Supplementary material

Matusik PT, Leśniak WJ, Heleniak Z, et al. Thromboembolism and bleeding in patients with atrial fibrillation and stage 4 chronic kidney disease: impact of biomarkers. Kardiol Pol. 2021.

Statistical analyses

A Pearson correlation coefficient or Spearman's rank correlation coefficient were used to assess the strength of associations between two continuous variables. Qualitative variables are expressed as numbers (percentages) and were compared by Pearson χ^2 test or Fisher's exact test. Optimal cut-off points of biomarkers to predict clinically significant bleeding were based on receiver operating characteristics curves and Youden's index. Bleeding-free survival analysis according to different biomarkers levels was compared using Kaplan-Meier curves and log-rank (Mantel-Cox) test. Associations between clinical data, biomarkers and outcomes (death, bleedings and thromboembolism) were also assessed using Cox regression analysis and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Variables which had a *P*-value <0.1 in univariable models were considered for inclusion in multivariable analysis. Backward elimination was used to build final multivariable models.

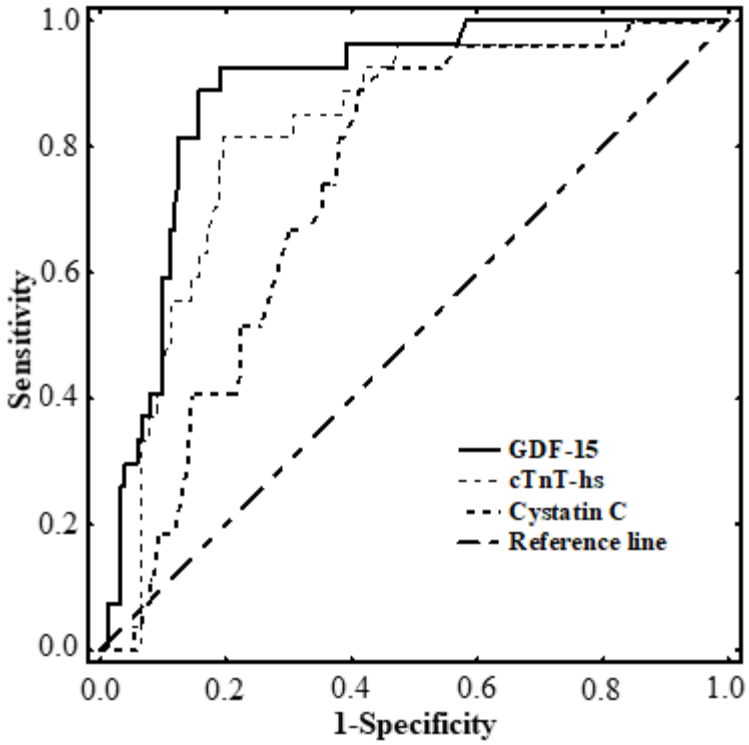

Figure S1. Receiver operating characteristics (ROC) curves of growth differentiation factor-15 (GDF-15), high-sensitivity cardiac troponin T (cTnT-hs) and cystatin C in the prediction of clinically significant bleedings among patients with stage 4 chronic kidney disease and atrial fibrillation

Table S1. Patient characteristics in survivors and non-survivors during follow-up

Variable	Whole group (n = 180)	Survivors (n = 155)	Non-survivors (n = 25)	*P*-value
Demographics				
Age, years	71.0 (64.0–75.0)	71.0 (64.0–75.0)	69.0 (64.0–78.0)	0.79
Male sex, n (%)	117 (65.0)	104 (67.1)	13 (52.0)	0.14
BMI, kg/m^2	27.8 (25.6–31.6)	28.0 (25.6–32.0)	27.0 (25.3–30.0)	0.41
Persistent AF, n (%)	84 (46.7)	75 (48.4)	9 (36.0)	0.25
Permanent AF, n (%)	96 (53.3)	80 (51.6)	16 (64.0)	
CHA_2DS_2-VASc score	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.47
Past bleeding, n (%)	11 (6.1)	10 (6.5)	1 (4.0)	1.0
Comorbidities and CVD risk factors, n (%)				
Hypertension	105 (58.3)	95 (61.3)	10 (40.0)	<0.05
Diabetes mellitus	64 (35.6)	57 (36.8)	7 (28.0)	0.40
Dyslipidemia	134 (74.4)	116 (74.8)	18 (72.0)	0.76
Smoking history	27 (15.0)	24 (15.5)	3 (12.0)	1.0
CAD	83 (46.1)	73 (47.1)	10 (40.0)	0.51
Previous MI	39 (21.7)	35 (22.6)	4 (16.0)	0.46
Heart failure	44 (24.4)	41 (26.5)	3 (12.0)	0.12
COPD	24 (13.3)	23 (14.8)	1 (4.0)	0.21
Cause of death, n (%)				

