

Thrombin-Activatable Fibrinolysis Inhibitor in Stable Angina Pectoris

Zakirova M.B.

Republican Specialized Scientific-Practical Center of Hematology, Uzbekistan

Iskandarova Sh.T.

Tashkent State Medical University, Uzbekistan

Received: 30 August 2026; **Accepted:** 25 September 2026; **Published:** 22 October 2026

Abstract: Impairment of endogenous fibrinolysis is considered a component of residual atherothrombotic risk. Data regarding the thrombin-activable fibrinolysis inhibitor (TAFI) in the context of chronic coronary syndromes remain inconsistent. This study aimed to evaluate the levels of TAFI and related hemostatic factors in patients with stable angina, determine their variation across functional classes, and describe the one-year clinical course of a specific subgroup characterized by high TAFI levels.

Elevated levels of TAFI and associated hemostatic factors are linked to a higher functional class of stable angina. These findings support the need for prospective validation of TAFI, utilizing individual patient data, standardized clinical endpoints, and multivariable adjustment.

Keywords: Chronic coronary syndrome; stable angina; TAFI; endogenous fibrinolysis; von Willebrand factor; thrombomodulin; protein C.

Introduction: Chronic coronary syndromes remain a dynamic condition with a persistent risk of ischemic events, despite contemporary antianginal, antiplatelet, and lipid-lowering therapies [1, 2]. Traditional risk assessment relies on clinical characteristics, coronary anatomy, and modifiable factors. At the same time, residual risk is partly linked to a prothrombotic phenotype and an insufficient capacity of the body to lyse forming fibrin clots.

TAFI, also known as procarboxypeptidase U/CPB2, this protein—upon activation by thrombin—removes C-terminal lysine residues from partially degraded fibrin, thereby reducing the binding of plasminogen and tissue plasminogen activator. The net result is a slowing of fibrinolysis [3]. Current evidence supports a link between dense, lysis-resistant fibrin clots and an adverse course of coronary artery disease; however, clinical findings regarding TAFI concentration and activity remain inconsistent [4–8].

In the AtheroGene study, activated TAFI was linked to

cardiovascular mortality in patients with coronary artery disease [7]. In a later study of patients with acute myocardial infarction, high TAFI levels were associated with a greater likelihood of infarction, even after adjusting for other factors [8]. Conversely, in patients with stable, angiographically confirmed coronary artery disease, studies have reported inverse or neutral associations between total TAFI antigen levels and the severity of stenosis [6]. These discrepancies underscore the importance of the type of assay used, the pre-analytical phase, the specific form of TAFI being measured, and the clinical context.

The objective of this study is to evaluate TAFI and related hemostatic factors in patients with stable angina compared to apparently healthy individuals, to determine the gradient of these parameters across functional classes, and to describe the one-year clinical course of a selected subgroup with high TAFI levels.

METHODS

A single-center observational study was conducted

between 2020 and 2022 in the 1st and 2nd Cardiology Departments of the multidisciplinary clinic at the Tashkent Medical Academy. The primary analysis included 120 patients hospitalized with stable angina pectoris (functional classes II–IV): 24 patients in class II, 58 in class III, and 38 in class IV. The control group consisted of 25 apparently healthy individuals with no history of angina or documented risk factors for ischemic heart disease.

The patient group comprised 69 men (57.5%) and 51 women (42.5%), with a mean age of 60.2 ± 0.76 years. The control group included 9 men (36.0%) and 16 women (64.0%); the age of the control group was not

specified in the source. The diagnosis and functional class were confirmed based on the clinical presentation and bicycle ergometry; for some patients in functional class IV, the classification was determined clinically, as they were unable to undergo exercise testing.

Patients with chronic obstructive pulmonary disease, diabetes mellitus, malignant neoplasms, acute or chronic heart failure, liver or kidney disease or insufficiency, as well as life-threatening complex arrhythmias, were excluded. The sequence of enrollment and the number of excluded patients are not specified in the source documentation.

Table 1. Analytical populations and the role of each data subset

Population	n	Use in analysis	Key limitation
Stable angina, CCS class II–IV	120	Comparison with control; analysis by functional class (FC)	No individual-level dataset or multifactorial adjustment
Apparently healthy controls	25	Reference values for four biomarkers	Age not specified; gender distribution varies
Coronary angiography	25	Exploratory association of TAFI with anatomy	Small, selected subgroup; 59 stenoses in 25 patients
High TAFI levels, 1-year follow-up	57	Descriptive clinical outcomes	No control group with normal TAFI levels; no data on loss to follow-up

Note. FC — functional class; TAFI — thrombin-activatable fibrinolysis inhibitor.

