Cardiac troponins and adverse outcomes in European patients with atrial fibrillation: a report from the ESC-EHRA EORP Atrial Fibrillation General Long-Term Registry

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Data availability

The data underlying this article were provided by the European Society of Cardiology by permission. Data will be shared on request to the corresponding author with permission of ESC Editorial is also expected but not yet confirmed.

ABSTRACT

Background. Cardiac troponins (cTn) have been reported to be predictors for adverse outcomes in atrial fibrillation (AF), patients, but their actual use is still unclear.

Aim. To assess the factors associated with cTn testing in routine practice and evaluate the association with outcomes.

Methods. Patients enrolled in the ESC-EHRA EORP-AF General Long-Term Registry were stratified into 3 groups according to cTn levels as (i) cTn not tested, (ii) cTn in range (≤99th percentile), (iii) cTn elevated (>99th percentile). The composite outcome of any thromboembolism /any acute coronary syndrome/cardiovascular (CV) death, defined as Major Adverse Cardiovascular Events (MACE) and all-cause death were the main endpoints.

Results. Among 10 445 AF patients (median age 71 years, 40.3% females) cTn were tested in 2834 (27.1%). cTn was elevated in 904/2834 (31.9%) and in-range in 1930/2834 (68.1%) patients. Female sex, in-hospital enrollment, first-detected AF, CV risk factors, history of coronary artery disease, and atypical AF symptoms were independently associated with cTn testing. Elevated cTn were independently associated with a higher risk for MACE (Model 1, hazard ratio [HR] 1.74, 95% confidence interval [CI] 1.40-2.16, Model 2, HR 1.62, 95% CI 1.28-2.05; Model 3 HR 1.76, 95% CI 1.37-2.26) and all-cause death (Model 1, HR 1.45, 95% CI 1.21-1.74; Model 2, HR 1.36, 95% CI 1.12-1.66; Model 3, HR 1.38, 95% CI 1.12 – 1.71).

Conclusions. Elevated cTn levels were associated with an increased risk of all-cause mortality and adverse CV events. Clinical factors that might enhance the need to rule out CAD were associated with cTn testing.

KEYWORDS: troponins; atrial fibrillation; biomarkers; outcomes; major adverse cardiovascular events; death; AF registry

ABBREVIATIONS AND ACRONYMS

ACS= acute coronary syndrome

AF = atrial fibrillation

CAD= coronary artery disease

CKD= chronic kidney disease

CI= confidence interval

cTn= cardiac troponins

CV= cardiovascular

EHRA= European Heart Rhythm Association

EORP= EURObservational Research Programme

ESC= European Society of Cardiology

HF=heart failure

HR= hazard ratio

IQR= interquartile range

MACE= major adverse cardiovascular events

MI= myocardial infarction

OR= odds ratio

RCTs= randomized controlled trials

SE=systemic embolisms

TE= thromboembolic events

Introduction

Cardiac troponins (cTn) are the preferred biomarkers for the detection of myocardial injury and the diagnosis of myocardial infarction (MI) [1-3]. However, with the advent of high-sensitivity (hs)-cTn assays, elevated levels of cTn may be a common finding in daily clinical practice even in several non-ischaemic, acute or chronic conditions, such as heart failure (HF), chronic kidney disease (CKD), sepsis, inflammatory diseases, etc. [4-10].

In the last decades, several biomarkers have emerged as significant predictors for adverse outcomes in atrial fibrillation (AF) patients [11-14]. As for the other clinical conditions reported above, independent of the specific assay used, cTn elevations may be detected in AF patients with or without overt coronary artery disease (CAD) [15, 16]. Additionally, elevated levels of cTn have been found to be independent predictors of AF in the general population [17, 18]. Despite the increasing number of studies investigating biomarkers in AF, including cTn, their value in daily clinical practice and routine risk prediction is still debated [19-22]. Since most of the studies available were based on a highly selected populations from randomized controlled trials (RCTs), [23-25] data on real-world AF patients are limited.

Accordingly, the aim of this study was to assess the factors associated with cTn testing in routine clinical practice and evaluate the association of elevated levels of cTn with adverse outcomes in a large contemporary cohort of AF patients from the European Society of Cardiology (ESC) EURObservational Research Programme (EORP) Atrial Fibrillation General Long-Term Registry.

Methods

Study design and cohort

The EORP-AF Long-Term General Registry is a prospective, observational, large-scale multicentre registry on AF patients in current cardiology practice held by the ESC and endorsed by the European Heart Rhythm Association (EHRA). A detailed description of the study design, baseline characteristics and 1-year follow-up results have been previously reported [26-28].

Briefly, the registry consecutively enrolled both in- and out- AF patients in 250 centres from 27 participating ESC countries when presenting with AF as a primary or secondary diagnosis from October 2013 to September 2016. All patients were ≥ 18 years old and provided written informed consent. The qualifying AF event had to be recorded by a 12-lead ECG, 24h ECG Holter, or other electrocardiographic documentation within the 12 months before enrolment. Exclusion criteria were: (i) no objective proof of AF; (ii) being previously enrolled in the EORP-AF Pilot Registry; or (iii) being or planned to be enrolled in a pharmacological interventional clinical trial. Institutional review board approved the study protocol for every institution. The study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

All data regarding baseline clinical characteristics, previous clinical history, history of previous interventional procedures and specific diagnostic procedures and interventional procedures performed during the admission/consultation were collected at the moment of enrolment by any investigator/sub-investigator using clinical notes and electronic clinical data archives, where available.

Thromboembolic risk was defined according to CHA_2DS_2-VASc score. 'Low risk' was defined as a CHA_2DS_2-VASc 0 in males and 1 in females; 'moderate risk' was defined for a CHA_2DS_2-VASc 1 in males; 'high risk' was defined as CHA_2DS_2-VASc ≥ 2. Bleeding risk was defined according to HAS-BLED score. 'Low risk' was defined as HAS-BLED 0–2, while 'high risk' was defined as HAS-BLED ≥ 3. Symptomatic status was defined according to EHRA score.

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

For the purpose of this analysis, all AF patients with available data on cTn testing and follow-up data were included. Elevated levels of cTn were defined when plasma levels of cTn (either troponin T or troponin I) were increased above the 99th percentile upper reference limit according to manufacturer indications and specific assay (conventional or high-sensitivity) available in each enrolling centre. Patients were stratified into three groups according to cTn measurement (according to the reference values of every site) as (i) cTn not tested, (ii) cTn tested in range (i.e. at or below the 99^{th} percentile) and (iii) cTn elevated (i.e above the 99^{th} percentile).

Follow-up and adverse outcomes

All follow-up was performed at 1 and 2 years after the enrolment. All of the following incident major adverse clinical events were recorded: (i) all cause death; (ii) any haemorrhagic events (i.e. intracranial bleeding, major bleeding or clinically relevant non-major bleeding; (iii) any thromboembolism (TE) (including stroke, transient ischaemic attack [TIA], and any peripheral embolism); (iv) any ACS; (v) CV-death and (vi) any myocardial revascularization (including percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]). The composite outcome of any TE/any ACS/CV death, defined as Major Adverse Cardiovascular Events (MACE) and all-cause death were the main endpoints of the study.

