Elevated Troponin T and enlarged left atrium predict the incidence of atrial fibrillation in patients with chronic kidney disease stage 4-5

Markus Hakamäki (markus.hakamaki@tyks.fi)
Turku University Hospital https://orcid.org/0000-0003-3523-4299
Tapio Hellman
TYKS
Roosa Lankinen
TYKS
Niina Koivuviita
TYKS
Jussi Pärkkä
TYKS
Petri Kallio
TYKS
Tuomas Kiviniemi
TYKS
Juhani KE Airaksinen
TYKS
Mikko J Järvisalo
TYKS
Kaj Metsärinne
TYKS

Research article

Keywords: Chronic kidney disease, atrial fibrillation, incidence, Troponin T, left atrial volume index

Posted Date: May 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-28001/v1

Abstract

Background

Atrial fibrillation (AF) and chronic kidney disease (CKD) are commonly co-existing conditions. However, data on epidemiology of AF in patients with CKD stage 4–5 is scarce.

Methods

We prospectively enrolled 210 consecutive non-dialysis patients with CKD stage 4–5 between 2013 and 2017. Follow-up data on AF incidence along with medical history, laboratory tests and echocardiography at baseline were gathered.

Results

At baseline, mean age was 62 years, estimated glomerular filtration rate 12.8 ml/min and 73/210 (34.8%) of the participants were female. Altogether 41/210 (19.5%) patients had a previous diagnosis of AF. After median follow-up of 46 [IQR 27] months, new-onset AF occurred in 33/169 (19.5%) patients (69.9 events/1000 person-years). Overall, 22/33 (66.7%) of patients with new-onset AF were identified with a triggering condition and 21/33 (63.6%) were receiving renal replacement therapy (dialysis or acquired kidney transplant) at the time of AF detection, respectively. In Cox proportional hazard model age > 60 years (HR 4.27, CI95% 1.57–11.64, $p < 0.01$), elevated troponin T (TnT) > 50 ng/l (HR 3.61, CI95% 1.55–8.37, $p < 0.01$) and left atrial volume index (LAVI) > 30 ml/m^2 (HR 4.82, CI95% 1.11-21.00, $p = 0.04$) independently predicted the incidence of new-onset AF.

Conclusions

The prevalence and incidence of AF was markedly high in this prospective study on patients with CKD stage 4–5. Elevated TnT and increased LAVI were identified as independent predictors for new-onset AF in patients with severe CKD.

Introduction

Atrial fibrillation (AF) and chronic kidney disease (CKD) are both common diseases with estimated prevalence rates of 2% and 13%, respectively, in the general population and projected to become more frequent further encumbering the healthcare system in the future (1, 2). Furthermore, AF is associated with increased risk for stroke, congestive heart failure, myocardial infarction, CKD progression and death in CKD patients (3, 4). AF and CKD share many common risk factors and worsening kidney function appears to increase the risk of AF (5). Overall, data on the prevalence and incidence of AF in patients with CKD stage 4–5 has been inconsistent (4, 6–9).

Thus, we sought to explore the occurrence and predictors of AF in a cohort of patients with CKD stage 4–5 in this prospective follow-up study.

Methods

The Chronic Arterial Disease, quality of life and mortality in chronic KIDney injury (CADKID)-study (http://www.ClinicalTrials.gov NCT04223726) is an ongoing prospective follow-up study protocol assessing arterial disease, quality of life, and mortality in patients with CKD stage 4–5. The present study is a prespecified report from the CADKID study.

The study enrolled 210 consecutive patients referred to the predialysis outpatient clinic in Kidney Center of Turku University Hospital between August 2013 and September 2017. All eligible patients had CKD stage 4–5 defined as estimated glomerular filtration rate (eGFR) < 30 ml/min per 1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula at baseline.

Relevant medical history and medications were manually gathered from the hospital electronic patient records by the researchers and laboratory tests and a 12-lead surface electrocardiogram (ECG) by the certified laboratory services of Turku University Hospital (TYKSLAB).

The ECGs were recorded at the paper speed of 50 mm per second and the standardized voltage ratio of 1 mm per 1 mV. All ECGs were manually assessed by the researchers.

