Log-Rank=126.885, p<0.001; Blue Line= Robust; Green Line= Pre-Frail; Red Line= Frail.

Supplemental Figure 5: Kaplan-Meier Curves for MACEs Cumulative Risk according to Frailty Classes



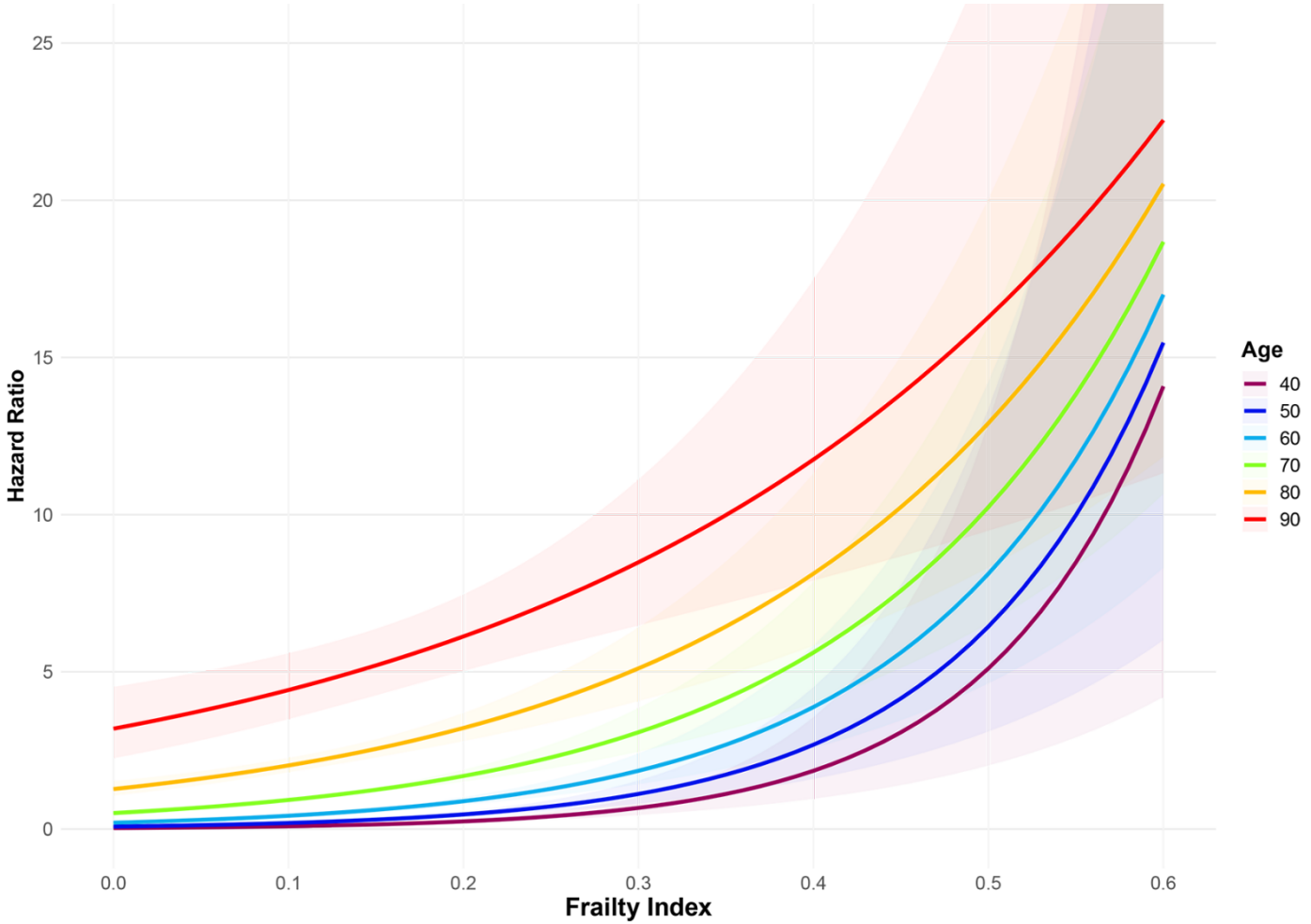
Legend: Log-Rank=201.847, p<0.001; Blue Line= Robust; Green Line= Pre-Frail; Red Line= Frail.