All data about hospital admissions (any admission, AF-related, CV-related and non CV-related) were also recorded. Investigators reported all available details about incident major adverse clinical events on the centralized electronic case report form. Events are reported according to the three groups (cTn not tested, cTn in range, and cTn elevated).

To further explore the possible association between cTn levels and adverse outcomes in "non-ischaemic" AF patients, we performed a secondary analysis excluding all the patients with a previous history of CAD and those who had a diagnosis at discharge/consultation of ACS, who underwent PCI and/CABG during the admission and/or were treated with oral anticoagulant (OAC) plus antiplatelet therapy.

Statistical analysis

All continuous variables were reported as median and interquartile range (IQR). Among-group comparisons were made using non-parametric tests, Mann-Whitney U or Kruskal–Wallis test where appropriate. Categorical variables were reported as counts and percentages. Among-group comparisons were made using a $\chi 2$ test or Fisher's exact test (if any expected cell count was less than five).

Univariate logistic regression analysis was performed to identify baseline characteristics associated with the measurement of cTn during admission or consultation. All variables with $p<0.10$ in the univariate analysis were used in the multivariable model to identify independent variables associated with cTn testing.

Plots of Kaplan–Meier curves for time to MACE and all-cause death according to cTn measurements were performed. Survival distributions were compared using the log-rank test. To identify which particular group had different survival distributions we performed a pairwise comparisons with a Bonferroni correction adjusting the level of significance by the number of comparisons (statistical significance accepted at the $p < 0.0167$ level).

We built three different Cox regression models to establish the relationship between cTn measurements and the risk of the primary endpoints of the study (MACE and all-cause death). Model 1 was adjusted for adjusted for CHA_2DS_2VASc score, site of inclusion (hospital vs outpatient clinic), use of OAC, presence of atypical AF-related symptoms (chest pain, dyspnoea or syncope), CKD (i.e. creatinine clearance <60 ml/min calculated with Cockcroft-Gault equation), malignancy and type of AF; Model 2 was adjusted for the individual components of the CHA_2DS_2VASc score in addition to the other covariates of Model 1; Model 3 was adjusted for the variables that were statistically different between patients without cTn tested and cTn tested at the univariate analysis. For the other outcomes (any TE, any ACS, any CV death and any PCI/CABG) a multivariable Cox regression analysis adjusted for CHA_2DS_2VASc score, site of inclusion (hospital vs outpatient clinic), use of OAC, presence of atypical AF-related symptoms (chest pain, dyspnoea

or syncope), CKD malignancy and type of AF was used. The proportional hazard assumption for Cox models was checked through visual procedures and by Schoenfeld residuals. Results were expressed as hazard ratio (HR) and 95% confidence interval (CI).

For the remaining outcomes of interest, time-to-event data was not available, therefore we built a multivariable logistic regression model to establish the relationship with the occurrence of any haemorrhagic events, any admission, including admission AF-, CV- and non CV-related according to cTn measurement. Adjustment for CHA_2DS_2VASc score, site of inclusion (hospital vs outpatient clinic), use of OAC, presence of atypical AF-related symptoms (chest pain, dyspnoea or syncope), CKD, malignancy and type of AF were undertaken for every outcome except for haemorrhagic events, which adjusted for the HASBLED score, sex, site of inclusion (hospital vs outpatient clinic), use of OAC, presence of atypical AF-related symptoms, malignancy and type of AF were used. Results were expressed as odds ratio (OR) and 95% confidence interval (CI)

A two-sided P-value <0.05 was considered statistically significant, expect for the pairwise comparisons of survival distributions with the Bonferroni correction where the statistical significance was accepted as $p < 0.0167$.

All analyses were performed using SPSS statistical software (version 26.0, Statistical Package for the Social Sciences, SPSS, IBM, Chicago, Illinois).

Results

Among the 11096 AF patients originally enrolled into the ESC-EHRA EORP Atrial Fibrillation General Long-Term Registry, a total of 10445 (94.1%) patients with available data on cTn measurement and follow-up status at 2-years were included in this analysis. Cardiac troponins were tested in 2834 (27.1%) being elevated in 904/2834 (31.9%) and in-range in 1930/2834 (68.1%) patients

Median (IQR) age was 71 (63-77) years, 40.3% were female and overall, the median (IQR) CHA_2DS_2VASc and HASBLED score were 3 (2-4) and 1 (1-2), respectively. Baseline

characteristics according to cTn testing are shown in **Table 1** and **Table S1** (Supplementary materials).

Patients in whom cTn was elevated tended to be older (p<0.001), more frequently enrolled in a hospital setting (p <0.001) with significantly higher baseline CHA_2DS_2VASc and HASBLED scores (p<0.001) (**Table 1**).

There was a significant association between the measurement of cTn and symptomatic status at admission/consultation. EHRA score was higher in patients in those where cTn was tested (median 2 (1-2) vs 2 (1-3), p<0.001) as well as the presence of atypical AF-related symptoms (i.e. chest pain, dyspnoea or syncope) (**Table 1 and Table S1**). Diabetes mellitus, current smoking and physical inactivity were reported less frequently in patients without a cTn assessment (all p <0.001). Heart failure, previous CAD, peripheral vascular disease, anaemia, CKD and malignancy were more prevalent in patients with elevated cTn (**Table 1**). AF was the main reason for admission or consultation in two-thirds (66.6%). Other reasons for admission or consultation included HF (10%), valvular heart disease (2.8%), hypertension (2.1%) and others CV and non-CV reasons in the remaining cases. Only 3.4% had a suspected ACS at admission/consultation, whereas a diagnosis of ACS was confirmed in 215 patients (2.1%) at discharge.

Pharmacological treatments, including antithrombotic patterns, and cardiac interventions performed during the admission/consultation are shown in **Table S2**. Overall, non-vitamin K antagonist OACs (NOACs) were prescribed in 3340 (32.0%) while 4303 (41.2%) patients received vitamin K antagonists (VKA). Patients with cTn tested were more frequently treated with OAC with concomitant antiplatelet(s) (p<0.001) **(Table S2**).

Overall, myocardial revascularization (either PCI or CABG) were performed in 245/10445 (2.3%) patients with a significant higher occurrence in patients with elevated cTn compared with patients without cTn testing or those with cTn in range (12.2% vs 1.0% vs 3.0%, p<0.001) (**Table S2**)

Factors associated with cardiac troponin assessment and regional differences

Univariate logistic regression analysis for factors associated with cTn assessment during admission or consultation in the whole cohort is presented in the Supplementary materials (**Table S3**).

On multivariable analysis (**Table 2**), female sex, site of inclusion (hospital vs outpatient clinic/office based), first detected AF, smoking, no physical activity, lipid disorder, history of CAD and presence of atypical AF-related symptoms were independently associated with cTn testing. Conversely, hypertension, hypothyroidism and valvular heart disease were inversely associated with cTn measurement (**Table 2**).