The echocardiographic measures were collected from a standardized transthoracic echocardiography performed at rest before stress testing by The Department of Clinical Physiology of Turku University Hospital. The systolic and diastolic dimensions and function of the left ventricle as well as left ventricular wall thicknesses and aortic and left atrial dimensions were measured. Since the traditional method (anteroposterior linear dimension of the left atrium in the parasternal view) in measuring left atrial size is inaccurate, we chose to assess the body surface area corrected left atrial volume index (LAVI) by using planimetry in apical 4- and 2-chamber views at end-systole while excluding the confluences of the pulmonary veins and left atrial appendage (10).

The primary outcome of the study was defined as the incidence of new-onset AF (in a patient with no prior AF history) confirmed by ECG or pacemaker log (defined as an overt AF episode lasting over 30 seconds) at 2 years of follow-up. Follow-up data were manually collected from the patient records.

Ethics

The study was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland. Each participant gave written informed consent before entering the study. Research was performed in accordance with the Declaration of Helsinki

Statistics

Demographics were reported as mean ± standard deviation (SD) and median [inter-quartile range (IQR)] for normally distributed covariates and skewed continuous variables, respectively. Normality in continuous covariates was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests. The unpaired t-test or Mann-Whitney test and Pearson x2 or Fisher's exact test were used to compare continuous covariates and categorical covariates, respectively, in the study subgroups. Categorical covariates were reported with absolute and relative (percentage) frequencies. Due to the large number of tested covariates and limited sample size the baseline covariates correlating at $p \leq 0.01$ significance level with the dependent variable in the univariate model were entered in multivariate logistic regression analysis or Cox proportional hazard analysis, as appropriate. All tests were two-sided and significance was set at $p = 0.05$. IBM SPSS Statistics software version 26.0 was used to perform all analyses.

Results

Prevalence and incidence of AF

Out of the 210 patients with CKD stage 4–5, a total of 41/210 (19.5%) patients had a prior diagnosis of AF. The mean overall duration of AF was 76 months in the patients with a prior AF diagnosis. The patients with a prior diagnosis of AF were markedly older and had a higher burden of comorbidities compared to those with no history of AF (Table 1). In a logistic regression analysis age > 60 years (OR 9.63, CI95% 2.17–42.80, $p < 0.01$) and LAVI > 30 ml/m^2 (OR 4.98, CI95% 1.01–22.73, $p = 0.04$) independently predicted the prior diagnosis of AF.

Table 1
Baseline characteristics of patients according to prevalence of AF.

	No AF (N = 169)	Prior AF (N = 41)	p
Age mean (median) years	60 (61)	74 (75)	0.01
Age ≥60 years	96 (56.8)	39 (95.1)	0.01
Female	56 (33.1)	17 (41.5)	0.36
BMI median (IQR) kg/m^2	27.5 (6.3)	28.7 (9.0)	0.11
Smoking	77 (46.1)	15 (37.5)	0.32
CHA_2DS_2-VASc-score ≥ 2	143 (84.6)	40 (97.6)	0.03
Hypertension	164 (97.0)	41 (100.0)	0.59
Diabetes	74 (43.8)	20 (48.8)	0.60
Coronary artery disease	20 (11.8)	15 (36.6)	0.01
Prior myocardial infarction	15 (8.9)	8 (19.5)	0.09
History of heart failure	26 (15.4)	22 (53.7)	0.01
Peripheral artery disease	27 (16.0)	10 (24.4)	0.25
Pulmonary embolism	5 (3.0)	2 (4.9)	0.63
Prior stroke	16 (9.5)	7 (17.1)	0.17
Prior TIA	7 (4.1)	1 (2.4)	1.0
Cirrhosis	1 (0.6)	1 (2.4)	0.35
Prior gastrointestinal bleeding	29 (17.2)	17 (41.5)	0.01
TTE			
EF mean (median) %	65 (65)	60 (60)	0.01
LVMI mean (median) g/m^2	108 (103)	115 (111)	0.21

[a] data is missing in 39 (18.6%) cases; [b] data is missing in 57 (27.1%) cases.

Values in parentheses are % unless stated otherwise. BMI = body mass index; IQR = interquartile range; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years and sex category (female, unless < 65 years and no other risk factors); TIA = transient ischemic attack; TTE = transthoracic echocardiography; EF = ejection fraction; LVMI = left ventricular mass indexed to body surface area; LVEDD = left ventricular end-diastolic dimension; LA = left atrium; LAVI = left atrial volume index; TnT = Troponin T; ProBNP = Prohormone of brain natriuretic peptide.

