

Measurement of Fibrin Degradation Products (FDPs) among Patients with Cardiovascular Diseases: A significant Target for Prognosis

Alaa Eltayeb Omer, Abdel Rahim Mahmoud Muddathir, Lienda Bashier Eltayeb*

Received: 07 July 2021 / Received in revised form: 28 October 2021, Accepted: 02 November 2021, Published online: 12 December 2021

Abstract

Fibrin degradation products have gained increasing interest. It is regarded as a crucial marker for the turnover of cross-linked fibrin and activation of the hemostatic system, specifically in cardiovascular diseases. So the current study aimed to measure the fibrin degradation products and other possible hazards in Sudanese patients with Acute Coronary Syndrome. A descriptive case-control study among 60 healthy controls with no history of heart disease, 60 with Myocardial Infarction (MI), 60 patients with Unstable Angina (UA), and 120 patients with Acute Coronary Syndrome. Venous blood samples were obtained from all participants on admission and gathered in Trisodium citrate depleted tubes. FDPs were measured by FDPs latex agglutination test. Results: A total of 180 participants aged from (30–70) years old, mean 49 ± 8.93 SD, there were no statistically significant differences considering gender and age among patients and control group. The FDPs were significantly higher in patients with ACS compared to a healthy population, FDPs were positive in 80 patients (67%). The mean \pm SD of FDPs was significant among MI and UA consequently. There was a significant correlation between FDPs with hypertension, hyper-lipidaemia, diabetes mellitus, and family history for myocardial infarction and unstable angina. Conclusion: Elevated FDPs levels were revealed among Sudanese patients with Acute Coronary Syndrome (ACS), which may be a prognostic marker for thrombotic tendency. As a consequence, FDPs must be included in regular laboratory investigations, as well as the ACS monitoring strategy.

Keywords: Acute coronary syndrome, Myocardial infarction, FDPs, Hemostatic

Introduction

Cardiovascular disease is still the major cause of death worldwide (Al-Shali *et al.*, 2019; Mathew *et al.*, 2019). Acute Coronary Syndromes (ACS) are caused by the puncture of an

Alaa Eltayeb Omer, Lienda Bashier Eltayeb*

Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University-Al-Kharj, Riyadh, KSA.

Abdel Rahim Mahmoud Muddathir

Department of Clinical Laboratory Sciences, Taibah University, KSA.

*E-mail: Lindarose009@hotmail.com

underprivileged atherosclerotic plaque, which sets off a sequence of reactions that ultimately result in thrombus formation, platelet aggregation, and initiation of the coagulation pathway at the coronary obstruction area (Buljubasic *et al.*, 2017). ACS generally happens due to any of the following problems: unstable angina (38%), segment (ST) elevation myocardial infarction (30%), or non-ST elevation myocardial infarction (25%) (Medina-Leyte *et al.*, 2021).

Biomarkers indicating numerous atherogenesis pathways, including inflammatory response, coagulation, and cell stress, have been indicated to improve risk discriminatory behavior for consequence occurrences of coronary heart disease (Eapen *et al.*, 2013).

Fibrinogen and Fibrin Degradation Products (FDP) are thrombin breakdown byproducts, and enhanced circulating levels may indicate sub-clinical vascular thrombosis. Serum FDP levels are linked to coronary artery disease (CAD) (Moreira *et al.*, 2015; Ząbczyk *et al.*, 2021). Cardiac chest pain can also be precipitated by bradycardias (excessively slow heart rate), tachycardias (excessively fast heart rate), or anemia. ACS shows a life-threatening manifestation of atherosclerosis. It is commonly accelerated by severe thrombosis resulted by a ruptured atherosclerotic coronary plaque, with or without concomitant vasoconstriction, resulting in an immediate and critical decrease in blood flow. Recently, enhancements in the plasma concentration of soluble fibrin have been suggested to be sensitive in ACS, specifically for Myocardial Infarction (MI) (Gaule & Ajjan, 2021). A current study aimed to measure the fibrin degradation products and other possible risk factors in Sudanese patients with cardiovascular disease.

