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# Impact of D-Dimers on the Differential Diagnosis of Acute Chest Pain: Current Aspects Besides the Widely Known

Kathrin Hahne[1,*], Pia Lebiedz[1,*] and Frank Breuckmann[2]

[1]Department of Cardiovascular Medicine, University Hospital Muenster, Muenster, Germany. [2]Department of Cardiology, Arnsberg Medical Center, Arnsberg, Germany. *Both authors contributed equally.

**ABSTRACT:** D-dimers are cleavage products of fibrin that occur during plasmin-mediated fibrinolysis of blood clots. In the emergency department, D-dimer measurement represents a valuable and cost-effective tool in the differential diagnosis of acute chest pain including the main life-threatening entities: acute coronary syndrome, pulmonary embolism, and acute aortic syndrome. Whereas the diagnostic and prognostic values of D-dimer testing in acute coronary syndrome is of less priority, increases of D-dimers are frequently found in venous thromboembolism and acute aortic syndromes, especially acute aortic dissection. As to the high negative predictive value of D-dimer in those disorders, patients with low to intermediate pretest probability may profit in terms of less necessity of further non-invasive or even invasive imaging, simultaneously reducing potential complications and healthcare-related costs. However, because of the low specificity of the different D-dimer tests in contrast to its frequent usage, adequate interpretation is required. Age-related adjustment of D-dimer levels may be used to increase its diagnostic power.

**KEY WORDS:** D-dimer, chest pain, acute coronary syndrome, acute aortic syndrome, pulmonary embolism

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**CORRESPONDENCE:** f.breuckmann@klinikum-arnsberg.de

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## Introduction

Fibrinolysis is a mechanism of fibrin breakdown in blood clot inducing enzymatic activation of plasminogen to plasmin, which cleaves fibrin molecules. As a degradation product of fibrin, D-dimers are produced when cross-linked fibrin is degraded by plasmin-induced fibrinolytic activity, thereby correlating with intravascular levels of fibrin turnover.[1]

D-dimer tests are broadly used as an excellent non-invasive triage biomarker in patients with acute thoracic pain especially in the absence of an ischemic origin of the symptoms in order to rule out or identify potential life-threatening differential diagnoses including acute aortic syndrome and pulmonary embolism. Owing to the high negative predictive value of the high-sensitive test, potential harmful diagnostic measures may be avoided.

## Laboratory Assessment

D-dimer levels can be assessed by microplate enzyme-linked immunosorbent assay, enzyme-linked immunofluorescence assay, whole-blood cell agglutination, or latex agglutination tests.[2] The sensitivity, specificity, and negative predictive value of D-dimer tests depend on the kind of used test, the cutoff value, and the kind of assumed disease.[3] Cutoff levels are influenced by the kind of test used and may differ between different laboratories. D-dimer levels are associated with the amount of clotted blood. Highest levels are reached

in massive venous thromboembolism and after cardiovascular arrest.[4]

## Differential Diagnosis of Acute Chest Pain

Acute chest pain as a heterogeneous symptom with several different causes still represents one of the cardinal symptoms of patients requiring emergency medical care.[5] Besides a broad variety of different non-cardiac conditions, among others, gastrointestinal as well as pulmonary diseases and musculoskeletal disorders, diseases of the heart and main vessels including acute coronary syndrome, pulmonary embolism, and acute aortic syndrome cause thoracic pain. Owing to the acute life-threatening implications especially of the latter, fast diagnosis is crucial. In this setup, the negative predictive value of D-dimer testing is particularly valuable. However, because of limitations in specificity, D-dimer testing is only one component in the diagnosis of acute chest pain. Still, echocardiography (ECG), serial laboratory parameters including markers of myocardial necrosis, and other imaging methods such as computed tomography, angiography, or magnetic resonance are essential for the diagnostic workup.[6–9]

## Impact of D-Dimers on Acute Coronary Syndrome

Acute myocardial ischemia is caused by thrombotic occlusion of coronary arteries, implicating that D-dimer levels should be raised in focal coronary thrombosis. Whereas troponin is a highly sensitive and specific parameter for myocardial injury, elevation is measurable not until 3–4 hours after onset of symptoms. By contrast, D-dimer propose earlier rise than common markers of cardiac injury. It has been demonstrated that increased D-dimer levels may serve as an independent diagnostic marker for myocardial infarction with an increase in diagnostic sensitivity of the electrocardiogram and clinical history plus D-dimer.[10] These data were supported by recent studies, additionally emphasizing a potential prognostic value on top of the diagnostic benefit.[11–14] However, D-dimer levels correlate with the amount of clotted blood and therefore may exhibit a much lower rise in coronary occlusion than in other conditions, partly even below the lower detection limit. Owing to considerably more specific diagnostics and parameters in myocardial ischemia, D-dimer measurement is not yet used as a standard biomarker in the diagnosis of acute coronary syndrome and especially does not allow for discrimination of its differential diagnoses.