We also performed additional sub-analyses by stratifying the population according to the site of inclusion (hospital vs outpatient clinic/office based) and by regions of enrolment (**Supplementary materials, Tables S4-S8**). There was a relatively higher frequency in cTn testing both in South and North European countries in the outpatient clinic setting (12.9% and 11.3% compared to 5.2% in Western and 7.3% in Easter Europe, p<0.001) (**Table S4**). On multivariable logistic regression analysis, only Southern European countries were independently associated with cTn testing as out-patients (OR 2.91, 95% CI 2.08-4.06) (**Table S6**). Conversely, when stratifying the analysis in hospitalized patients, Southern and Eastern regions were inversely associated with cTn testing in this setting (OR 0.65, 95% CI 0.52-0.83 and OR 0.48, 95% CI 0.37-0.63, respectively) (**Table S8**).

Follow-up and survival analysis

Crude rates of adverse events during the follow-up according to cTn levels are shown in **Table 3**. After a median (IQR) follow-up of 730 (692-749) days, there were 957 (9.7%) MACE and 994 (9.5%) deaths; additionally, 405 (4.1%) haemorrhagic events were recorded. Patients with elevated cTn levels had significantly higher rates of almost all of the adverse outcomes (all p<0.001), when compared with the other groups (**Table 3**), with the exception of any TE (p=0.07) and stroke/TIA (p=0.77). Patients with elevated levels of cTn also reported higher crude rates of any hospital readmission, including any CV-, any non-CV- and any CV non-AF related (all p<0.001) (**Table 3**).

Kaplan–Meier analysis showed a lower cumulative survival for MACE and all-cause death in patients with elevated cTn levels (**Figure 1A, 1B)** (Log Rank tests, p<0.001). The multivariable adjusted Cox regression analyses (**Table 4 and Table S9**) showed that patients with elevated levels of cTn had an independent higher risk for the main outcomes (Model 1: HR 1.74, 95% CI 1.40-2.16; Model 2: HR 1.62, 95% CI 1.28-2.05; Model 3: HR 1.76, 95% CI 1.37-2.26 for MACE; Model :1 HR 1.45, 95% CI 1.21-1.74; Model 2: 1.36, 95%CI 1.12-1.66; Model 3: HR 1.38, 95% CI 1.12-1.71, for all-cause death). Additionally, elevated levels of cTn were significantly associated with a higher risk of any ACS, CV death and any PCI/CABG (**Table 5**).

On multivariable logistic regression analysis, adjusted for HASBLED score, sex, site of inclusion (hospital vs outpatient), use of OAC, presence of atypical symptoms, malignancy and type of AF, elevated levels of cTn were independently associated with the occurrence of haemorrhagic events (OR 2.00, 95% CI 1.49-2.69) (**Table S10**). Other events, such as any readmission, including any CV readmission, any AF-, any CV non-AF related, were also significantly associated with elevated cTn levels (**Table S10**).

Similar results were found when excluding patients with history of CAD, diagnosis of ACS at discharge, those who underwent a PCI or CABG during the admission and/or who were treated with OAC plus antiplatelet therapy. In particular, elevated levels of cTn were independently associated with a higher occurrence of MACE, all-cause death, any ACS, CV death, haemorrhagic events and hospital readmission (**Table S11-S12**).

Finally, restricting the analysis to truly low-risk AF patients (i.e. CHA_2DS_2-VASc 0 (males), or score of 1 (females)]) we found higher crude rates of MACE in patients with elevated levels of cTn compared to patients with no cTn elevations (12.5% vs 2.6%, p=0.007). On Cox regression analysis adjusted for the site of inclusion (hospital vs outpatient), use of OAC, presence of symptoms [chest pain, dyspnoea or syncope], CKD, malignancy and type of AF, these results were suggestive of a 3 fold risk but this was not statistically significant, given the small numbers and wide 95%CIs (HR 3.06, 95% CI 0.83-11.40, p=0.09).

Discussion

The principal findings of this analysis based on the EORP-AF General Long-Term Registry are: (i) cTn was assessed in more than a quarter of AF patients enrolled; (ii) overall, clinical factors that might enhance the need to rule out an underlying ACS, such as presence of atypical AF-related symptoms, previous history of CAD and first detected AF were independently associated with cTn measurement in daily clinical practice; and (iii) AF patients with elevated cTn levels had a significant independent increased risk for CV adverse events, all-cause mortality, haemorrhagic events and hospital readmissions, even after the exclusion of patients with CAD or history of CAD.

To the best of our knowledge, the present study represents one of the largest analysis assessing the current use, as well as the prognostic implications, of cTn measurement in unselected AF patients and had the advantage of exploring AF management in the "real world". The present analysis offers a "real-world" snapshot on unselected AF patients showing that cTn testing is common in daily clinical practice and provides new insights in the possible diagnostic and predictive implications of cTn measurement in such patients. Indeed, a reasonable application of biomarkers, according to clinical judgment and patient profile, appears to support clinical-decision making at first patient assessment, but may also integrate outcome prediction and clinical risk stratification. However, cTn should be considered only in selected AF patients since inappropriate use or interpretation of cTn, could results in unnecessary and even harmful procedures, and a waste of healthcare resources.

It is noteworthy that at the time of data collection (2013-2016) no specific indications for measuring cTn were included in the guidelines for the management of AF [29]. Even later, the role of cTn has remained undefined, with some indications for improving risk stratification for stroke and bleeding, apart the expected (and more established) role of ruling out cardiac ischemia [30-32]. Our analysis highlights that the practice of use of cTn is variable, with a wider use in some geographical regions and contexts. In interpreting this heterogeneity, both the variability in local protocols and habits, as

well as regional differences in patient characteristics, and management options, should be considered, as previously suggested by other analysis from the EORP-AF Pilot registry [33].

In the literature, the use of cTn is variable, even in the context of assessment of patients presenting with chest pain [34]. This variability may involve patients presenting with AF, especially patients presenting at emergency departments (ED), where the use of cTn evaluation may differ among countries in quantitative terms, as well as in terms of clinical guidance [35, 36]. In view of the variable positive predictive accuracy for cardiac ischemia according to patient selection, it appears appropriate, according to our findings, to better define the indications for using cTn, either in terms of diagnostic testing and separately, to risk stratify patient outcomes.

The first part on our analysis focused on describing how frequently cTn was tested in general AF patients and which clinical variables could drive the clinician to proceed with such measurements. As expected, most of the cTn assessments were performed in hospitalized AF patients. Nevertheless, since our registry enrolled both in and out-patients, it was quite surprising that 16% of cTn tests were performed during regular out-patient clinic consultations and theoretically, in stable AF patients, with significant differences among European countries that could reflect differences in habits, protocols or characteristics of healthcare systems [33, 37]. In the "real world", cTn testing may be frequent even in the absence of symptoms or clinical presentation suggestive of CAD or ACS [15, 35, 38] and in this setting the most recent guidelines take into consideration a potential role in refining risk stratification for stroke or bleeding [31, 32].
In a large retrospective study of emergency department (ED) visits from the National Hospital Ambulatory Medical Care Survey in the United States, cardiac biomarkers were tested in 8.2% (95% CI, 7.1-9.5%) of visits in the absence of ACS-related symptoms [38]. Of note, more than a quarter of all visits with cardiac biomarker testing did not have an electrocardiogram recorded which should be one of the first diagnostic tests in patients with suspected ACS [38, 39]. These data

further confirm that in some settings cTn may be widely used in the ED, as a first line routine assessment, even before a full clinical evaluation [40].