Laboratory and instrumental methods

Venous blood was collected into 4 ml vacuum tubes containing EDTA-K3. TAFI levels were measured using the Immunoclone TAFI ELISA assay at the laboratory of Genoteknologiya LLC, under a contract with the Tashkent Medical Academy dated February 2, 2021. Von Willebrand factor, protein C, and thrombomodulin were also measured. The dissertation does not provide the catalog numbers for the assay kits, the measurement ranges, the intra- and inter-assay variability, the time elapsed between blood collection and centrifugation, or the plasma storage conditions; this information is required for the final version of the

article.

Coronary angiography was performed on 25 patients at the Akfa Medline clinic based on clinical indications. The number of affected vessels, as well as the location and severity of stenosis, were evaluated. A total of 59 stenotic lesions were identified in this subgroup: 12 (20.3%) were 60–70% stenotic, 19 (32.2%) were 70–80% stenotic, and 28 (47.5%) were 80–90% stenotic.

The primary cross-sectional endpoint was the TAFI level in patients compared with controls, as well as differences in this level across functional classes II, III, and IV. Secondary endpoints included von Willebrand factor, protein C, thrombomodulin, and exploratory

correlations involving TAFI. For a selected subgroup with high TAFI levels, three outcomes recorded over the course of one year were described: progression of clinical symptoms, unstable angina, and acute myocardial infarction. The criteria for high TAFI levels and the rules for classifying these outcomes require further validation.

Statistical analysis

In the original source, continuous data are presented as $M \pm m$, where m is the standard error of the mean. For independent two-group comparisons, Welch's test with 95% CI of the mean difference was performed. One-way Welch ANOVA was used for the three functional classes; Welch's pairwise tests were adjusted using the Holm method within each indicator family [13, 14]. Wilson's 95% CIs were calculated for proportions. Confidence intervals of correlations were

obtained by Fisher transformation assuming $n=120$ or $n=25$. All recalculations are based on published summary values; Individual-level analyses, distribution testing, missingness handling, and multivariate regression were not possible. Two-sided significance level - 0.05.

RESULTS

Biomaterial was collected, on average, on the $2^{\text{nd}} \pm 0.7$ day of hospitalization, while patients were already receiving treatment. All 120 patients were receiving 75 mg of acetylsalicylic acid and a β -blocker; 82 (68.3%) were receiving an ACE inhibitor, 25 (20.8%) an angiotensin II receptor blocker, 43 (35.8%) a calcium channel blocker, 58 (48.3%) a statin, and 16 (13.3%) nitrates. Thus, the biomarkers reflect the status of an inpatient population that was already undergoing treatment, rather than baseline, untreated levels.