## Value of D-Dimer Measurement in Pulmonary Embolism

D-dimers have been shown to be highly sensitive in venous thromboembolism.[2,15,16] Owing to the fact that deep vein thrombosis and pulmonary embolism often occur at the same time and up to 50% of patients with deep vein thrombosis have clinically inapparent pulmonary embolism, D-dimer levels can be used similarly in patients with deep vein thrombosis and pulmonary embolism.[17] Therefore, the D-dimer test as a fast and cost-effective method is recommended in suspected pulmonary embolism. In this respect, a negative D-dimer test may exclude thromboembolism in approximately 30% of the patients presenting with suspicion of pulmonary embolism in the emergency department, thereby reducing potential complications and costs of further tests.[18–20] The use of pretest probability-adapted D-dimer cutoff values can even further decrease the number of imaging tests in patients with low pretest probability.[21] However, rule-out should be restricted to normal D-dimer concentrations combined with only low to intermediate pretest probability.

## D-Dimers in Aortic Dissection and Other Aortic Syndromes

The term acute aortic syndrome includes different conditions ranging from an intramural hematoma to typical aortic dissection, together characterized by a disruption of the structural integrity of the aortic wall with subsequent initiation of coagulation. Apart from clinical presentation, imaging methods, and other biomarkers, D-dimers might be of diagnostic as well as prognostic value.[22] It has been shown that a positive D-dimer test has a sensitivity of about 97%, a specificity of 56%, a positive predictive value of about 60%, and a negative predictive value of up to 96%.[23,24] Furthermore, D-dimer levels seem to correlate with the anatomic extension of the dissection.[25] D-Dimer levels are higher in patients with type A than in those with type B dissection, and are predictors of acute mortality in type A aortic dissection patients.[26] Thus, even if limited sample sizes, a lack of randomization and different testing methods, as well as different cutoff values so far biased the study results, D-dimer measurement represents a useful tool in order to identify subjects with a low probability of acute aortic syndrome when presenting with atypical chest pain.

## Disturbing Factors in D-Dimer Measurement

Despite the high negative predictive value of D-dimer, the specificity is poor because of a multitude of other disorders going along with elevated D-dimer levels. Due to intravasal coagulation and fibrinolysis, representing a strong limitation in its usage as a single diagnostic procedure, D-dimers are also elevated in cardiac arrest and after resuscitation, severe circulatory disorders like shock and severe infection or systemic inflammatory response syndrome or ARDS as well as in disseminated intravascular coagulation, hemorrhage, trauma, after surgery, in pregnancy and in malignancies.[27–36]

## Age-Related Adjustment of D-Dimer Levels

As D-dimer levels are known to increase with age leading to a significantly lower specificity of only about 15% with increasing false-positive results especially in patients aged ≥80 years, their clinical usefulness is limited in elderly patients. Several studies investigated the positive effect of using age-adjusted cutoff values in venous thromboembolism.[37–39] In line with

these results and according to the most recent ADJUST-PE study, pretest clinical probability assessment combined with an age-adjusted D-dimer cutoff value increases specificity in older patients with a low likelihood of venous thromboembolism.[40] As referred to the differential diagnoses of acute chest pain, further studies on age-adjusted cutoff values in acute aortic syndrome are warranted, especially with respect to the initial stages such as intramural hematoma and penetrating aortic ulcers. Additionally, to date, age-adjustment in acute coronary syndrome lacks further scientific evaluation, but is thought to be of less priority in clinical routine.

## Conclusions

D-dimer as a marker for activation of coagulation system is a fast and cost-effective parameter used in emergency medicine in the discrimination of acute thoracic pain. Nonetheless, because of reduced specificity, D-dimer measurement is unsuited to serve as a single diagnostic procedure. Diagnostic analysis might be accelerated by correct interpretation of D-dimer values in context to clinical presentation, adequate pretest likelihood, ECG diagnostics, laboratory parameters, and extended non-invasive or invasive imaging procedures.

## Author Contributions

Conceived and designed the review article: FB. Analyzed the data: KH, PL. Wrote the first draft of the manuscript: KH, PL. Contributed to the writing of the manuscript: KH, PL, FB. Agreed with manuscript results and conclusions: PL, FB. Jointly developed the structure and arguments for the paper: PL, FB. Made critical revisions and approved the final version: KH, PL, FB. All authors reviewed and approved the final manuscript.