We also investigated the factors associated with troponin testing. The main reasons why clinicians performed cTn testing in AF patients were mostly related to a suspicion of underlying ACS, both in hospitalized and outpatient clinic setting. Indeed, atypical AF-related symptoms (such as chest pain, dyspnoea or syncope), first detected AF, history of CAD or CV risk factors such as smoking or physical inactivity, were independent predictors of cTn testing. The findings that atypical AF-related symptoms were significantly associated with cTn testing may be justified either by the need to rule-out cardiac ischemia, or by the fact that atypical AF clinical presentation seems to be associated with less favourable outcome. As reported, AF patients presenting with atypical symptoms had higher rates of cerebrovascular events and mortality compared to patients with typical presentation even after adjustment for the CHA_2DS_2-VASc score, comorbidities, and OAC therapy [41].

In the recent years, it has been discussion over whether elevated levels of cTn in AF patients, either symptomatic or asymptomatic, could indicate the presence of masked CAD, cardiac ischemia or myocardial injury. In daily clinical practice, cardiac biomarkers are often tested in patients with AF presenting to the hospital, especially in patients with new onset AF, to rule out an underlying ACS. However, the use of cTn in this setting and its predictive value to detected significant CAD, are not well established [12, 42, 43]. Recent results from the Troponins in Atrial Fibrillation study (The Tropo-AF Study) found that AF patients presenting to the ED had often minor cTn elevation related to non-ischaemic causes (such as infections, cerebrovascular events, HF, bone fractures, chronic kidney disease etc) [15]. Different mechanisms have been proposed to explain the release of cTn during AF. Indeed, masked CAD may be just one of the cause of cTn elevation in AF patients, since AF itself, as any other supraventricular tachycardia, may cause cTn elevation in the absence of significant underlying heart disease due only to the high ventricular heart rate. A recent

retrospective Finnish study, investigated the association of heart rate with hs-cTnT levels in patients admitted to the ED for AF, finding that high ventricular heart rate was significantly related with troponin release with a nonlinear association that became evident only above the heart rate threshold of 125 bpm [44].

In support of these results, the Rate Control in Atrial Fibrillation (RATAF) trial found that cTn was detectable even in stable patients with permanent AF, preserved left ventricular ejection fraction and without ischemic heart disease or HF and a moderate reduction of heart rate by beta-blockers and calcium channel blockers, was significantly associated with lower cTn levels [45]. Other known mechanisms of cTn release in AF patients, include high atrial rates, reduced ventricular perfusion during AF, cell injury, apoptosis, myocardial strain, inflammation, and acute or chronic renal impairment [4, 46-49].

In our cohort, AF patients with elevated cTn levels had a significant independent higher risk of all cause-death and MACE. These findings integrate and extend to the "real-world" setting the results of different sub-analyses focused on cardiac biomarkers of the pivotal RCTs on NOACs, performed in highly selected patients [23-25, 50]. Our analysis actually expands the implications for the outcomes of elevated cTn levels highlighted by these studies performed in selected trial populations. It is noteworthy that we found similar results even after excluding those AF patients with various form of CAD, thus empathizing the negative prognostic impact of elevated levels of cTn, independent of a known history of CAD.

Although the present analyses were adjusted for CHA_2DS_2-VASc score and presence of comorbidities, the association between AF and coronary events could also be justified by the similar risk factors and pathophysiological processes such as inflammation, prothrombotic state, endothelial dysfunction etc., shared by AF and CAD patients [51, 52]. In a study by Conti and colleagues, the relationship between of coronary atherosclerosis and adverse outcomes was analysed using troponin levels rises in more than 3500 recent-onset AF patients without severe

comorbidities [43]. Patients with a recent-onset AF and a troponin rise had significantly increased risk of adverse coronary events when compared with patients without troponin rise (19% vs 1%) and during a 5-year follow-up almost 50% of the patients with a troponin rise underwent coronary revascularization [43].

In consideration of the observational nature of our study and available data, we were able to simply stratify our cohort between patients with normal or elevated plasma cTn levels, but we were not able to investigate differences in outcome across specific ranges of elevated cTn values. Serial troponins were not tested in some patients and in some cases our results were based on a single cTn determination. We could not determinate a "rise and fall" or temporal pattern of cTn release that is used to rule out ACS. However, our aim was to evaluate if even one cTn assessment could have prognostic implications independently from the diagnosis of myocardial infarction in a general AF population. It has been reported that any abnormally elevated cTn at any level were associated with adverse outcomes [49, 50, 53]. Even a single elevated cTn value at presentation indicates an increased risk of adverse clinical outcomes (e.g. all-cause or cardiovascular death) in different patient populations (including those without acute ischemic conditions) [4]. This was confirmed by the additional subanalysis that we performed excluding patients with ACS or CAD in whom elevated cTn were still significantly associated with adverse outcomes. Of note, our study actually reflects what frequently occurs in clinical practice where troponin levels are often dichotomized into "positive" (i.e. >99th percentile of the upper limit of normal for the cTn assay) or "negative". Finally our study also showed that patients with cTn tested in range were associated with higher occurrence of adverse events during follow-up. Given the observational nature of the study, our findings have to be interpreted in terms of associations, and may be affected by confounding. We can hypothesize that the patient clinical profile that let physicians to test for cTn may imply some additional risk of bleeding or hospital re-admission, to explain the associations found.

Limitations

The main limitation of our study is related to its observational nature, since cTn assessment was not predefined. Additionally, the data presented do not imply causality, but simply report associations. Second, some patients were lost at follow-up, notwithstanding similar proportion of losses were reported by other registries. Another limitation is related to the study setting, based exclusively on cardiology practices. Lastly, a specific limitation of this analysis was the analytic accuracy of the prognostic value of troponin, given the different assays used at each centre. We could not discriminate between hs-cTn and conventional cTn since each centre used his own cTn assay. We could only stratify our cohort as normal or elevated plasma cTn and we were not able to investigate differences in outcome across specific ranges of elevated cTn values. Nevertheless, as found by a recent meta-analysis on more than 20,000 AF patients, the prognostic value of cTn seems to be independent of the method of determination and type of troponin measured [16].

Conclusions

In this large contemporary cohort of European AF patients a clinical presentation or baseline characteristics that might enhance the need to rule out an underlying ACS, such as presence of atypical AF-related symptoms, previous history of CAD and first detected AF were independently associated with cTn measurement in daily clinical practice. Elevated levels of cTn were independently associated with an increased risk of all-cause mortality and adverse CV events, including hospital readmissions, even after exclusion of patients with CAD or history of CAD.

Appendix

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Figure Legend

Figure 1. Kaplan–Meier curves for main study outcomes according to cTn assessment

Panel A. MACE (Any TE/ACS/CV death); Panel B. All-cause death

Legend: ACS= acute coronary syndrome; cTn= cardiac troponins; CV= cardiovascular; MACE= major adverse cardiovascular events; TE= thromboembolic events.