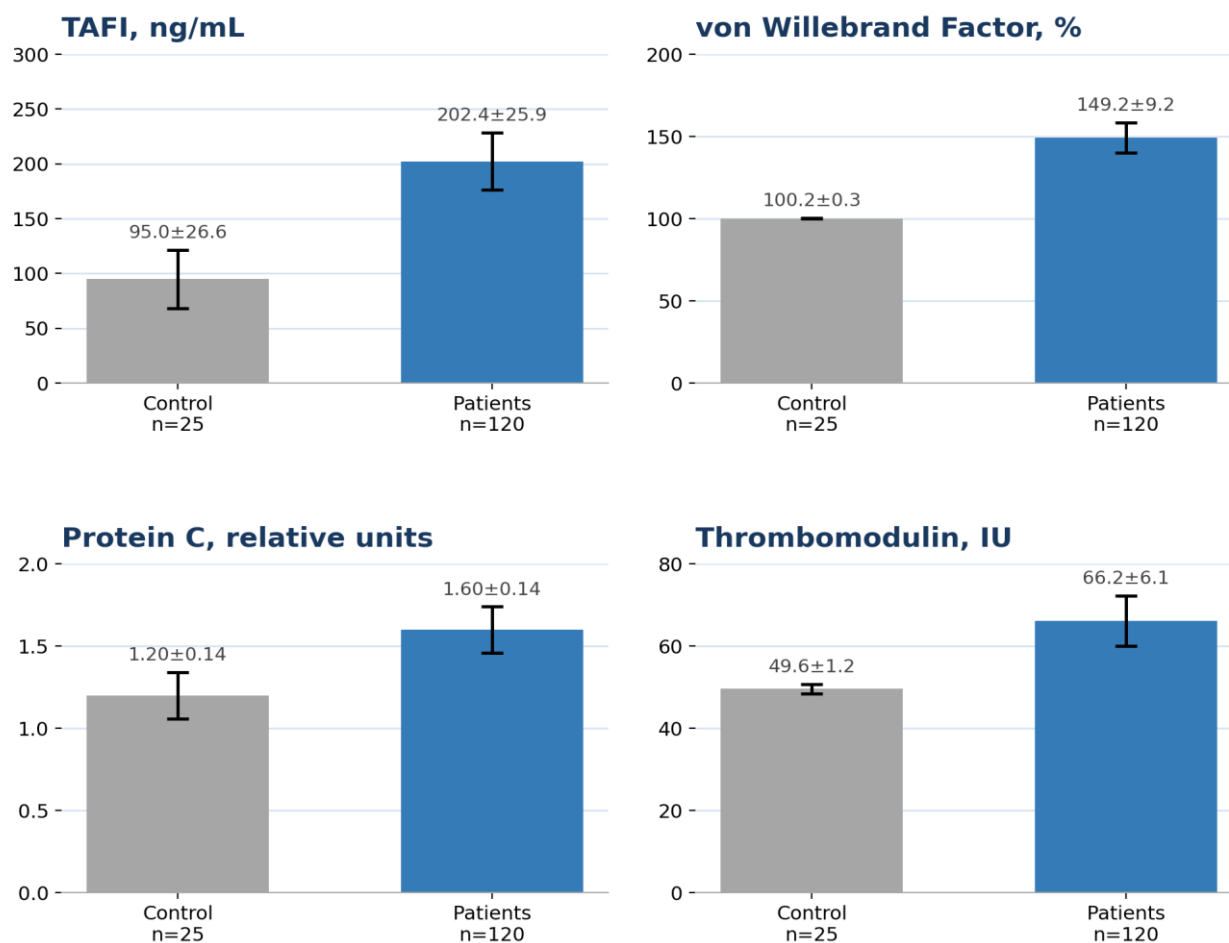
Table 2. Coagulation and fibrinolysis factors in patients and the control group

Indicator	Control n=25	Patients n=120	Difference M (95% DR)	p	p Holm
TAFI, ng/mL	95,00 $\pm$ 26,6 0	202,43 $\pm$ 25,9 0	107,43 (33,50– 181,36)	0,005	0,015
von Willebrand factor, %	100,20 $\pm$ 0,3 0	149,15 $\pm$ 9,20	48,95 (30,72–67,18)	<0,001	<0,001
Protein C, arbitrary units	1,20 $\pm$ 0,14	1,60 $\pm$ 0,14	0,40 (0,01–0,79)	0,047	0,047
Thrombomodulin, IU	49,60 $\pm$ 1,20	66,18 $\pm$ 6,10	16,58 (4,28–28,88)	0,009	0,017

Note. Data are presented as $M \pm m$. The p-value is based on Welch's test, calculated using summary statistics; the Holm-adjusted p-value accounts for four comparisons. The units for protein C are not specified in the thesis.

Figure 1. Profile of TAFI and related hemostatic factors in patients with stable angina and in apparently healthy individuals

Coagulation and Fibrinolysis Factor Profile



Bars — mean; error bars — 95% CI of the mean ($1.96 \times m$). Labels above bars — $M \pm m$.

Note. The whiskers show the 95% CI for the mean, calculated as $M \pm 1.96m$; the numerical labels represent $M \pm m$.

Table 3. Hemostasis biomarkers by functional class of stable angina pectoris

Indicator	II FC n=24	III FC n=58	IV FC n=38	Welch F	p	IV/II
TAFI, ng/ml	106,20±2 1,30	208,70±1 9,60	292,40±14,40	26,55	<0,001	2,75
von Willebrand factor, %	88,85±9,2 0	155,20±9, 00	203,40±9,20	38,71	<0,001	2,29
Protein C, arbitrary units	0,90±0,14	1,80±0,12	2,10±0,14	20,02	<0,001	2,33
Thrombomodulin, IU	34,60±6,1 0	79,30±5,4 0	84,60±6,20	20,52	<0,001	2,45

Note. Data are presented as $M \pm m$; IV/II represents the ratio of the means. Global test: Welch ANOVA based on aggregated data.