	No AF (N = 169)	Prior AF (N = 41)	p
LVEDD mean (median) mm	54 (55)	54 (54)	0.89
LA diameter mean (median) mm [a]	41 (40)	47 (48)	0.01
LAVI mean (median) ml/m^2 [b]	35.3 (33.7)	48.9 (51.7)	0.01
Laboratory tests			
TnT median (IQR) ng/l	32 (42)	50 (46)	0.01
ProBNP median (IQR) ng/l	921 (2014)	4040 (6260)	0.01

[a] data is missing in 39 (18.6%) cases; [b] data is missing in 57 (27.1%) cases.

Values in parentheses are % unless stated otherwise. BMI = body mass index; IQR = interquartile range; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years and sex category (female, unless < 65 years and no other risk factors); TIA = transient ischemic attack; TTE = transthoracic echocardiography; EF = ejection fraction; LVMI = left ventricular mass indexed to body surface area; LVEDD = left ventricular end-diastolic dimension; LA = left atrium; LAVI = left atrial volume index; TnT = Troponin T; ProBNP = Prohormone of brain natriuretic peptide.

After a median follow-up of 46 [IQR 27] months, a total of 33/169 (19.5%) patients were diagnosed with a new-onset AF corresponding with the incidence rate of 69.9 cases per 1000 person-years. The median time to AF diagnosis after study recruitment was 11 [IQR 26] months. The baseline characteristics of patients with and without new-onset AF are depicted in Table 2. At the time of AF diagnosis 11 patients were undergoing hemodialysis, 8 were undergoing peritoneal dialysis, 2 had received a kidney transplant and 12 were not undergoing renal replacement therapy (RRT), respectively. The patients who developed AF after initiation of dialysis or after kidney transplantation received the diagnosis of AF after median 8 [IQR 28] months since the onset of dialysis. Conversely, RRT was initiated median 0.5 [IQR 4.5] months after the diagnosis of AF in the patients who developed new-onset AF before dialysis. Two patients with new-onset AF did not receive RRT during the study.

Altogether, 26 new-onset AF episodes were detected during hospital visits and 7 cases were detected in an outpatient setting (Table 3). The most common triggering conditions for AF were infection 11/33 (33.3%), major surgery 5/33 (15.2%) and congestive heart failure 4/33 (12.1%), respectively.

Table 2
Baseline characteristics of patients according to incidence of new-onset AF during follow-up.

	No AF (N = 136)	Incident AF (N = 33)	p
Age mean (median) years	58 (60)	66 (68)	0.01
Age ≥60 years	70 (51.5)	26 (78.8)	0.01
Female	50 (36.8)	6 (18.2)	0.06
BMI median (IQR) kg/m^2	27.2 (5.8)	29.3 (9.4)	0.05
Smoking	64 (47.4)	13 (40.6)	0.71
CHA_2DS_2-VASc-score ≥ 2	114 (83.8)	29 (87.9)	0.79
Hypertension	131 (96.3)	33 (100.0)	0.58
Diabetes	59 (43.4)	15 (45.5)	0.85
Coronary artery disease	14 (10.3)	6 (18.2)	0.23
Prior myocardial infarction	11 (8.1)	4 (12.1)	0.50
History of heart failure	18 (13.2)	8 (24.2)	0.16
Peripheral artery disease	16 (11.8)	11 (33.3)	0.01
Pulmonary embolism	3 (2.2)	2 (6.1)	0.25
Prior stroke	9 (6.6)	7 (21.2)	0.02
Prior TIA	4 (2.9)	3 (9.1)	0.14
Cirrhosis	0 (0.0)	1 (3.0)	0.20
Prior gastrointestinal bleeding	22 (16.2)	7 (21.2)	0.45
TTE			
EF mean (median) %	65 (65)	65 (66)	0.21

[a] data is missing in 29 (17.2%) cases; [b] data is missing in 44 (26.0%) cases, [c] data is missing in 49 (29.0%) cases.

Values in parentheses are % unless stated otherwise. IQR = interquartile range; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years and sex category (female, unless < 65 years and no other risk factors); TIA = transient ischemic attack; TTE = transthoracic echocardiography; EF = ejection fraction; LVMI = left ventricular mass indexed to body surface area; LVEDD = left ventricular end-diastolic diameter; LA = left atrium; LAVI = left atrial volume index; SD = standard deviation; CRP = C-reactive protein; BUN = Blood urea nitrogen; eGFR = estimated glomerular filtration rate; HbA1c = Glycated hemoglobin A1c; TnT = Troponin T; ProBNP = Prohormone of brain natriuretic peptide; HDL = high density lipoprotein; LDL = low density lipoprotein.