Materials and Methods

A descriptive case-control hospital-based research was carried out in Ahmed Gassim Hospital in Khartoum state in Sudan. The study was conducted between September 2013 to February 2014. Patients satisfied with the diagnostic criteria of Acute Coronary Syndromes were included in the first group. Patients receiving anticoagulant therapy, such as warfarin, which can induce fibrinolysis, and those with the chronic renal failure, malignancy, hemostatic disorder, and limited venous access were excluded.

Sample Size and Sampling Technique



A total of one hundred and twenty Sudanese subjects who confirmed diagnosis as Acute Coronary Syndrome patients were recruited, and 60 matched the healthy control group without Acute Coronary Syndrome. Samples were collected using non-probability sampling methods.

Sample Collection

A 2.5 ml venous blood sample was drawn from all patients after admission before initiation of treatment. For blood collection, evacuated Tri sodium citrate tubes were used, and all specimen were processed within 6 hours after blood collection, using the FDPs agglutination test (qualitative and semi-quantitative).

Qualitative Method

A 20 µl from Platelets Poor Plasma (PPP) was placed on a test card with positive and negative control in different circles. After that, one drop from FDPs latex was added and mixed with stirrers until the latex was consistently disseminated. The test card was rocked gently by hand for exactly three minutes then agglutination under a strong light source was recorded.

Semi-quantitative Method

For each positive result on a qualitative method, we performed a semi-quantitative method. Serial solutions of test plasma with buffer were prepared as follow: 1:2 dilution 100 µl plasma plus 100 µl buffer solution, 1:4 dilution 100 µl from p1:2 dilution plasma plus 100 µl buffer solution, 1:8 dilution 100 µl from p1:4 dilution plasma plus 100 µl buffer solution, all dilution displayed in **Table 1**.

Statistical Analysis

The SPSS version 19 for Windows was used for data analysis. Cross tabulation tests were applied for comparing the three groups, the calculated p-value of 0.05 was considered significant.

Table 1. Levels of XL-FDPs in Semi-quantitative Method

Approximate range (FDPs) mg/dl (ng/ml)	Sample dilution			
	Undiluted	1:2	1:4	1:8
<0.20 (<200)	-	-	-	-
0.20-0.40 (200-400)	+	-	-	-
0.40-0.80 (400-800)	+	+	-	-
0.80-1.60 (800-1600)	+	+	+	-
1.60-3.20 (1600-3200)	+	+	+	+

(+) = agglutination (-) = no agglutination

The level of XL-FDPs greater than 3.20 mg/l (3200 ng/ml) can be estimated by further dilutions beyond 1:8.

Results and Discussion

One hundred and twenty Sudanese patients with Acute Coronary Syndrome and sixty healthy control subjects enrolled to estimate

Fibrin Degradation Products (FDPs). Among patients, 60 (50%) had a Myocardial Infarction, and others had unstable angina. In the patients' group, the majority of them with MI (60%) were male, where females were more prevalent (41.1%) among UA group, their age ranged from (30–70) years-old, mean 49 ± 8.93 SD. There were no statistically significant differences regarding age and gender among patients and the control group (P-value ≥ 0.080 , 0.738, respectively). There was an equal distribution of risk factors within patient's groups, except participants with MI were frequently 30 (50%) suffer from diabetes comparing with AU ($P \leq 0.21$). All data were summarized in **Table 2**.