Supplemental Figure 6: Kaplan-Meier Curves for Major Bleeding Cumulative Risk according to Frailty Classes

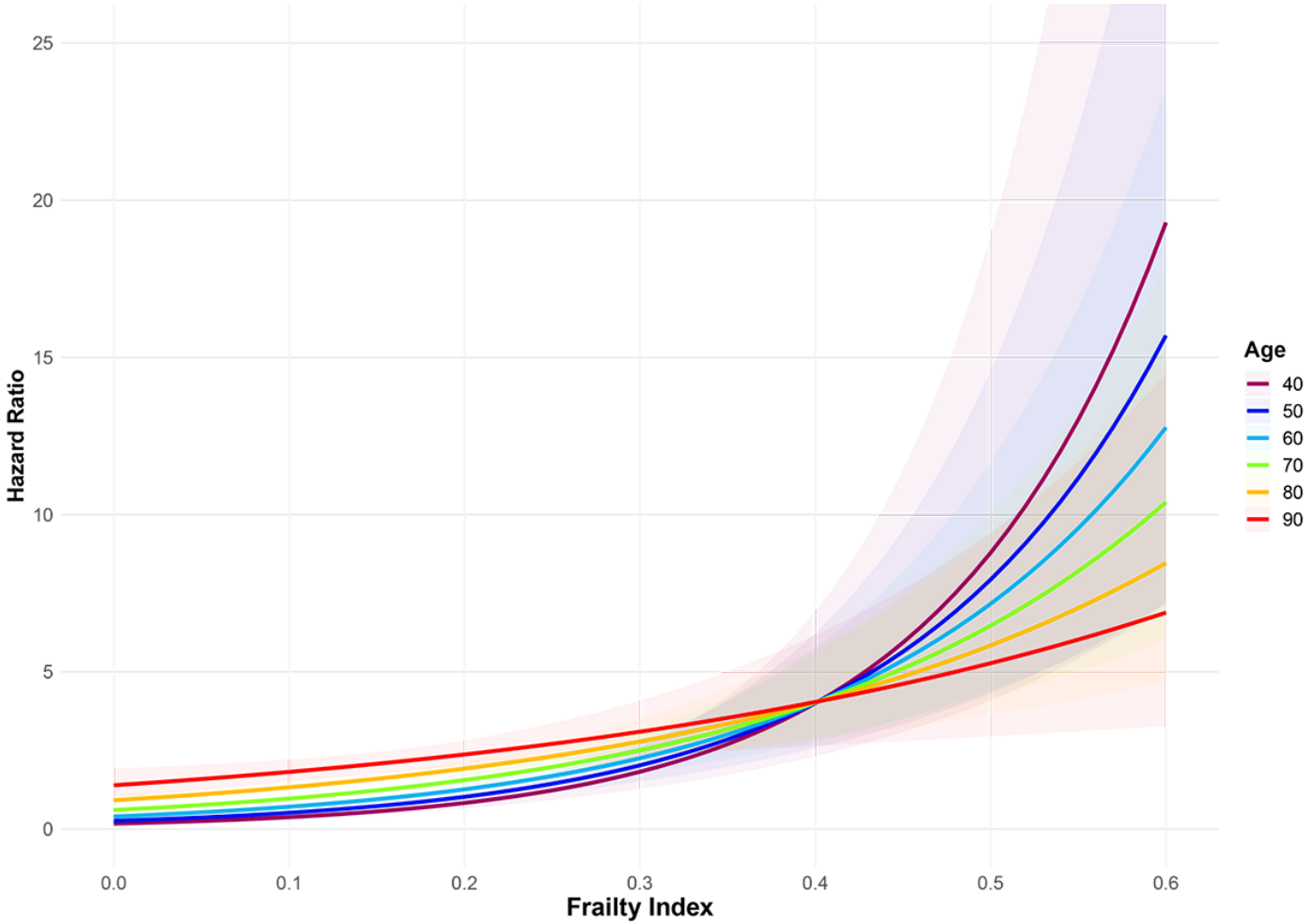


Legend: Log-Rank=29.846, p<0.001; Blue Line= Robust; Green Line= Pre-Frail; Red Line= Frail.