	No AF (N = 136)	Incident AF (N = 33)	p
LVMI mean (median) g/m^2	106 (102)	117 (115)	0.03
LVEDD mean (median) mm	54 (53)	55 (56)	0.33
LA diameter mean (median) mm[a]	40 (39)	44 (42)	0.01
LAVI mean (median) ml/m^2 [b]	33.6 (31.9)	42.7 (40.3)	0.01
Laboratory tests			
Hemoglobin mean (SD) g/l	114 (12)	113 (12)	0.61
CRP median (IQR) mg/l	2 (3)	3 (5)	0.09
Creatinine median (IQR) umol/l	402 (151)	420 (132)	0.57
BUN median (IQR) mmol/l	22 (8)	23 (11)	0.63
eGFR median (IQR) ml/min/1,73 m^2	12.8 (5)	12.2 (4)	0.22
Urine volume mean (SD) ml[c]	2514 (848)	2322 (813)	0.34
HbA1c median (IQR) %	5.6 (1.5)	5.4 (1.3)	0.43
TnT median (IQR) ng/l	29 (32)	54 (62)	0.01
ProBNP median (IQR) ng/l	809 (1632)	1650 (5050)	0.03
Total cholesterol median (IQR) mmol/l	4.5 (1.3)	4.0 (1.7)	0.05
HDL median (IQR) mmol/l	1.2 (0.6)	1.0 (0.4)	0.01
LDL median (IQR) mmol/l	2.4 (1.2)	2.1 (1.5)	0.18
Triglycerides median (IQR) mmol/l	1.5 (0.8)	1.6 (1.2)	0.90

[a] data is missing in 29 (17.2%) cases; [b] data is missing in 44 (26.0%) cases, [c] data is missing in 49 (29.0%) cases.

Values in parentheses are % unless stated otherwise. IQR = interquartile range; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years and sex category (female, unless < 65 years and no other risk factors); TIA = transient ischemic attack; TTE = transthoracic echocardiography; EF = ejection fraction; LVMI = left ventricular mass indexed to body surface area; LVEDD = left ventricular end-diastolic diameter; LA = left atrium; LAVI = left atrial volume index; SD = standard deviation; CRP = C-reactive protein; BUN = Blood urea nitrogen; eGFR = estimated glomerular filtration rate; HbA1c = Glycated hemoglobin A1c; TnT = Troponin T; ProBNP = Prohormone of brain natriuretic peptide; HDL = high density lipoprotein; LDL = low density lipoprotein.

Table 3
Predisposing circumstances at the time of detection of the new-onset AF episodes.

New-onset AF cases	Trigger	Care	Other
11	Infection	Admitted	
5	Operation	Admitted	2 CABGs, 1 TAVI, 1 laparotomy, 1 AV fistula
4	CHF	Admitted	
2	Initiation of HD	Admitted	1 case of uremic pericarditis
4	Unknown	Admitted	1 case of stroke, 1 case of amaurosis fugax, 1 case of acute vertigo, 1 case of pemfigoid
4	Unknown	Outpatient	Asymptomatic episodes of AF
3	Unknown	Outpatient	Symptomatic episodes of lone AF + ED contact

CABG = coronary artery bypass grafting; TAVI = transcatheter aortic valve implantation; AV fistula = arteriovenous fistula; CHF = congestive heart failure; HD = hemodialysis; AF = atrial fibrillation; ED = emergency department.

Associations with occurrence of AF

Older age, higher body mass index (BMI), history of peripheral artery disease, prior stroke, higher left ventricular mass index (LVMI), higher interventricular septal and left ventricular posterior wall thickness, increased LAVI, elevated troponin T (TnT) and lower total cholesterol and high density lipoprotein levels were associated with the incidence of AF within follow-up in the univariate model. In a Cox proportional hazard model age > 60 years (HR 4.27, CI95% 1.57–11.64, $p < 0.01$), elevated TnT > 50 ng/l (HR 3.61, CI95% 1.55–8.37, $p < 0.01$) and LAVI > 30 ml/m^2 (HR 4.82, CI95% 1.11-21.00, $p = 0.04$) independently predicted new-onset AF (Figs. 1 and 2). The predictive effect of TnT and LAVI was additive as depicted in Fig. 3.