Table 3 displays the result of the fibrin degradation products (FDPs) significantly higher among people with Acute Coronary Syndrome in comparison to the control (p-value 0.001). The result showed that FDPs were positive in 80 patients (67%) and negative in 40 patients (33%), level of Fdps (1600-3200) was higher 25 (41.7%) among MI, while its level was between (800-1600) was much higher among UA 30 (50%). **Figure 1** shows the Fibrin Degradation Products (FDPs) frequency among control and Acute Coronary Syndrome groups. Also, the result showed that there was an increase in FDPs concentrations among ACS patients with MI (78.3%) compared with UA (55%). The analyzed data showed that was a significant correlation of FDPs between MI and UA

Table 4 summarized the mean levels of Fdps and other study parameters, where the mean \pm SD was (4.08 ± 0.96 and 3.03 ± 0.71) among MI and UA consequently. Moreover, the mean level of smoking increased in UA (1.73 ± 0.446) more than in MI (1.65 ± 0.481).

Regarding the correlation between FDPs and risk factors, the analyzed data showed a significant correlation between fibrin degradation products (FDPs) and hypertension, hyperlipidemia, diabetes mellitus, and family history (P-value 0.001) among myocardial infarction unstable angina, respectively. And there was an insignificance correlation between fibrin degradation products (FDPs) and smoking and alcohol consumption (P-value = 0.117, and 0.571) for myocardial infarction respectively and (P-value = 0.173 and 0.695) for unstable angina, respectively (**Table 5**).

Table 2. Specifications of Research Participants

	MI n=60 (%)	UA n=60 (%)	Control n=60 (%)	P value
Gender				
Male	36 (60%)	29 (48.3%)	41 (68.3%)	0.080
Female	24 (40%)	31 (51.7%)	19 (31.7%)	
Total	60 (100%)	60 (100%)	60 (100%)	
Age				
31-40 years	3 (5%)	6 (10%)	37 (61.7%)	0.738
41-50 years	13 (21.7%)	4 (6.7%)	21 (35%)	
51- 60 years	16 (26.7%)	13 (21.7%)	2 (3.3%)	
61-70 years	28 (46.6%)	34 (56.6%)	0	
Total	60 (100%)	60 (100%)	60 (100%)	
Risk factors				
Hypertension	25 (41.7%)	28 (46.7%)	0	0.542

Diabetic mellitus	30 (50%)	23 (38.3%)	0	0.021
hyperlipidemia	28 (46.7%)	26 (43.3%)	0	0.072
Smoking	21 (35%)	16 (26.7%)	0	0.316
Alcohol consumption	10 (16.7%)	10 (16.7%)	0	0.953
Total	60 (100%)	60 (100%)	0	

* UA=Unstable angina, MI=Myocardial infarction

Table 3. Frequency of FDPs among Study Subjects

FDPs Levels	MI n=60 (%)	UA n=60 (%)	Control n=60 (%)	P value
≤200	0	0	60 (100%)	0.001
200-400	5 (8.3%)	14 (23.3%)	0	
400-800	10 (16.7%)	30 (50%)	0	
800-1600	20 (33.3%)	16 (26.7%)	0	
1600-3200	25 (41.7%)	0	0	
Total	60 (100%)	60 (100%)	0	

Table 4. Mean Level of Study Variables among Cardiovascular Participants

Pattern	MI n=60 Mean ±SD	UA n=60 Mean ±SD	P value
FDPs	4.08±0.96	3.03±0.71	0.052
Hypertension	1.58±0.49	1.53±0.50	0.821
Diabetic Mellitus	1.50±0.50	1.62±0.49	0.074
History of lipid	1.53±0.50	1.57±0.50	0.212
Smoking	1.65 ±0.481	1.73±0.446	0.416
Alcohol	1.83±0.376	1.83±0.376	0.532

Table 5. Correlation between Fibrinogen Degradation Products and Risk Factors among Study Subjects

Characteristics	Fdps levels					P-value
	<200	200-400	400-800	800-1600	1600-3200	
Hypertension						
MI	0	2	5	12	6	0.001
UA	0	7	14	7		0.001
Control	60	0	0	0	0	—
Diabetes mellitus						
MI	0	5	7	7	11	0.001
UA	0	3	14	6	0	0.001
Control	60	0	0	0	0	—
Hyperlipidemia						
MI	0	1	7	9	11	0.001
UA	0	6	12	8	0	0.001
Control	60	0	0	0	0	—
Smoking						
MI	0	3	5	4	9	0.117