Supplemental Figure 7: Regression Analysis between Frailty Index and Risk of All-Cause Death according to Age Strata

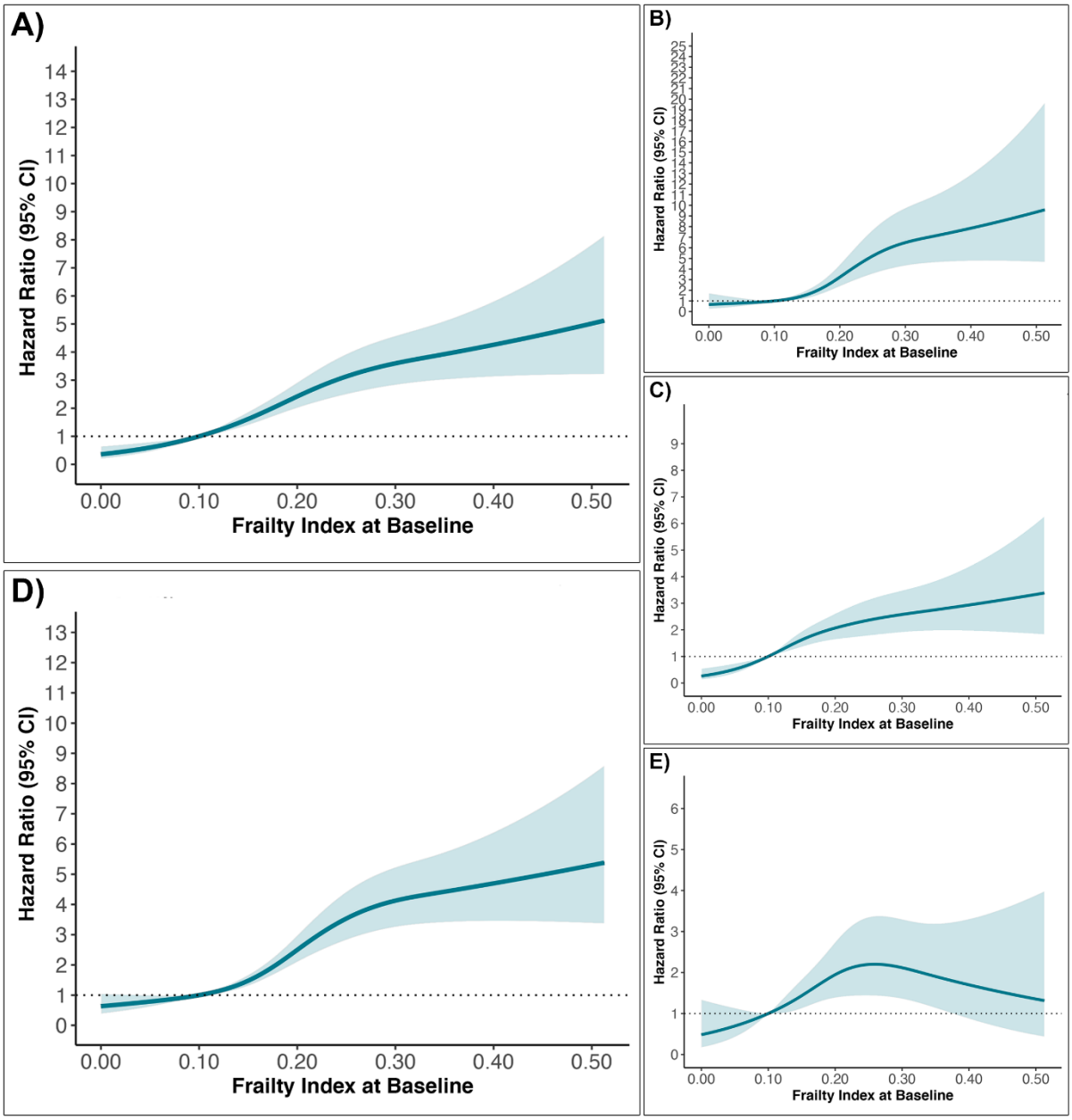


Supplemental Figure 8: Regression Analysis between Frailty Index and Risk of MACEs according to Age Strata