*= statistical significance is accepted at the $p < 0.0167$ level with Bonferroni correction

Table 1. Baseline characteristics of study population according to cTn assessment

	Total (N= 10445)	**cTn not tested** (n=7611, 72.9%)	**cTn in range** (n=1930, 18.5%)	**cTn elevated** (n=904, 8.7%)	**p**
Age (years), median (IQR)	71 (63-77)	71 (63-78)	68 (60-76)	73 (65-79)	<0.001**
Female, n (%)	4214/10445 (40.3)	3014/7611 (39.6)	849/1930 (44.0)	351/904 (38.8)	0.001*
BMI (kg/m^2), median (IQR)	27.5 (24.8-31.1)	27.5 (24.8-31.1)	27.6 (24.7-31.2)	27.7 (24.8-31.2)	0.86**
Site of inclusion, n (%)					<0.001*
Hospital	5321/10445 (50.9)	2939/7611 (38.6)	1559/1930 (80.8)	823/904 (91.0)	
Outpatient or office based	5214/10445 (49.1)	4672/7611 (61.4)	371/1930 (19.2)	81/904 (9.0)	
Region of enrolment§, n (%)					<0.001*
Western Europe	3368/10445 (32.2)	2598/7611 (34.1)	529/1930 (27.4)	241/904 (26.7)	
Southern Europe	3812/10445 (36.5)	2621/7611 (34.4)	832/1930 (43.1)	359/904 (39.7)	
Northern Europe	1380/10445 (13.2)	965/7611 (12.7)	273/1930 (14.1)	142/904 (15.7)	
Eastern Europe	1885/10445 (18.0)	1427/7611 (18.7)	296/1930 (15.3)	162/904 (17.9)	
AF type, n (%)					<0.001*
First diagnosed	1611/10264 (15.7)	841/7481 (11.2)	492/1898 (25.9)	278/885 (31.4)	
Paroxysmal	2690/10264 (26.2)	1880/7481 (25.1)	589/1898 (31.0)	221/885 (25.0)	
Persistent	2024/10264 (19.7)	1562/7481 (20.9)	349/1898 (18.4)	113/885 (12.8)	
Long-standing persistent	456/10264 (4.4)	369/7481 (4.9)	65/1898 (3.4)	22/885 (2.5)	
Permanent	3483/10264 (33.9)	2829/7481 (37.8)	403/1898 (21.2)	251/885 (28.4)	
Hypertension, n (%)	6433/10354 (62.1)	4817/7556 (63.8)	1107/1905 (58.1)	509/893 (57.0)	<0.001*
Diabetes mellitus, n (%)	2393/10378 (23.1)	1686/7572 (22.3)	418/1909 (21.9)	289/897 (32.2)	<0.001*
Smoking (current) , n (%)	909/9687 (9.4)	562/6985 (8.0)	239/1832 (13.0)	108/870 (12.4)	<0.001*
No physical activity, n (%)	3798/8973 (42.3)	2600/6453 (40.3)	764/1706 (44.8)	434/814 (53.3)	<0.001*
Lipid disorder, n (%)	4139/9990 (41.4)	3067/7273 (42.2)	690/1842 (37.5)	382/875 (43.7)	<0.001*
Heart failure, n (%)	4039/10357 (39.0)	2856/7553 (37.8)	722/1908 (37.8)	461/896 (51.5)	<0.001*
NYHA III/IV, n (%)	1421/4033 (35.2)	912/2852 (32.0)	293/721 (40.6)	216/460 (47.0)	<0.001*
Dilated CMP, n (%)	908/10322 (8.8)	610/7533 (8.1)	208/1899 (11.0)	90/890 (10.1)	<0.001*
Hypertrophic CMP, n (%)	320/10315 (3.1)	233/7531 (3.1)	52/1894 (2.7)	35/890 (3.9)	0.24*
Pulmonary arterial hypertension, n (%)	721/10266 (7.0)	533/7501 (7.1)	134/1878 (7.1)	54/887 (6.1)	0.52*
LVEF (%), median (IQR)	55 (45-62)	56 (48-63)	55 (45-60)	50 (35-58)	<0.001**
Bundle Branch Block, n (%)					<0.001*
No	8207/9670 (84.9)	6049/7100 (85.2)	1549/1773 (87.4)	609/797 (76.4)	
LBBB	816/9670 (8.4)	583/7100 (8.2)	129/1773 (7.3)	104/797 (13.0)	
RBBB	647/9670 (6.7)	468/7100 (6.6)	95/1773 (5.4)	84/797 (10.5)	
Coronary artery disease, n (%)	2856/9851 (29.0)	1877/7207 (26.0)	506/1771 (28.6)	473/873 (54.2)	<0.001*
Previous MI	1263/2856 (44.2)	744/1877 (39.6)	196/506 (38.7)	323/473 (68.3)	<0.001*
Previous PCI	1173/2856 (41.1)	776/1877 (41.3)	185/506 (36.6)	212/473 (44.8)	0.03*
Previous CABG	541/2856 (18.9)	396/1877 (21.1)	74/506 (14.6)	71/473 (15.0)	<0.001*
Previous angina	930/2856 (32.6)	590/1877 (31.4)	208/506 (41.1)	132/473 (27.9)	<0.001*
Valvular alterations, n (%)	5149/10234 (50.3)	3913/7463 (52.4)	797/1882 (42.3)	439/889 (49.4)	<0.001*
Previous TE events, n (%)	1200/10348 (11.6)	871/7542 (11.5)	206/1911 (10.8)	123/895 (13.7)	0.07*

Previous ischaemic stroke, n (%)	632/10347 (6.1)	461/7541 (6.1)	102/1911 (5.3)	69/895 (7.7)	0.05*
Previous TIA, n (%)	322/10347 (3.1)	236/7541 (3.1)	52/1911 (2.7)	34/895 (3.8)	0.31*
Previous EP/DVT, n (%)	224/10347 (2.2)	156/7541 (2.1)	51/1911 (2.7)	17/895 (1.9)	0.23*
Previous haemorrhagic events, n (%)	550/10342 (5.3)	397/7541 (5.3)	84/1902 (4.4)	69/899 (7.7)	0.001*
Peripheral vascular disease, n (%)	813/10230 (7.9)	603/7484 (8.1)	108/1872 (5.8)	102/874 (11.7)	<0.001*
Liver disease, n (%)	283/10387 (2.7)	204/7568 (2.7)	46/1922 (2.4)	33/897 (3.7)	0.14*
COPD, n (%)	923/10367 (8.9)	666/7553 (8.8)	168/1913 (8.8)	89/901 (9.9)	0.56*
Dementia, n (%)	134/10404 (1.3)	95/7585 (1.3)	25/1921 (1.3)	14/898 (1.6)	0.74*
Anaemia, n (%)	560/10412 (5.4)	358/7587 (4.7)	102/1922 (5.3)	100/903 (11.1)	<0.001*
Malignancy (current+prior), n (%)	785/10375 (7.6)	557/7561 (7.4)	128/1918 (6.7)	100/896 (11.2)	<0.001*
Hyperthyroidism, n (%)	470/10216 (4.6)	339/7442 (4.6)	96/1887 (5.1)	35/887 (3.9)	0.38*
Hypothyroidism, n (%)	974/10232 (9.5)	741/7448 (9.9)	154/1894 (8.1)	79/890 (8.9)	0.04*
CKD, n (%)	1283/10365 (12.4)	893/7541 (11.8)	196/1923 (10.2)	194/901 (21.5)	<0.001*
CrCl (C-G) (ml/min), median (IQR)	75 (55-97)	75 (56-97)	78 (57-103)	63 (46-86)	<0.001**
CHA_2DS_2VASc, median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	4 (2-5)	<0.001**
Truly low-risk[#]	957/10438 (9.2)	670/7610 (8.8)	246/1925 (12.8)	41/903 (4.5)	<0.001*
HASBLED, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	2 (1-3)	<0.001**
EHRA score, median (IQR)	2 (1-2)	1 (1-2)	2 (1-3)	2 (1-3)	<0.001**
Chest pain, dyspnoea and/or syncope, n (%)	3789/10445 (36.3)	2446/7611 (32.1)	935/1930 (48.4)	408/904 (45.1)	<0.001*
Multimorbidity, n (%)	6750/8578 (78.7)	4995/6307 (79.2)	1094/1512 (72.4)	661/759 (87.1)	<0.001**