UA	0	3	7	6	0	0.173
Control	60	0	0	0	0	—
Family history						
MI	1	0	8	14	16	0.001
UA	8	11	7	10	0	0.001
Control	60	0	0	0	0	—
Alcohol						
MI	0	0	3	3	4	0.571
UA	0	4	3	3	0	0.695
Control	10	0	0	0	0	—

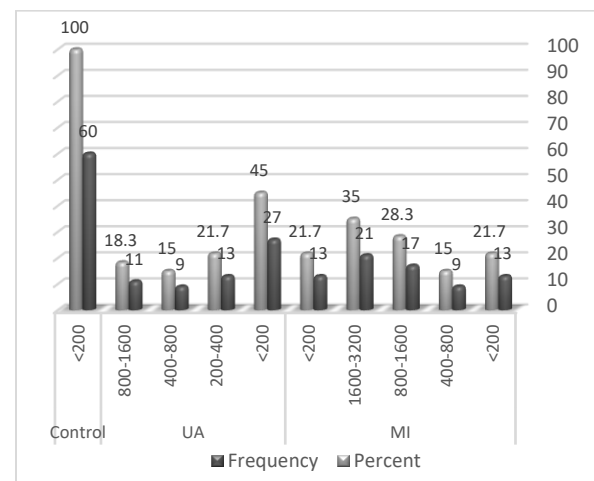


Figure 1. The Frequency of the Fibrin Degradation Products (FDPs) Results among Control and Acute Coronary Syndrome Groups

Screening and accelerated exclusion of Acute Myocardial Infarction (AMI) have often been major concerns to minimize mortality, morbidity, and hospitalization costs while avoiding additional diagnostic and inconsequential measures in reduced risk patients. Fibrinogen has indeed been regarded as an independent potential risk factor. It has been linked to cardiovascular risk, implying that fibrinogen acceleration may be a mechanism by which these risk factors impose their consequence. Thus, an analytical case-control hospital-based study was carried out and aimed to estimate the level of FDPs among Sudanese patients with Acute Coronary Syndrome.

This research revealed a statistically significant ($P\text{-value} \leq 0.001$) elevated concentration of FDPs among about 50% ACS patients in contrast with control subjects, which is alarming critical findings as increased FDPs level is considered a potential biomarker for thrombosis due to their association with a greater incidence of cardiovascular death. Our findings come in contact with a study conducted Undas A *et al.* (2020), who reported a higher concentration of FDPs in ACS patients. Moreover, fibrin degradation products, and D-dimer, which are degradation products of cross-linked fibrin and are frequently used as a

coagulation marker in clinical practice, plays a critical role in the coagulation and coagulation factors system (Danesh *et al.*, 2001).

Recently many researches have revealed that D-dimer (as recommended as a more specific marker for thrombosis) levels are positively correlated to the disease hazard in patients with coronary artery disease. Furthermore, a study revealed that raised D-dimer is a strong independent hazard for cardiac and all-cause mortality in ACS patients (Kikkert *et al.*, 2014; Sarli *et al.*, 2015; Zhao *et al.*, 2020). Accordingly, in patients with no history of cardiovascular disease CVD, elevated FDPs and D-dimer levels were implicated in the development of cardiovascular disease incidents (Wannamethee *et al.*, 2009). As a result, FDPs may be a reliable biomarker for early prediction of ACS in patients with nonobstructive CAD.

We evidenced that elevated mean levels of FDP were a better predictor of myocardial infarction than UA. among myocardial infarction patients more than UA (4.08 ± 0.96 , and 3.03 ± 0.71), respectively. The same conclusion was documented by Eapen DJ (Eapen *et al.*, 2013). Also, Song *et al.* (2020) concluded that the plasma FIB content is a helpful biomarker to anticipate disease in MI subjects.