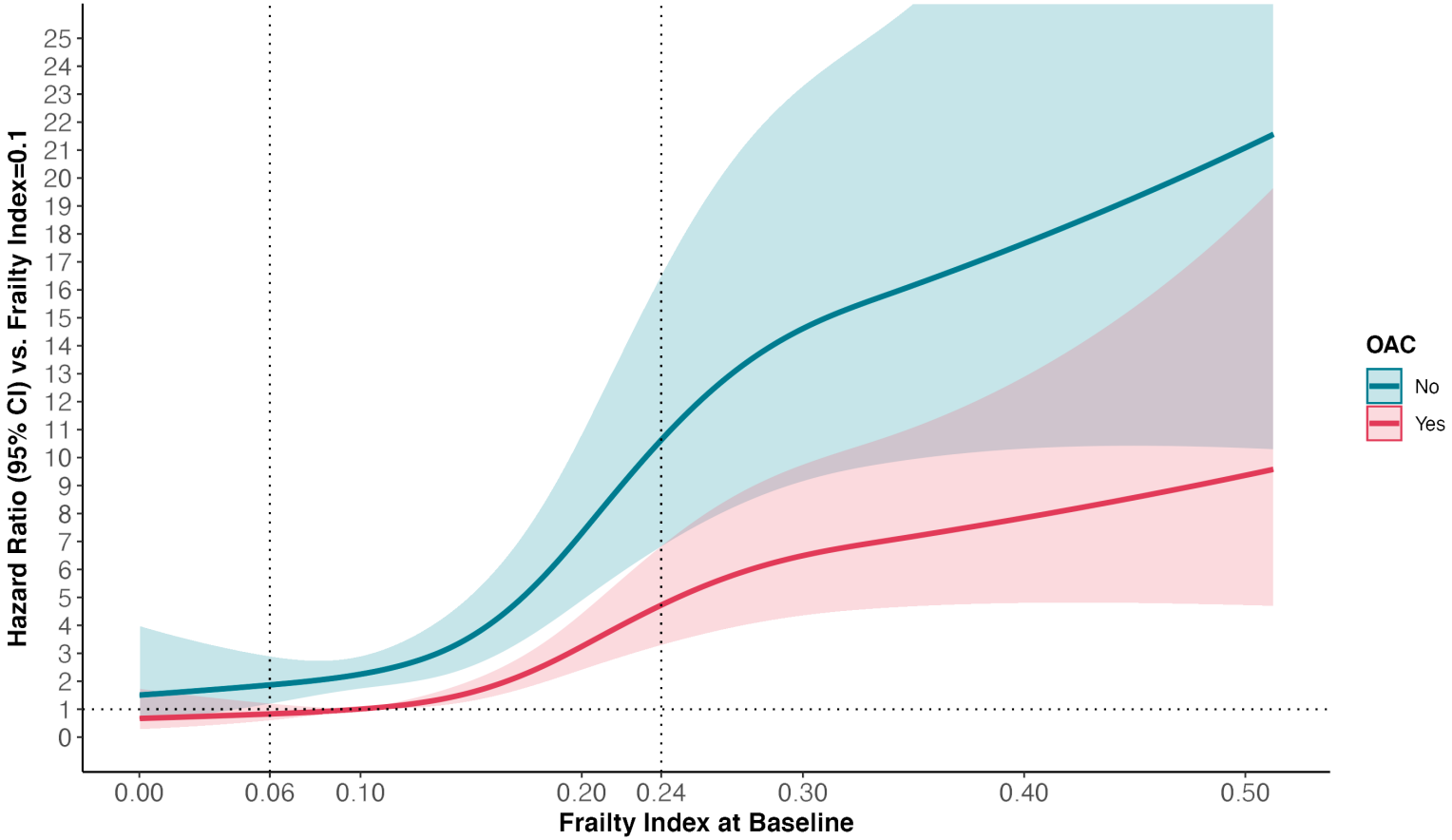
Legend: MACEs= Major Adverse Cardiovascular Events.