Discussion

The present study demonstrated a high prevalence and incidence of AF in patients with CKD stage 4–5. By the end of the follow-up period a third of the patients had been diagnosed with AF. Older age, elevated TnT and increased LAVI assessed from transthoracic echocardiography independently predicted the occurrence of new-onset AF in the study patients.

Our study demonstrated for the first time the association between AF incidence and elevated TnT or increased LAVI in patients with CKD stage 4–5. While older age and greater left atrial diameter have been linked to AF incidence in CKD patients in previous studies, there are no prior data on the association between TnT or LAVI and AF incidence in patients with CKD stage 4–5 (9). Reasons for higher troponin

levels in new-onset AF patients remain unknown. However, these findings have important clinical implications in AF prediction in the CKD population. In fact, our results suggest that almost every other CKD stage 4–5 patient with TnT > 50 ng/l and LAVI > 30 ml/m^2 was at risk for developing new-onset AF within 4 years, and the risk among patients aged over 60 years was even higher (~ 60%). Conversely, only 3% of patients with new-onset AF had TnT ≤ 50 ng/l and LAVI ≤ 30 ml/m^2 (Fig. 3).

The association between elevated high-sensitivity troponin and incidence of new-onset AF in CKD patients was explored in a recent study but the cohort comprised patients with only mild to moderate CKD (11). Nevertheless, elevated TnT and increased LAVI are common findings in CKD patients and associated with the risk of left ventricular hypertrophy and heart failure – predictors of AF themselves (12–15). Thus, measurement of TnT and LAVI especially in elderly CKD patients might be reasonable in predicting AF.

Nearly one fifth of the study patients had a prior diagnosis of AF and this was in line with previous reports on CKD patients (7, 8). Older age and dilatation of the left atrium were associated with the history of AF in our study and have consistently predicted AF prevalence in CKD patients irrespective of dialysis treatment in previous studies. Other consistent predictors for positive AF history have been congestive heart failure and male sex (7, 8, 16).

The incidence rate of AF was remarkably high in our study compared to previous studies – even those on dialysis patients. This might be partly explained by the high prevalence of hypertension in our study compared to previous reports (5, 9, 12). Furthermore, two thirds of the patients with new-onset AF were receiving RRT at the time of AF detection. In fact, hemodialysis procedure itself has been identified as a trigger for AF (17). Studies comparing the incidence rate of AF in non-dialysis and dialysis patients with CKD do not exist, but AF incidence has been numerically higher in CKD patients undergoing dialysis (5, 9, 11–13). One previous trial reported a higher incidence rate of AF in dialysis patients compared to healthy controls (13).

Interestingly, most new-onset AF cases were detected during hospital treatment and in two thirds of the patients a predisposing condition was identified (Table 3). The figure is higher compared to previous studies and the most common predisposing condition in our study was infection (33%) while in the study by Lubitz et al most new-onset AFs with a predisposing condition were triggered by surgery (50%) (18). These findings are possibly explained by the relative lability of CKD patients due to the high burden of comorbidities and shared risk factors with AF as well as susceptibility to infections, fluid overload and electrolyte imbalance compared to patients without CKD (19–21). These data suggest that CKD patients recovering from a major surgery or suffering from an acute infection might benefit from screening of AF.

This study has the limitations of an observational study. The study sample of patients was relatively small and the echocardiography data was partly incomplete. However, the patients were extensively and consistently examined by the same clinicians and the quality of the data is high. Some new-onset AF episodes may have been missed since AF is commonly asymptomatic. Nevertheless, all the study

patients resided in the catchment area of the research hospital and all AF episodes are recorded in the patient registry of the same hospital. Despite these limitations, we believe that these data can benefit clinical practice and guide future research.

Conclusions

The prevalence and incidence of AF was high in our study exploring patients with CKD stage 4–5. Furthermore, elevated TnT and increased LAVI were identified as predictors for new-onset AF in this patient group. Thus, screening for AF in hospitalized CKD patients might be reasonable.