FIB can be converted into fibrin by thrombin in the coagulation system. The initiation of fibrinolysis increases fibrin degradation products such as D-dimer attributed to major adverse cardiovascular events (Mahmud *et al.*, 2016).

Inflammatory processes are caused by the circulation of FDPs and D Dimer, which cause the release of mediators such as IL-6, the primary procoagulant cytokine. Even though the precise interaction is uncertain, it has been proposed that IL-6 can increase plasma concentrations of both fibrinogen and CRP, thereby amplifying inflammatory and procoagulant reactions (Battes *et al.*, 2014; Held *et al.*, 2017).

Surprisingly, subsequent experimental studies have shown that FDP has a mechanism of action proinflammatory role at the molecular level. It's been proposed that fibrin and its degradation products have a critical role in the inflammatory procedure, specifically by promoting the production of interleukin (IL)-1 and IL-8 and increasing the expression of intracellular adhesion molecule-1 (ICAM-1). Furthermore, the particular proinflammatory involvement of fibrin E-fragments (part of the FDP elongated complement spectrum investigated in the present research) has previously been explained, in which E1-fragments stimulate transmigration of proinflammatory cytokines from the bloodstream to the subendothelial layer by establishing a bridge between monocytes/neutrophils (binding to CD11c/CD18) and the endothelial layer (binding to VE-Cadherin) (Corban *et al.*, 2016; Buljubasic *et al.*, 2017).

Concerning potential risk factors associated with FDPs level in ACS patients, our study noted a significant correlation between ACS (MI and UN) and diabetes, hypertension, as well as family history (P-value 0.001). Such findings are similar to previous studies (Battes *et al.*, 2014; Corban *et al.*, 2016), which reported a

significant correlation between such risk factors and cardiovascular. As they conclude that among the most important advancements in the field of CAD, is the involvement of various risk factors in its progression, in which having smoked, arterial hypertension, diabetes, and dyslipidemia all play separate roles; 13–16 their role in the prognosis of ACS patients has piqued our interest (Canto *et al.*, 2011).

Limitation of the Study and Prospective

This study has some limitations that must be addressed. First, it cannot be ruled out that fibrinogen as an acute-phase reactant could result from clinical manifestations rather than potentially trigger, especially for patients with ACS. Our conceptual framework does not allow for causality even though our findings on fibrinogen to in-vivo arterial wall assessment are innovative.

The result of the present study shouldn't be generalized due to the small sample size. Then further studies were done on FDPs among patients with Acute Coronary Syndrome with a large sample size. The well-constructed cohort study design is crucial. Other thrombotic markers such as (D dimer, fibrinogen, and platelets parameters) and other inflammatory mediators like proinflammatory cytokines (IL 1, IL 6, and IL 8) should be assessed.

Conclusion

Elevated FDPs levels were revealed among Sudanese patients with Acute Coronary Syndrome (ACS), which may be a prognostic marker for thrombotic tendency. As a consequence, FDPs must be included in regular laboratory investigations, as well as the ACS monitoring strategy. Moreover, diabetes mellitus, hypertension, hyperlipidemia, and family history were significant associated risk factors.

Acknowledgments: This publication was supported by the Deanship of scientific research at Prince Sattam bin Abdul-Aziz University.

Conflict of interest: None

Financial support: None

Ethics statement: The ethical committee of the faculty of medical laboratory science, Al Zeaim Al-Azhary university, and the ministry of health approved the study.

References

- Al-Shali, K. Z., Alama, M. N., Ajabnoor, M. A., Al-Fayaz, F. F., & Balubaid, K. H. (2019). Osteoprotegerin Levels among Saudi Cardiovascular Patients. *International Journal of Pharmaceutical Research & Allied Sciences*, 8(1), 95-101.
- Battes, L. C., Cheng, J. M., Oemrawsingh, R. M., Boersma, E., Garcia-Garcia, H. M., de Boer, S. P., Buljubasic, N., van Mieghem, N. A., Regar, E., van Geuns, R. J., et al. (2014).