Cardiovascular death	9 (5.0)	0 (0)	9 (36.0)	—
Non-cardiovascular death	16 (8.9)	0 (0)	16 (64.0)	—
Medications, n (%)				
Beta-blocker	152 (84.4)	131 (84.5)	21 (84.0)	1.0
ACE-I	119 (66.1)	109 (70.3)	10 (40.0)	0.003
ARB	22 (12.2)	17 (11.0)	5 (20.0)	0.20
CCB	38 (21.1)	34 (21.9)	4 (16.0)	0.50
Aspirin	73 (40.6)	65 (41.9)	8 (32.0)	0.35
Clopidogrel	8 (4.4)	7 (4.5)	1 (4.0)	1.0
Statin	125 (69.4)	107 (69.0)	18 (72.0)	0.77
Digoxin	34 (18.9)	31 (20.0)	3 (12.0)	0.42
Amiodarone	28 (15.6)	23 (14.8)	5 (20.0)	0.55
Anticoagulants used during follow-up, n (%)				
NOAC	90 (50.0)	72 (46.5)	18 (72.0)	0.02
Vitamin K antagonist	90 (50.0)	83 (53.5)	7 (28.0)	

Data are presented as median (interquartile range) or number (percentage).

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; n, number; NOAC, non-vitamin K antagonist oral anticoagulant; TE, thromboembolic

Table S2. Laboratory and hemostatic parameters in survivors and non-survivors during follow-up

Variable	**Whole group (n = 180)**	**Survivors (n = 155)**	**Non-survivors (n = 25)**	***P*-value**
eGFR, ml/min/1.73 m^2	24.0 (21.0–25.0)	24.0 (21.0–25.0)	23.0 (21.0–26.0)	0.81
Hemoglobin, g/dl	12.2 (1.3)	12.2 (1.3)	12.2 (1.4)	0.86
Platelets, × 1000/µl	217.5 (189.0–288.0)	216.0 (185.0–292.0)	234.0 (198.0–270.5)	0.58
Cystatin C, mg/l	1.2 (1.0–1.3)	1.2 (1.0–1.3)	1.2 (1.1–1.3)	0.63
hs-CRP, mg/l	2.8 (1.5–4.1)	3.0 (1.7–4.1)	2.0 (1.1–3.9)	0.18
GDF-15, pg/ml	1729.0 (1564.5–2051.8)	1712.0 (1561.0–2005.0)	1810.0 (1635.5–2258.5)	0.29
NT-proBNP, pg/ml	684.0 (399.0–1092.5)	684.0 (399.0–1102.0)	578.0 (408.5–995.5)	0.95
cTnT-hs, ng/l	7.8 (6.1–9.7)	7.9 (6.1–9.8)	7.8 (6.1–9.2)	0.81
Hemostatic parameters				
Fibrinogen, g/l	3.2 (2.4–3.9)	3.2 (2.5–4.1)	2.5 (2.4–3.5)	<0.05
D-dimer, ng/ml	369.5 (240.8–515.3)	376.0 (250.0–538.0)	275.0 (212.0–412.5)	0.06
TAFI: Ag (%)	102.0 (93.0–113.8)	103.0 (94.0–116.0)	99.0 (91.5–104.5)	0.10
PAI-1: Ag, ng/ml	27.4 (8.4)	27.6 (8.5)	26.4 (8.1)	0.51

ETP, nM × min	1672.2 (1510.9–1889.8)	1674.0 (1510.2–1895.0)	1643.9 (1534.0–1788.4)	0.63
K_s, × 10^{-9} cm^2	6.4 (1.0)	6.4 (1.0)	6.6 (0.9)	0.21
CLT, min	105.0 (21.4)	105.2 (20.9)	104.0 (24.9)	0.80

Data are presented as mean (standard deviation) or median (interquartile range).

Abbreviations: Ag, antigen; CLT, clot lysis time; cTnT-hs, high-sensitivity cardiac troponin T; eGFR, estimated glomerular filtration rate; ETP, endogenous thrombin potential; GDF-15, growth differentiation factor-15; hs-CRP, high-sensitivity C-reactive protein; K_s, clot permeability; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin-activatable fibrinolysis inhibitor; other see *Table S1*

Table S3. Cox regression analysis for the occurrence of death in patients with atrial fibrillation and stage 4 chronic kidney disease (Panel A) and after adjustment for age and comorbidities in the final model (Panel B)

Panel A

	Univariable analysis		**Multivariable analysis**	
Predictors of mortality	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Cystatin C, mg/l	3.64 (1.09–12.10)	0.04	3.47 (1.06–11.37)	0.04
GDF-15, per 100 pg/ml	1.11 (1.00–1.23)	<0.05	—	—
Hypertension	0.40 (0.17–0.95)	0.04	0.41 (0.17–0.96)	0.04

Panel B

	Univariable analysis		**Multivariable analysis**	
Predictors of mortality	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Cystatin C, mg/l	3.64 (1.09–12.10)	0.04	3.95 (1.08–14.37)	0.04*
GDF-15, per 100 pg/ml	1.11 (1.00–1.23)	<0.05	—	—
Hypertension	0.40 (0.17–0.95)	0.04	0.44 (0.18–1.04)	0.06*

*Adjusted for age and comorbidities (coronary artery disease, heart failure and diabetes mellitus).

Abbreviations: CI, confidence interval; GDF-15, growth differentiation factor-15; HR, hazard ratio