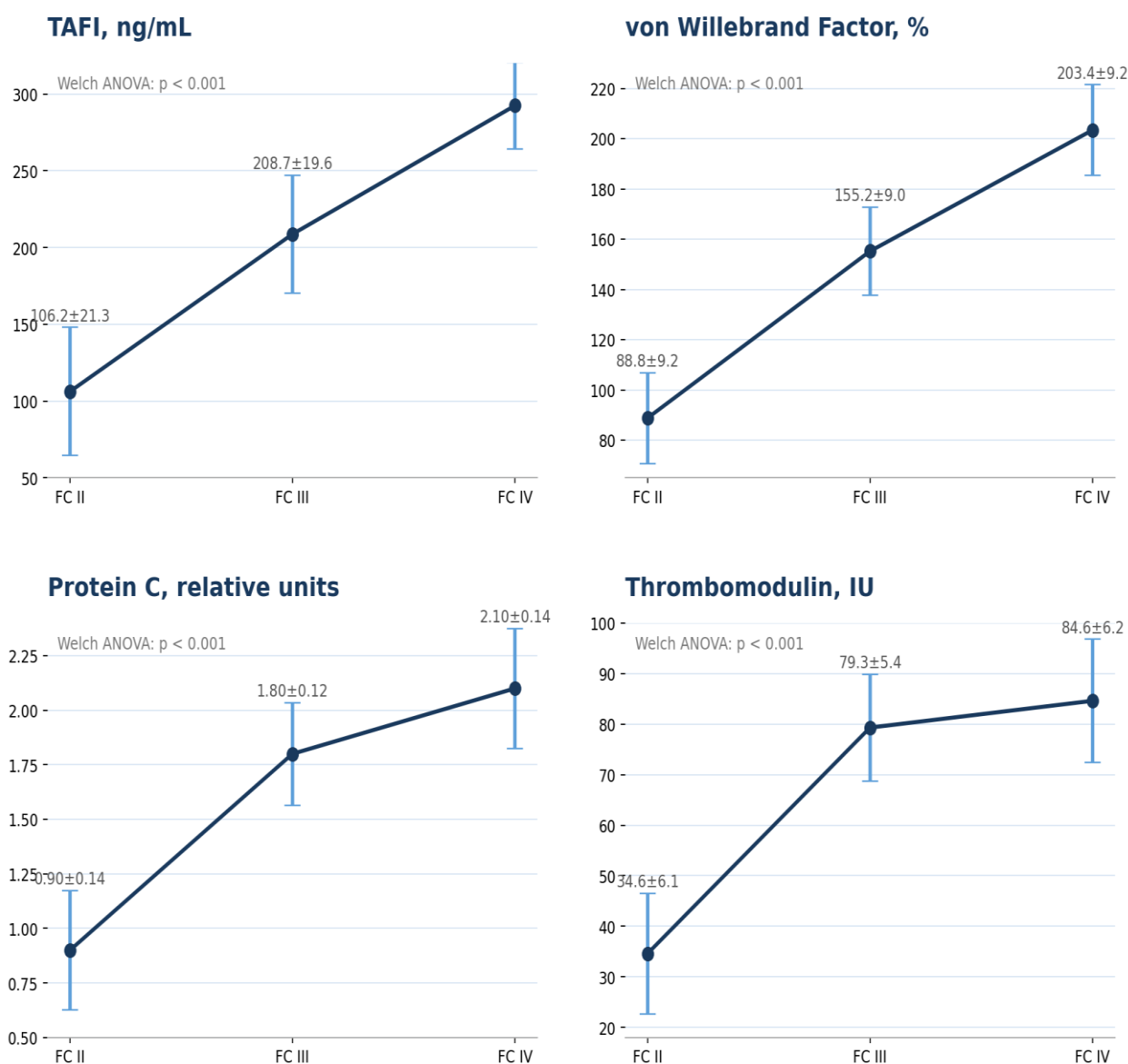
For TAFI, all three pairwise contrasts remained significant after the Holm correction: functional class (FC) II vs. III ($p=0.002$), FC II vs. IV ($p<0.001$), and FC III vs. IV ($p=0.002$). The difference between FC IV and FC II was 186.2 ng/mL (95% CI 134.36–238.04), with a ratio of means of 2.75.