- Circulating cytokines in relation to the extent and composition of coronary atherosclerosis: results from the ATHEROREMO-IVUS study. *Atherosclerosis*, 236(1), 18-24.
- Buljubasic, N., Akkerhuis, K. M., Cheng, J. M., Oemrawsingh, R. M., Garcia-Garcia, H. M., de Boer, S. P., Regar, E., van Geuns, R. J. M., Serruys, P. W., Boersma, E., et al. (2017). Fibrinogen in relation to degree and composition of coronary plaque on intravascular ultrasound in patients undergoing coronary angiography. *Coronary Artery Disease*, 28(1), 23-32. doi:10.1097/MCA.0000000000000442.
- Canto, J. G., Kiefe, C. I., Rogers, W. J., Peterson, E. D., Frederick, P. D., French, W. J., Gibson, C. M., Pollack, C. V., Ornato, J. P., Zalenski, R. J., et al. (2011). Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction. *Jama*, 306(19), 2120-2127.
- Corban, M. T., Hung, O. Y., Mekonnen, G., Eshtehardi, P., Eapen, D. J., Rasoul-Arzumly, E., Al Kassem, H., Manocha, P., Ko, Y. A., Sperling, L. S., et al. (2016). Elevated levels of serum fibrin and fibrinogen degradation products are independent predictors of larger coronary plaques and greater plaque necrotic core. *Circulation Journal*, 80(4), 931-937. doi:10.1253/circj.CJ-15-0768
- Corban, M. T., Hung, O. Y., Mekonnen, G., Eshtehardi, P., Eapen, D. J., Rasoul-Arzumly, E., Al Kassem, H., Manocha, P., Ko, Y. A., Sperling, L. S., et al. (2016). Elevated levels of serum fibrin and fibrinogen degradation products are independent predictors of larger coronary plaques and greater plaque necrotic core. *Circulation Journal*, 80(4), 931-937. doi:10.1253/circj.CJ-15-0768
- Danesh, J., Whincup, P., Walker, M., Lennon, L., Thomson, A., Appleby, P., Rumley, A., & Lowe, G. D. (2001). Fibrin D-dimer and coronary heart disease: prospective study and meta-analysis. *Circulation*, 103(19), 2323-2327. doi:10.1161/01.cir.103.19.2323
- Eapen, D. J., Manocha, P., Patel, R. S., Hammadah, M., Veledar, E., Wassel, C., Nanjundappa, R. A., Sikora, S., Malayter, D., Wilson, P. W., et al. (2013). Aggregate risk score based on markers of inflammation, cell stress, and coagulation is an independent predictor of adverse cardiovascular outcomes. *Journal of the American College of Cardiology*, 62(4), 329-337. doi:10.1016/j.jacc.2013.03.072
- Eapen, D. J., Manocha, P., Patel, R. S., Hammadah, M., Veledar, E., Wassel, C., Nanjundappa, R. A., Sikora, S., Malayter, D., Wilson, P. W., et al. (2013). Aggregate risk score based on markers of inflammation, cell stress, and coagulation is an independent predictor of adverse cardiovascular outcomes. *Journal of the American College of Cardiology*, 62(4), 329-337.
- Gaule, T. G., & Ajjan, R. A. (2021). Fibrin (ogen) as a Therapeutic Target: Opportunities and Challenges. *International Journal of Molecular Sciences*, 22(13), 6916. doi:10.3390/ijms22136916
- Held, C., White, H. D., Stewart, R. A., Budaj, A., Cannon, C. P., Hochman, J. S., Koenig, W., Siegbahn, A., Steg, P. G., Soffer, J., et al. (2017). Inflammatory biomarkers interleukin-6 and C-reactive protein and outcomes in stable coronary heart disease: experiences from the STABILITY (stabilization of atherosclerotic plaque by initiation of darapladib therapy) trial. *Journal of the American Heart Association*, 6(10), e005077. doi:10.1161/JAHA.116.005077