Supplemental Figure 9 - Association between Frailty Index and Risk of Major Adverse Outcomes



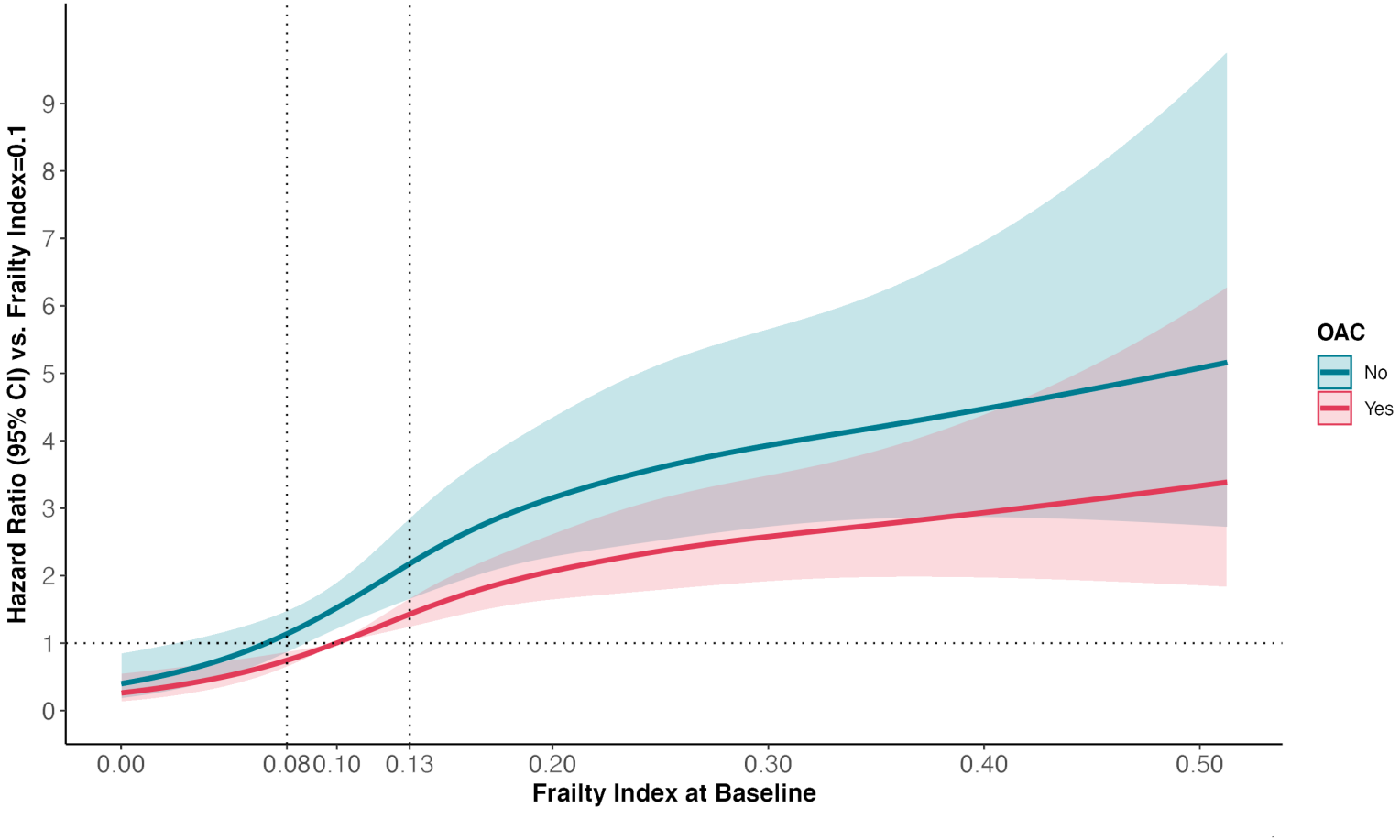
Legend: A) All-Cause Death; B) Cardiovascular Death; C) Non-Cardiovascular Death; D) Major Adverse Cardiovascular Events; E) Major Bleeding; CI= Confidence Interval.

Supplemental Figure 10: Association between Frailty Index and Risk of Cardiovascular Death according to OAC Use