Abbreviations

Atrial fibrillation = AF, chronic kidney disease = CKD, Chronic Arterial Disease, quality of life and mortality in chronic KIDney injury study = CADKID-study, estimated glomerular filtration rate = eGFR, Chronic Kidney Disease Epidemiology Collaboration = CKD-EPI, electrocardiogram = ECG, certified laboratory services of Turku University Hospital = TYKSLAB, left atrial volume index = LAVI, standard deviation = SD, inter-quartile range = IQR, renal replacement therapy = RRT, body mass index = BMI, left ventricular mass index = LVMI, troponin T = TnT, confidence interval = CI

Declarations

Ethics approval and consent to participate

The study received approval of the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. The study adheres to the Declaration of Helsinki. Each patient provided written informed consent for the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

MH, RL, TH, NK, JP, PK, MJJ, KM designed the study and were responsible for the data collection. MJJ and TH performed the statistical analysis. MH and TH drafted the manuscript. TH, NK, JP, PK, TK, KEJA,

MJJ and KM revised the manuscript. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by the Finska Läkaresällskapet and the Perklén Foundation, Helsinki, Finland; the Aarne Koskelo Foundation; and the expert responsibility area (ERVA) of the Tyks Turku University Hospital.

Acknowledgements

Not Applicable

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Figures

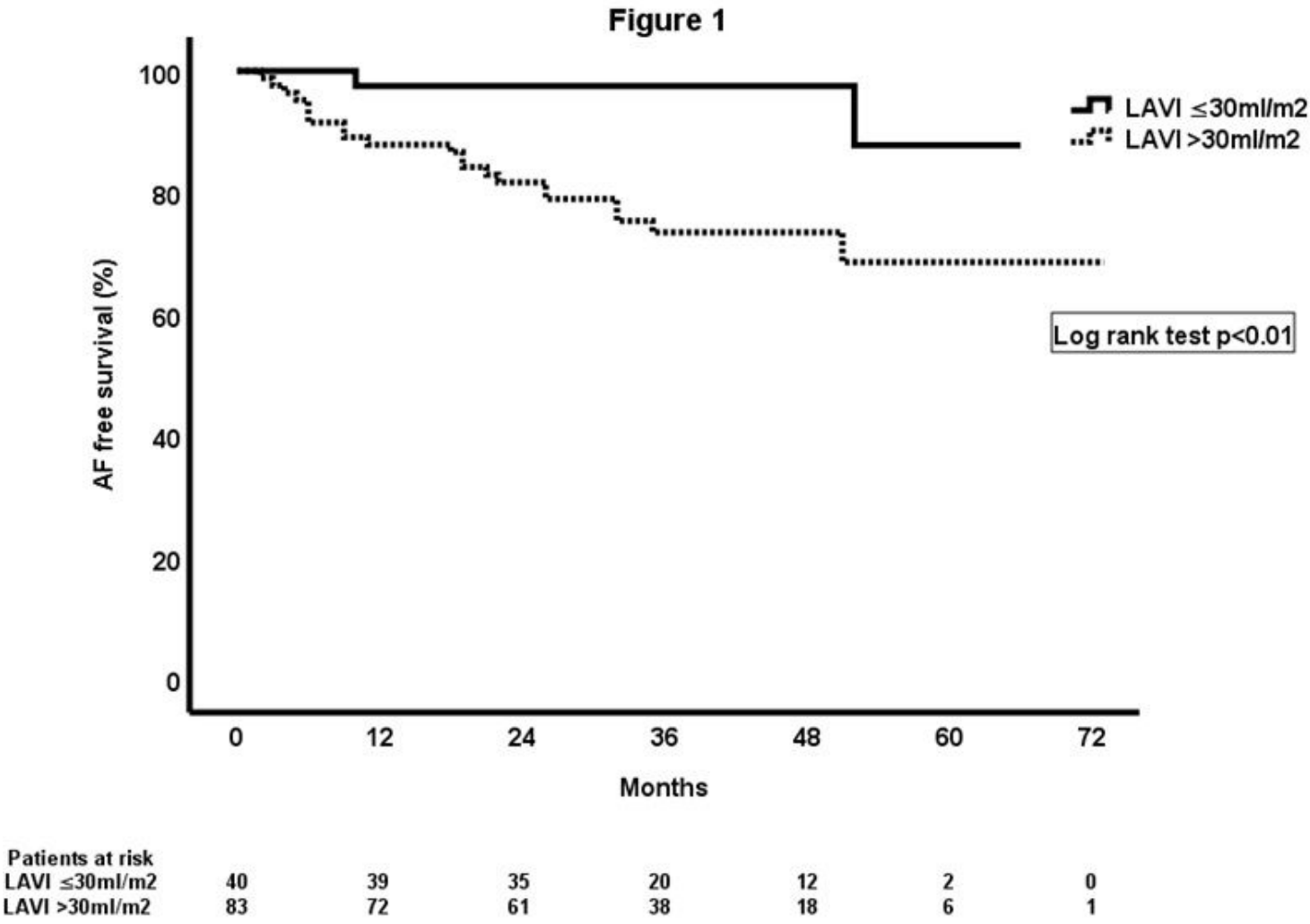

Figure 1

Kaplan-Meier survival curve for AF incidence according to increased LAVI

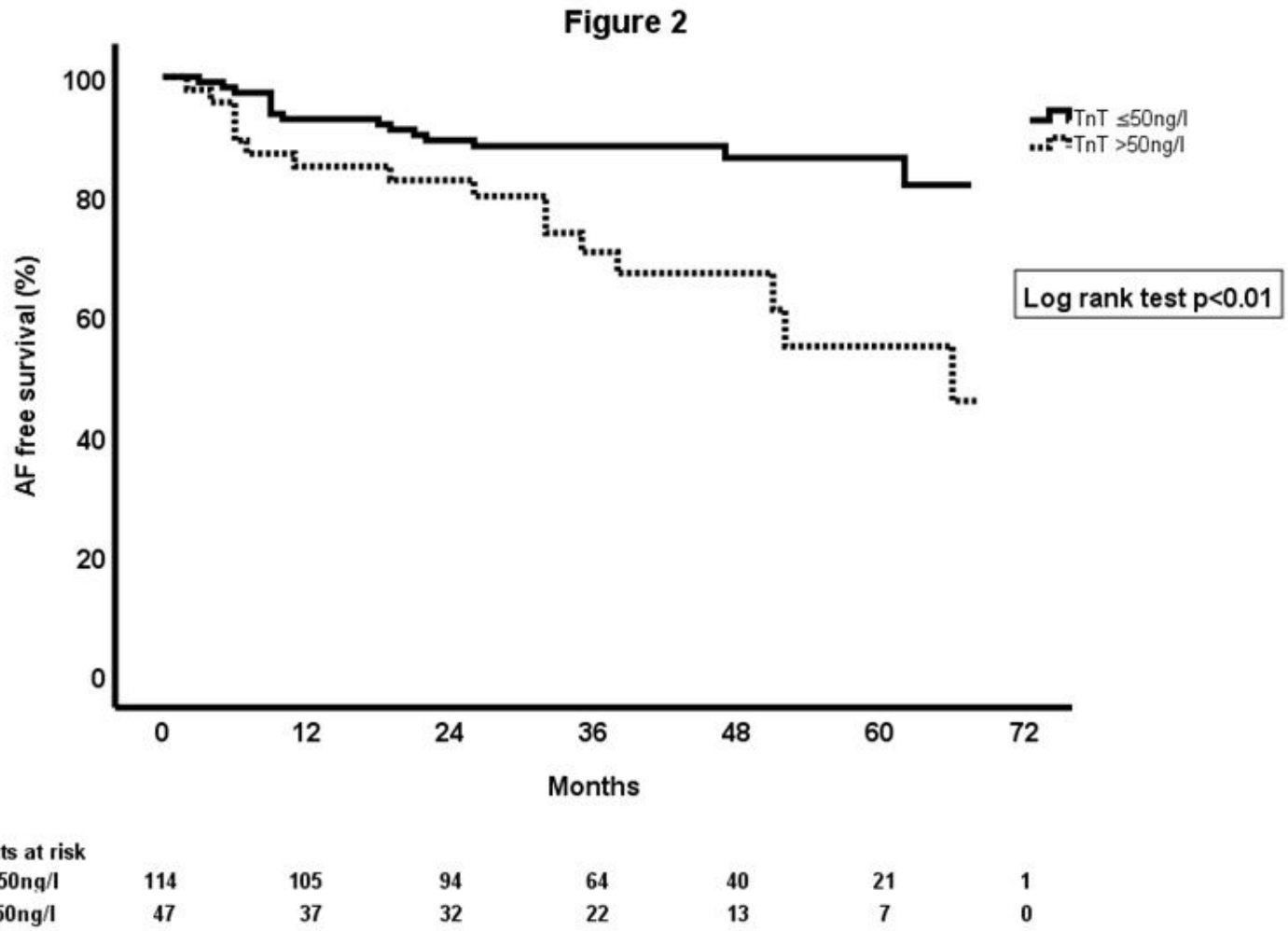

Figure 2

Kaplan-Meier survival curve for AF incidence according to elevated TnT

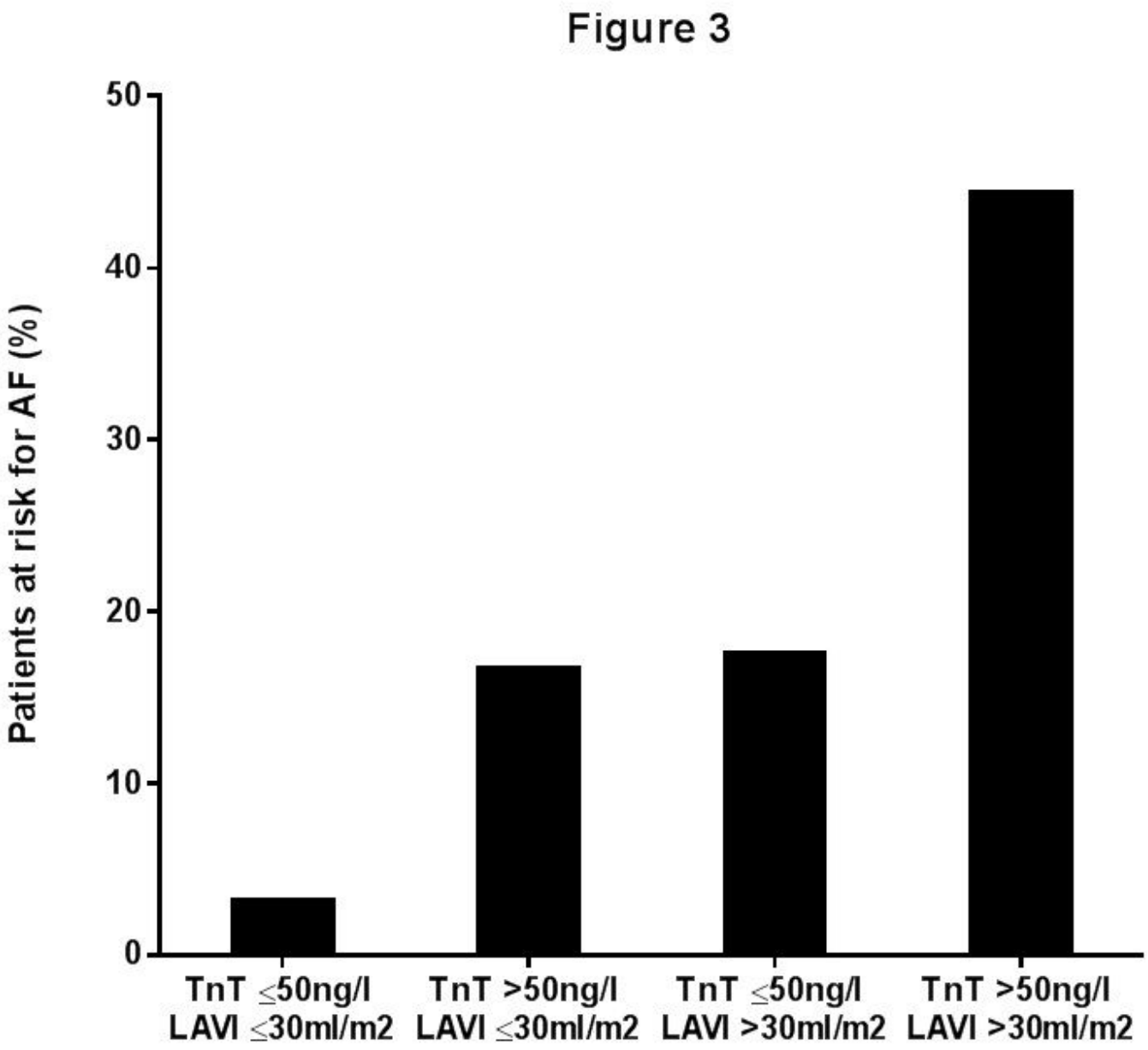

Figure 3

The cumulative effect of TnT and LAVI on the risk of AF among patients with new-onset AF