Legend: AF= atrial fibrillation; BMI= body mass index; CABG= coronary artery bypass grafting; CAD= coronary artery disease; CKD= chronic kidney disease; CMP= cardiomyopathy; COPD=chronic obstructive pulmonary disease; cTn= cardiac troponin; CV= cardiovascular; EHRA= European Heart Rate Association; DVT= deep vein thrombosis; CrCl C-G=creatinine clearance according to Cockroft-Gault formula; IQR, interquartile range; LBBB= left bundle branch block; LVEF, left ventricular ejection fraction; NYHA=New York Heart Association PCI= percutaneous coronary intervention; PE= pulmonary embolism; RBBB= right bundle branch block; TE= thromboembolic; TIA= transient ischaemic attack. [§]Regions of enrolment. Northern Europe: Denmark, Estonia, Latvia, Norway, UK; Western Europe: Belgium, France, Germany, Netherlands, Switzerland; Eastern Europe: Bulgaria, Czech Republic, Georgia, Kazakhstan, Kyrgyzstan, Poland, Romania, Russia; Southern Europe: Albania, FYR Macedonia, Italy, Malta, Montenegro, Portugal, Serbia, Spain, Turkey. [#]Truly low-risk patients were defined as CHA_2DS_2-VASc 0 in males or score of 1 in females. *p-values for among-group comparisons are from Pearson's χ^2 test; **p-values for among-group comparisons are from Kruskal–Wallis test.

Table 2. Multivariable logistic regression analysis for factors associated with cardiac troponins testing during admission or consultation

	Multivariable Analysis		
	Odds Ratio	**95% CI**	**p value**
Age	1.00	0.99-1.00	0.48
Female sex	1.23	1.08-1.40	0.001
Site of inclusion (hospital)	7.69	6.70-8.83	<0.001
Region of enrolment			
Western Europe *(reference)*	-	-	-
Southern Europe	0.83	0.71-0.96	<0.01
Northern Europe	0.91	0.74-1.12	0.39
Eastern Europe	0.51	0.42-0.62	<0.001
First detected AF	2.14	1.84-2.48	<0.001
Hypertension	0.82	0.72-0.93	0.002
Diabetes mellitus	1.01	0.88-1.17	0.84
Smoking	1.43	1.17-1.74	<0.001
No physical activity	1.28	1.14-1.45	<0.001
Lipid disorder	1.21	1.061.36	0.003
Heart failure	0.89	0.78-1.02	0.10
Dilated cardiomyopathy	1.14	0.92-1.41	0.23
Coronary artery disease	1.78	1.56-2.04	<0.001
Valvular alterations	0.60	0.53-0.68	<0.001
COPD	0.95	0.77-1.17	0.65
Anaemia	1.07	0.84-1.37	0.55
Hypothyroidism	0.76	0.62-0.93	0.008
CKD	1.13	0.94-1.35	0.17
Chest pain, dyspnoea or syncope	1.46	1.30-1.65	<0.001

Legend: CI=confidence interval, for other abbreviations see Table 1.

Table 3. Major adverse events during follow-up according to cTn assessment

	Total (N= 10445)	cTn not tested (n=7611, 72.9%)	cTn in range (n=1930, 18.5%)	cTn elevated (n=904, 8.7%)	p
MACE†, n (%)	957/9818 (9.7)	499/7210 (6.9)	205/1734 (11.8)	253/874 (28.9)	<0.001*
All cause death, n (%)	994/10445 (9.5)	636/7611 (8.4)	177/1930 (9.2)	181/904 (20.0)	<0.001*
Haemorrhagic events, n (%)	405/9756 (4.1)	261/7188 (3.6)	66/1726 (3.8)	78/851 (9.2)	<0.001*
Any TE, n (%)	228/9766 (2.3)	153/7190 (2.1)	52/1742 (3.0)	23/852 (2.7)	0.07*
Stroke/TIA, n (%)	171/10445 (1.6)	121/7611 (1.6)	33/1930 (1.7)	17/904 (1.9)	0.77*
Any ACS, n (%)	422/9782 (4.3)	154(7192 (2.1)	88/1727 (5.1)	180/863 (20.9)	<0.001*
CV death, n (%)	377/9805 (3.8)	217/7209 (3.0)	77/1730 (4.5)	83/866 (9.6)	<0.001*
Any PCI/CABG, n (%)	263/10445 (2.5)	148/7611 (1.9)	54/1930 (2.8)	61/904 (6.7)	<0.001*
Any readmission, n (%)	3794/9762 (38.9)	2539/7189 (35.3)	798/1723 (46.3)	457/850 (53.8)	<0.001*
Any CV readmission, n (%)	2450/9762 (25.1)	1625/7189 (22.6)	517/1723 (30.0)	308/850 (36.2)	<0.001*
Any AF readmission, n (%)	1294/9762 (13.3)	824/7189 (11.5)	320/1723 (18.6)	150/850 (17.6)	<0.001*
Any non-CV readmission, n (%)	1133/9762 (11.6)	787/7189 (10.9)	217/1723 (12.6)	129/850 (15.2)	<0.001*
Any CV non-AF readmission, n (%)	1600/9762 (16.4)	1077/7189 (15.0)	296/1723 (17.2)	227/850 (26.7)	<0.001*

Legend: †MACE= Any TE/ACS/CV death; *p-values for among-group comparisons are from Pearson's χ^2 test. For abbreviations see Table 1

Table 4. Multivariable Cox regression analysis for cTn levels and the main outcomes