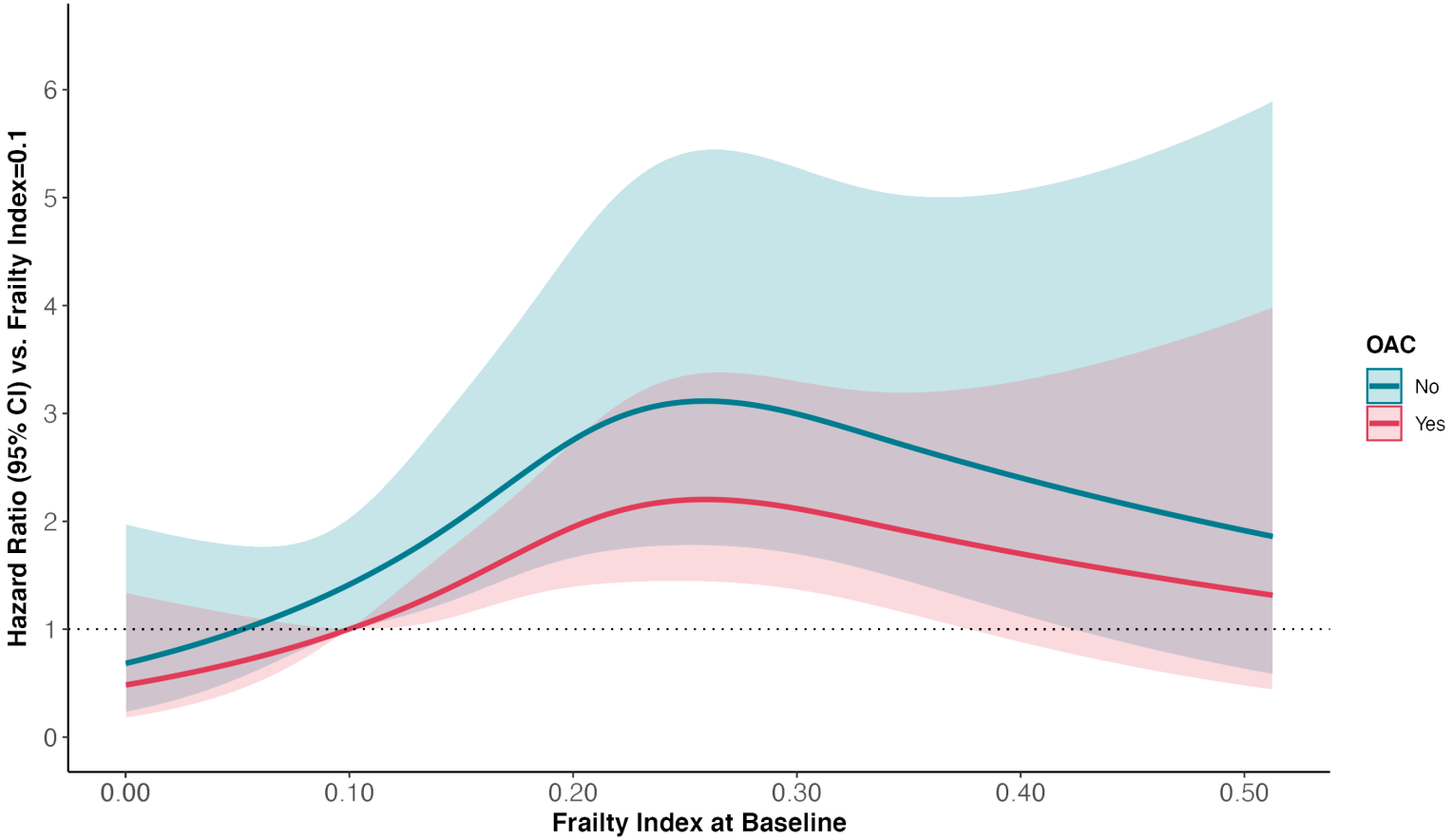
Legend: Red Line) OAC prescribed; Blue Line) OAC not prescribed; CI= Confidence Interval; OAC= Oral Anticoagulant.

Supplemental Figure 11: Association between Frailty Index and Risk of Non-Cardiovascular Death according to OAC Use



Legend: Red Line) OAC prescribed; Blue Line) OAC not prescribed; CI= Confidence Interval; OAC= Oral Anticoagulant.

Supplemental Figure 12: Association between Frailty Index and Risk of Major Bleeding according to OAC Use



Legend: Red Line) OAC prescribed; Blue Line) OAC not prescribed; CI= Confidence Interval; OAC= Oral Anticoagulant.

SUPPLEMENTAL REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur. Heart J. 2021;42:373–498. Available at: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa612/5899003.

2. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17:230. Available at: http://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-017-0621-2. Accessed April 5, 2019.

3. Dudink EAMP, Erküner Ö, Berg J, et al. The influence of progression of atrial fibrillation on quality of life: A report from the Euro Heart Survey. Europace 2018;20:929–934. Available at: https://academic.oup.com/europace/article/20/6/929/3979528.