- Kikkert, W. J., Claessen, B. E., Stone, G. W., Mehran, R., Witzenbichler, B., Brodie, B. R., Wöhrle, J., Witkowski, A., Guagliumi, G., Zmudka, K., et al. (2014). D-dimer levels predict ischemic and hemorrhagic outcomes after acute myocardial infarction: a HORIZONS-AMI biomarker substudy. *Journal of Thrombosis and Thrombolysis*, 37(2), 155-164.
- Mahmud, E., Behnamfar, O., Lin, F., Reeves, R., Patel, M., & Ang, L. (2016). Elevated serum fibrinogen is associated with 12-month major adverse cardiovascular events following percutaneous coronary intervention. *Journal of the American College of Cardiology*, 67(21), 2556-2557. doi:10.1016/j.jacc.2016.03.540
- Mathew, S. T., Al-Mutlaq, M. A., Al-Eidan, R. F., Al-Khuraishi, D. M., & Adam, H. (2019). Prevalence of Pulp Stones and its Relation with Cardiovascular Diseases and Diabetes Mellitus Using Digital Radiographs: A Retrospective Study. *Annals of Dental Specialty*, 7(4), 18-23.
- Medina-Leyte, D. J., Zepeda-García, O., Domínguez-Pérez, M., González-Garrido, A., Villarreal-Molina, T., & Jacobo-Albavera, L. (2021). Endothelial Dysfunction, Inflammation and Coronary Artery Disease: Potential Biomarkers and Promising Therapeutic Approaches. *International Journal of Molecular Sciences*, 22(8), 3850. doi:10.3390/ijms22083850.
- Moreira, D. M., da Silva, R. L., Vieira, J. L., Fattah, T., Lueneberg, M. E., & Gottschall, C. A. M. (2015). Role of vascular inflammation in coronary artery disease: potential of anti-inflammatory drugs in the prevention of atherothrombosis. *American Journal of Cardiovascular Drugs*, 15(1), 1-11. doi:10.1007/s40256-014-0094-z.
- Sarli, B., Akpek, M., Baktir, A. O., Sahin, O., Saglam, H., Arinc, H., Odabasi, H., Dogan, S., Kurtul, S., Dogan, Y., et al. (2015). Impact of D-dimer level on postinterventional coronary flow and in-hospital MACE in ST-segment elevation myocardial infarction. *Herz*, 40(3), 507-513.
- Song, J., Yu, T., Sun, Z., Li, Z., He, D., & Sun, Z. (2020). Comparison of prognostic significance between serum fibrinogen and Global Registry of Acute Coronary Events score for prognosis of patients with non-ST-elevation acute coronary syndromes undergoing percutaneous coronary intervention. *Coronary Artery Disease*, 31(2), 124-129.
- Undas, A. (2020). Altered fibrin clot properties and fibrinolysis in patients with atrial fibrillation: practical implications. *EP Europace*, 22(2), 185-194. doi:10.1093/europace/euz271.
- Wannamethee, S. G., Whincup, P. H., Shaper, A. G., Rumley, A., Lennon, L., & Lowe, G. D. O. (2009). Circulating inflammatory and hemostatic biomarkers are associated with risk of myocardial infarction and coronary death, but not angina pectoris, in older men. *Journal of Thrombosis and Haemostasis*, 7(10), 1605-1611.
- Zabczyk, M., Natarska, J., & Undas, A. (2021). Fibrin Clot Properties in Atherosclerotic Vascular Disease: From Pathophysiology to Clinical Outcomes. *Journal of Clinical Medicine*, 10(13), 2999. doi:10.3390/jcm10132999.

Zhao, X., Li, J., Tang, X., Jiang, L., Chen, J., Qiao, S., Yang, Y., Gao, R., Xu, B., & Yuan, J. (2020). D-dimer as a thrombus biomarker for predicting 2-year mortality after percutaneous coronary intervention. *Therapeutic advances in chronic disease*, 11, 2040622320904302. doi:2040622320 904302