Von Willebrand factor also showed a consistent increase across all pairwise comparisons (all Holm-

adjusted p -values <0.001). For protein C and thrombomodulin, the increase was most pronounced between FC II and the subsequent classes; differences between FC III and IV did not reach significance after correction ($p=0.108$ and $p=0.521$, respectively). This suggests a more linear gradient for TAFI and von Willebrand factor, in contrast to a potential plateau for protein C and thrombomodulin beyond FC III.

Figure 2. Gradient of TAFI, von Willebrand factor, protein C, and thrombomodulin across functional classes II–IV

Biomarker Gradient Across Functional Classes



Points = mean; error bars = 95% confidence interval of the mean ($1.96 \times m$). Overall p -values calculated from pooled $M \pm m$.

Note. Points represent means; whiskers represent 95% CIs for the mean. The p -value refers to the global Welch ANOVA.

Table 4. Exploratory correlations for TAFI in the main group (n=120)

Indicator	r	95% DR	p Holma
Protein C	0,82	0,75–0,87	<0,001
Hypercholesterolemia	0,73	0,63–0,80	<0,001
Obesity	0,71	0,61–0,79	<0,001
Physical inactivity	0,68	0,57–0,77	<0,001
Thrombomodulin	0,60	0,47–0,70	<0,001
HADS symptoms	0,52	0,38–0,64	<0,001
Von Willebrand factor	0,32	0,15–0,47	<0,001
Smoking	0,28	0,11–0,44	0,002

Note: The r-values are taken from the dissertation; 95% CIs and Holm-adjusted p-values were calculated assuming Pearson's correlation coefficient and a total sample size of n=120. The correlation method and the number of observations for each specific metric should be verified against the original dataset; these results should be considered exploratory.

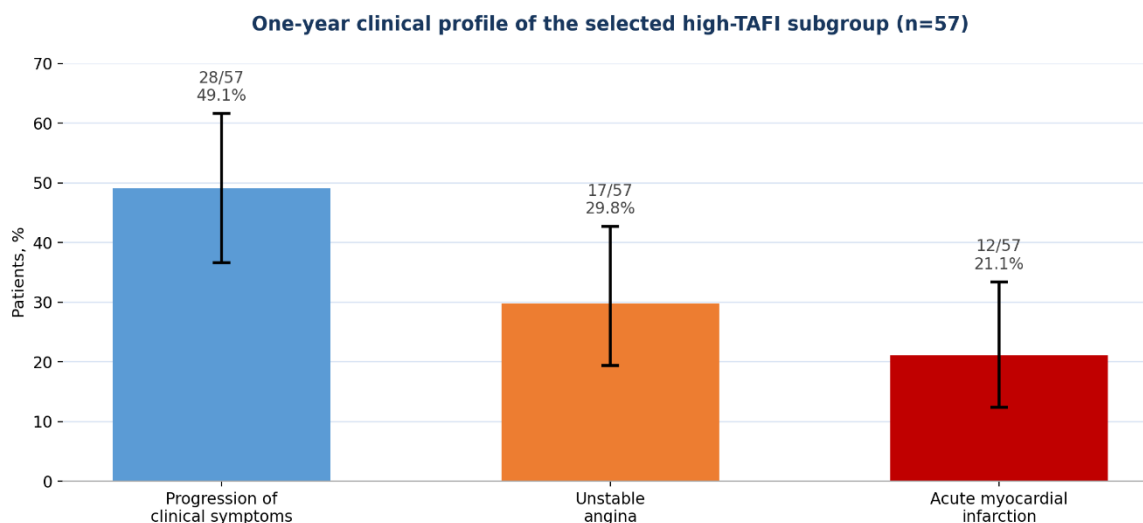
The strongest associations with TAFI were observed for protein C ($r=0.82$), followed by hypercholesterolemia ($r=0.73$) and obesity ($r=0.71$). Associations with von Willebrand factor and smoking were weaker. As the source does not provide scatter plots, data distributions, information on missing values, or the specific type of correlation coefficient used, these estimates cannot serve as a basis for causal interpretation or the establishment of clinical thresholds.