Multivariable Cox Regression Analysis									
MACE	***Model 1***			***Model 2***			***Model 3***		
	HR	**[95% CI]**	**p value**	**HR**	**[95% CI]**	**p value**	**HR**	**[95% CI]**	**p value**
cTn not tested (ref)	-	-	-	-	-	-	-	-	-
cTn in range	1.20	[0.99-1.46]	0.07	1.06	[0.85-1.33]	0.60	1.13	[0.89-1.43]	0.30
cTn elevated	1.74	1.40-2.16	<0.001	1.62	[1.28-2.05]	<0.001	1.76	[1.37-2.26]	<0.001
All-cause death	***Model 1***			***Model 2***			***Model 3***		
	HR	**[95% CI]**	**p value**	**HR**	**[95% CI]**	**p value**	**HR**	**[95% CI]**	**p value**
cTn not tested (ref)	-	-	-	-	-	-	-	-	-
cTn in range	0.94	0.79-1.13	0.54	0.86	0.71-1.06	0.16	0.86	0.69-1.07	0.18
cTn elevated	1.45	1.21-1.74	<0.001	1.36	1.12-1.66	0.002	1.38	1.12-1.71	0.002

Legend: HR, hazard ratio; CI confidence interval. For other abbreviations see Table 1. †MACE= composite of any TE/ACS/CV death. Model 1 was adjusted for CHA_2DS_2VASc score, site of inclusion (hospital vs outpatient clinic), use of OAC, presence of atypical AF-related symptoms (chest pain, dyspnoea or syncope), CKD (i.e. creatinine clearance <60 ml/min calculated with Cockcroft-Gault equation), malignancy and type of AF; Model 2 was adjusted for the individual components of the CHA_2DS_2VASc score in addition to the other covariates of Model 1; Model 3 was adjusted for the variables that were statistically different between patients without cTn tested and cTn tested at the univariate analysis. The full Cox models are reported in the Supplementary materials (Table S9).

Table 5. Multivariable Cox regression analysis for cTn levels and adverse outcomes

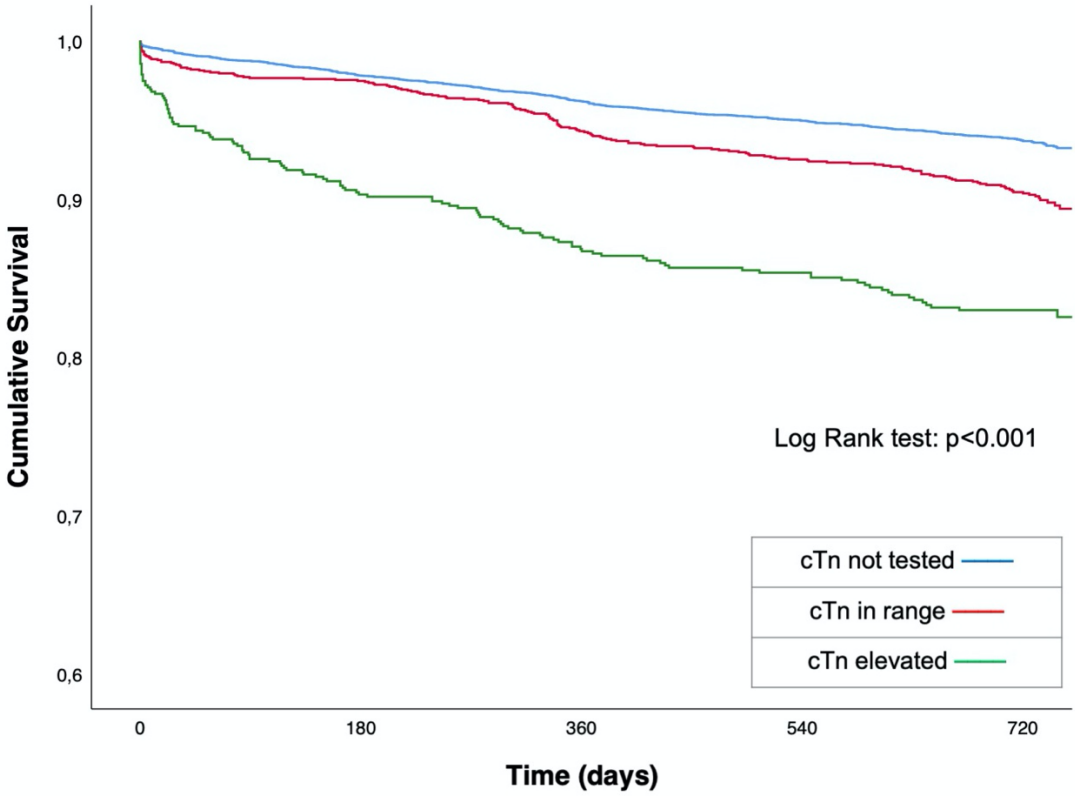
Multivariable Cox Regression Analysis		
	HR [95 % CI]	**p value**
Any TE*		
cTn not tested (ref)	-	-
cTn in range	1.24 [0.86-1.79]	0.24
cTn elevated	1.01 [0.61-1.65]	0.98
Any ACS*		
cTn not tested (ref)	-	-
cTn in range	1.34 [0.96-1.87]	0.09
cTn elevated	2.56 [1.79-3.65]	<0.001
CV death*		
cTn not tested (ref)	-	-
cTn in range	1.07 [0.81-1.41]	0.65
cTn elevated	1.66 [1.26-2.18]	<0.001
Any PCI/CABG*		
cTn not tested (ref)	-	-
cTn in range	1.18 [0.84-1.67]	0.30
cTn elevated	2.58 [1.82-3.63]	<0.001

Legend
HR, hazard ratio; CI confidence interval. For other abbreviations see Table 1.

†MACE= composite of any TE/ACS/CV death; *Adjusted analysis for CHA_2DS_2VASc score, site of inclusion (hospital vs outpatient), use of OAC, presence of symptoms [chest pain, dyspnoea or syncope], CKD, malignancy and type of AF.

Figures. Kaplan–Meier curves for main study outcomes according to cTn assessment

Figure 1 A. MACE (Any TE/ACS/CV death)