Coronary Anatomy and One-Year Follow-up

Among 25 patients who underwent coronary angiography, single-vessel disease was identified in 4 (16%), two-vessel disease in 8 (32%), and three-vessel (or more) disease in 13 (52%). Of the 59 documented stenoses, the most frequently affected vessel was the left anterior descending artery ($n=27$; 45.7%), followed by the right coronary artery ($n=19$; 32.3%) and the left

coronary artery ($n=13$; 22.0%). The dissertation reports strong correlations between TAFI levels and three-vessel (or more) disease ($r=0.86$), involvement of the left anterior descending artery ($r=0.91$), and 80–90% stenosis ($r=0.76$). Given the small sample size ($n=25$), the presence of multiple stenoses in individual patients, and the lack of a detailed statistical model, these associations should be viewed solely as hypothesis-generating.

Over the course of one year, 57 patients—selected on the basis of high TAFI levels—were re-evaluated. Symptom progression was observed in 28 patients (49.1%; 95% CI 36.6–61.7%), unstable angina in 17 (29.8%; 95% CI 19.5–42.7%), and acute myocardial infarction in 12 (21.1%; 95% CI 12.5–33.3%). These categories sum to 57 and are treated as mutually exclusive; however, this requires verification against primary medical records.

Figure 3. Descriptive clinical outcomes over one year in a selected subgroup with high TAFI levels

Error bars: 95% Wilson confidence intervals. No normal-TAFI comparison group; these data do not establish prognostic value.

Note. In the absence of a parallel group with normal TAFI levels, it is not possible to calculate relative risk, odds ratio, AUC, or independent prognostic value.

DISCUSSION

The study identified two consistent signals. First, in patients with stable angina, mean TAFI levels were approximately 2.1 times higher than in apparently healthy individuals, and this difference remained significant after adjusting for multiple comparisons. Second, TAFI levels showed a consistent gradient across functional classes II–IV, with the increase between each adjacent group remaining statistically significant. Concurrently, levels of von Willebrand factor, protein C, and thrombomodulin also increased—a finding consistent with a complex reorganization of the interplay between coagulation, the endothelium, and fibrinolysis.

The most significant methodological distinction between TAFI and the other two factors was the absence of a plateau between functional classes (FC) III and IV. For protein C and thrombomodulin, this contrast was statistically indeterminate, whereas TAFI levels continued to increase. This pattern suggests that TAFI is a candidate for further investigation as a quantitative marker for the severity of the symptomatic profile; however, it does not confirm that TAFI is independent of age, sex, disease duration, therapy, obesity, or lipid status.

The biological plausibility of this finding is based on the ability of activated TAFI to suppress the positive feedback loop of fibrinolysis [3]. A contemporary review of fibrin clot properties indicates that stable coronary artery disease is often accompanied by

hypofibrinolysis and the formation of a dense fibrin network, with prolonged lysis times being linked to adverse outcomes [4]. In a sub-study of the PLATO trial, clot resistance to lysis was an independent predictor of outcomes following an acute coronary syndrome [10], while in the RISK-PPCI study, marked impairment of endogenous fibrinolysis was associated with recurrent events after a myocardial infarction [9]. As these studies assessed the functional phenotype of fibrinolysis rather than TAFI concentration alone, direct comparison is limited. The clinical literature on TAFI is inconsistent. The AtheroGene study linked activated TAFI to cardiovascular mortality in patients with coronary artery disease [7]. In 2022, Zhao et al. demonstrated a dose-dependent association between high serum TAFI levels and acute myocardial infarction; the adjusted odds of an infarction were approximately 2.7 times higher [8]. In contrast, Fernandes et al., in a study of 123 patients evaluated via angiography, found no increase in total TAFI levels in cases of more extensive atherosclerosis, and instead reported lower levels in patients with stenosis $\geq 70\%$ [6].

CONCLUSION

In 120 patients with stable angina, TAFI levels were higher than in 25 apparently healthy individuals: 202.43 ± 25.90 ng/mL versus 95.00 ± 26.60 ng/mL; a difference of 107.43 ng/mL (95% CI 33.50–181.36; Welch's $p=0.005$; Holm's $p=0.015$). Across functional classes (FC), TAFI levels increased progressively: from 106.2 ± 21.3 ng/mL in FC II to 208.7 ± 19.6 ng/mL in FC III, and 292.4 ± 14.4 ng/mL in FC IV (Welch's $F=26.55$;

$p < 0.001$). The contrast between FC IV and FC II was 186.2 ng/mL, with a ratio of means of 2.75.