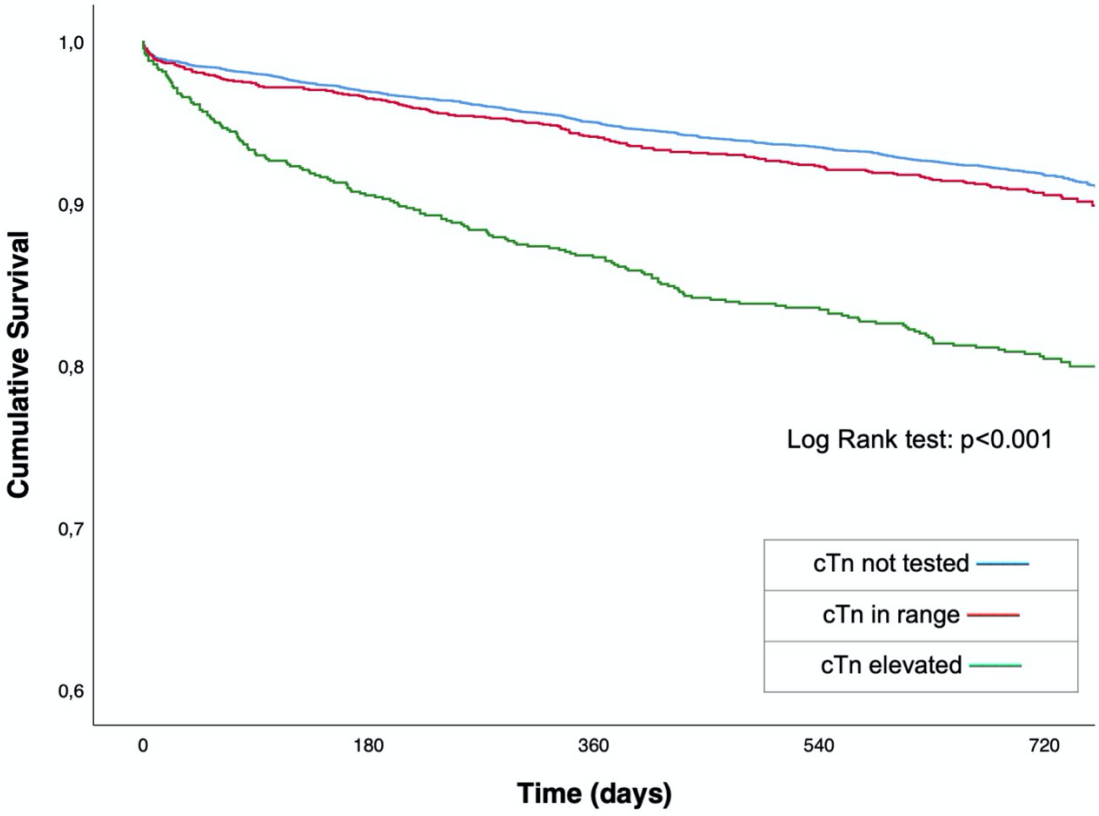


N at risk					
cTn not tested	7165	6870	6583	6121	4415
cTn in range	1692	1612	1527	1423	1110
cTn elevated	744	643	600	555	412

Pairwise comparison - Log Rank test						
	No		In-range		Elevated	
	Chi-Square	p*	Chi-Square	p*	Chi-Square	p*
No			22.115	<0.001	118.736	<0.001
In-range	22.115	<0.001			28.455	<0.001
Elevated	118.736	<0.001	28.455	<0.001		

*= statistical significance is accepted at the p < 0.0167 level with Bonferroni correction

Figure 1 B. All-cause death



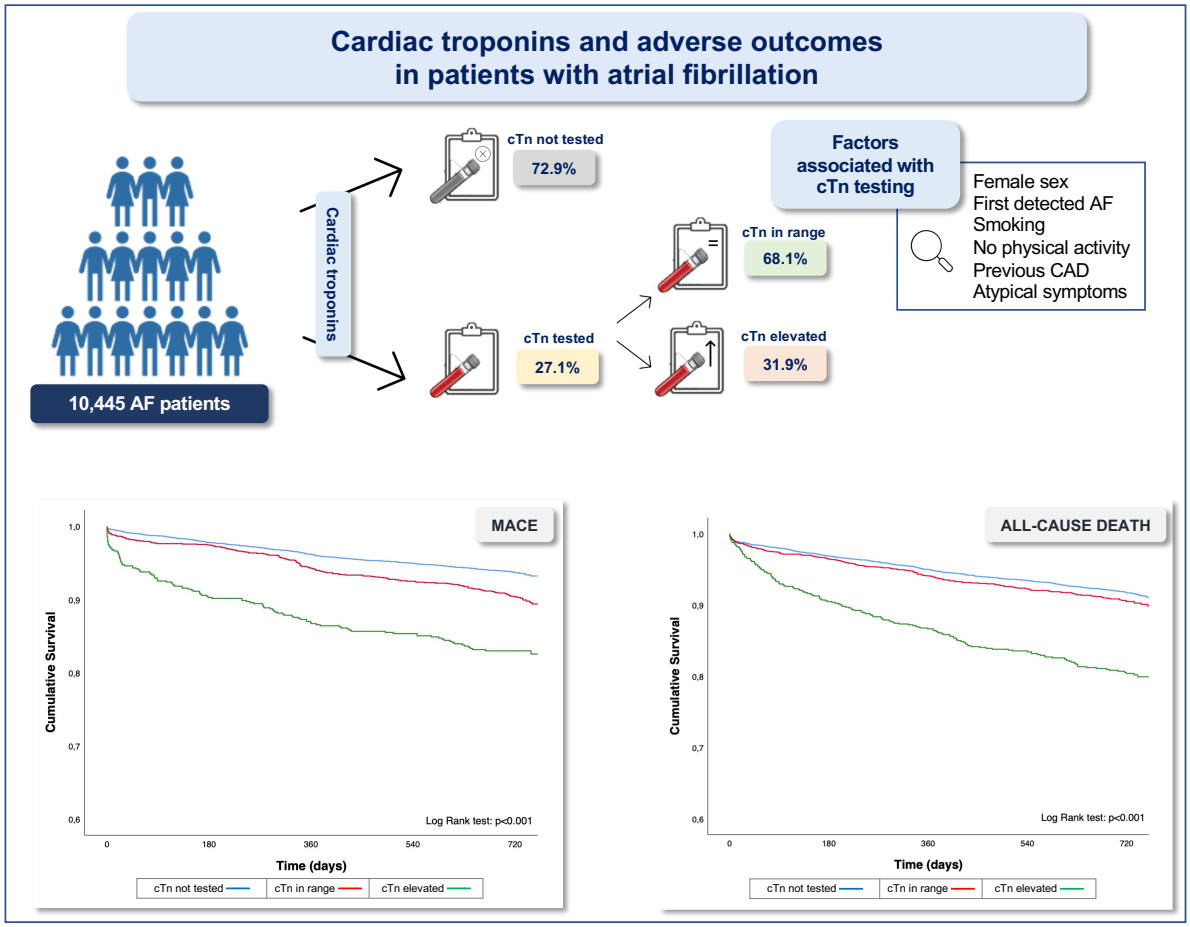
N at risk					
cTn not tested	7440	7195	6918	6319	4591
cTn in range	1878	1810	1740	1505	1194
cTn elevated	893	806	764	687	524

Pairwise comparison - Log Rank test						
	No		In-range		Elevated	
	Chi-Square	p*	Chi-Square	p*	Chi-Square	p*
No			1.623	0.203	130.951	<0.001
In-range	1.623	0.203			63.108	<0.001
Elevated	130.951	<0.001	63.108	<0.001		

*= statistical significance is accepted at the p < 0.0167 level with Bonferroni correction

GRAPHICAL ABSTRACT

Cardiac troponins and adverse outcomes in patients with atrial fibrillation



Legend: AF= atrial fibrillation; CAD= coronary artery disease; cTn= cardiac troponins;

MACE= major adverse cardiovascular events

ARTICLE HIGHLIGHTS

- Elevated levels of cTn were independently associated with an increased risk adverse cardiovascular events, even in AF patients without coronary artery disease.
- A reasonable application of cardiac troponins in AF patients may support clinical-decision making and also integrate outcome prediction and risk stratification.
- Future studies are needed to investigate the mechanisms of cardiac troponins elevation in AF patients independently of cardiac ischemia.