Von Willebrand factor showed a similar progressive gradient, whereas for protein C and thrombomodulin, the difference between FC III and FC IV was statistically inconclusive. In a subgroup of 57 patients with high TAFI levels, the one-year follow-up revealed symptom progression in 49.1%, unstable angina in 29.8%, and myocardial infarction in 21.1%; in the absence of a comparison group, these findings remain descriptive.

TAFI may be considered a candidate marker for the severity of impaired endogenous fibrinolysis and the functional severity of stable angina. Before clinical application, standardization of the assay, multivariate analysis of individual-level data, independent prospective validation, and an assessment of incremental prognostic value are required.

REFERENCES

1. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45(36):3415–3537. doi: 10.1093/eurheartj/ehae177
2. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease. *Circulation*. 2023;148:e9–e119. doi: 10.1161/CIR.0000000000001168
3. Sillen M, Declerck PJ. Thrombin Activatable Fibrinolysis Inhibitor (TAFI): An Updated Narrative Review. *Int J Mol Sci*. 2021;22(7):3670. doi: 10.3390/ijms22073670
4. Ząbczyk M, Ariëns RAS, Undas A. Fibrin clot properties in cardiovascular disease: from basic mechanisms to clinical practice. *Cardiovasc Res*. 2023;119(1):94–111. doi: 10.1093/cvr/cvad017
5. Schroeder V, Chatterjee T, Mehta H, et al. Thrombin activatable fibrinolysis inhibitor (TAFI) levels in patients with coronary artery disease investigated by angiography. *Thromb Haemost*. 2002;88(6):1020–1025. doi: 10.1055/s-0037-1613349
6. Fernandes AB, Lima LM, Sousa MO, et al. Impaired fibrinolysis in angiographically documented coronary artery disease. *Adv Hematol*. 2015;2015:214680. doi: 10.1155/2015/214680
7. Tregouet DA, Schnabel R, Alessi MC, et al. Activated TAFI levels are associated with cardiovascular death in coronary artery disease: the AtheroGene study. *J Thromb Haemost*. 2009;7(1):49–57. doi: 10.1111/j.1538-7836.2008.03221.x
8. Zhao M, Zhao D, Li Y, et al. A Case-Control Study of the Dose-Response Relationship Between TAFI and Acute Myocardial Infarction. *Front Cardiovasc Med*. 2022;9:823381. doi: 10.3389/fcvm.2022.823381
9. Farag M, Spinhakis N, Gue YX, et al. Impaired endogenous fibrinolysis in STEMI patients undergoing primary PCI predicts recurrent cardiovascular events: the RISK PPCI study. *Eur Heart J*. 2019;40(3):295–305. doi: 10.1093/eurheartj/ehy656
10. Sumaya W, Wallentin L, James SK, et al. Fibrin clot properties independently predict adverse clinical outcome following acute coronary syndrome: a PLATO substudy. *Eur Heart J*. 2018;39(13):1078–1085. doi: 10.1093/eurheartj/ehy013
11. Kraler S, Liberale L, Tirandi A, et al. The junctional protein associated with coronary artery disease predicts adverse cardiovascular events in patients with acute coronary syndromes at high residual risk. *Eur Heart J*. 2026;47(28):3693–3707. doi: 10.1093/eurheartj/ehaf979
12. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. *Lancet*. 2007;370(9596):1453–1457. doi: 10.1016/S0140-6736(07)61602-X
13. Welch BL. On the comparison of several mean values: an alternative approach. *Biometrika*. 1951;38(3–4):330–336. doi: 10.1093/biomet/38.3-4.330
14. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6(2):65–70.
15. Muborakkhon Zokirova, Kayumov Abdurakhman, Nargiza Nurillaeva and Jakhongir Khaydarov An Integrated Model of Cardiotoxicity: Interaction of Age, Sex, and Genetic Polymorphisms in Patients with Acute Leukemia. *Biomedicines* 2026, 14(9), 1929; <https://doi.org/10.3390/biomedicines14091929> (registering DOI) - 28 Aug 2026