## REFERENCES


1. Bruinstroop E, van de Ree MA, Huisman MV. The use of D-dimer in specific clinical conditions: A narrative review. *Eur J Intern Med*. 2009;20(5):441–6.
2. Di Nisio M, Squizzato A, Rutjes AW, Buller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: A systematic review. *J Thromb Haemost*. 2007;5(2):296–304.
3. Sadosty AT, Goyal DG, Boie ET, Chiu CK. Emergency department D-dimer testing. *J Emerg Med*. 2001;21(4):423–9.
4. Koracevic GP. Pragmatic classification of the causes of high D-dimer. *Am J Emerg Med*. 2009;27(8):e5–1016.
5. Steurer J, Held U, Schmid D, Ruckstuhl J, Bachmann LM. Clinical value of diagnostic instruments for ruling out acute coronary syndrome in patients with chest pain: A systematic review. *Emerg Med J*. 2010;27(12):896–902.
6. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J*. 2011;32(23):2999–3054.
7. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33(20):2569–619.
8. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: The task force for the diagnosis and management of acute pulmonary embolism of the European society of cardiology (ESC). *Eur Heart J*. 2008;29(18):2276–315.
9. Nienaber CA, Powell JT. Management of acute aortic syndromes. *Eur Heart J*. 2012;33(1):26b–35b.
10. Bayes-Genis A, Mateo J, Santalo M, et al. D-dimer is an early diagnostic marker of coronary ischemia in patients with chest pain. *Am Heart J*. 2000;140(3):379–84.
11. Shitrit D, Bar-Gil Shitrit A, Rudensky B, Sulkes J, Gutterer N, Zviony D. Role of ELISA D-dimer test in patients with unstable angina pectoris presenting at the emergency department with a normal electrocardiogram. *Am J Hematol*. 2004;77(2):147–50.
12. Oldgren J, Linder R, Grip L, Siegbahn A, Wallentin L. Coagulation activity and clinical outcome in unstable coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2001;21(6):1059–64.
13. Orak M, Ustundag M, Guloglu C, Alyan O, Sayhan MB. The role of serum D-dimer level in the diagnosis of patients admitted to the emergency department complaining of chest pain. *J Int Med Res*. 2010;38(5):1772–9.
14. Shitrit AB, Tzivony D, Shilon Y, et al. The role of enzyme-linked immunosorbent assay D-dimer in patients with acute coronary syndrome presenting with normal cardiac enzymes. *Blood Coagul Fibrinolysis*. 2006;17(8):621–4.
15. Bounameaux H, Slosman D, de Moerloose P, Reber G. Diagnostic value of plasma D-dimer in suspected pulmonary embolism. *Lancet*. 1988;2(8611):628–9.
16. Goldhaber SZ, Vaughan DE, Tumeh SS, Loscalzo J. Utility of cross-linked fibrin degradation products in the diagnosis of pulmonary embolism. *Am Heart J*. 1988;116(2 pt 1):505–8.
17. Janssen MC, Wollersheim H, Verbruggen B, Novakova IR. Rapid D-dimer assays to exclude deep venous thrombosis and pulmonary embolism: Current status and new developments. *Semin Thromb Hemost*. 1998;24(4):393–400.
18. Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. *N Engl J Med*. 2005;352(17):1760–8.
19. Brown MD, Rowe BH, Reeves MJ, Bermingham JM, Goldhaber SZ. The accuracy of the enzyme-linked immunosorbent assay D-dimer test in the diagnosis of pulmonary embolism: A meta-analysis. *Ann Emerg Med*. 2002;40(2):133–44.
20. Duriseti RS, Brandeau ML. Cost-effectiveness of strategies for diagnosing pulmonary embolism among emergency department patients presenting with undifferentiated symptoms. *Ann Emerg Med*. 2010;56(4):321.e–32.e.
21. Kabrhel C, Mark Courtney D, Camargo CA Jr, et al. Potential impact of adjusting the threshold of the quantitative D-dimer based on pretest probability of acute pulmonary embolism. *Acad Emerg Med*. 2009;16(4):325–32.
22. Parthenakis F, Koutalas E, Patrianakos A, Koukouvas M, Nyktari E, Vardas P. Diagnosing acute aortic syndromes: The role of specific biochemical markers. *Int J Cardiol*. 2010;145(1):3–8.
23. Weber T, Högler S, Auer J, et al. D-dimer in acute aortic dissection. *Chest*. 2003;123(5):1375–8.
24. Shimony A, Filion KB, Mottillo S, Dourian T, Eisenberg MJ. Meta-analysis of usefulness of D-dimer to diagnose acute aortic dissection. *Am J Cardiol*. 2011;107(8):1227–34.
25. Ohlmann P, Faure A, Morel O, et al. Diagnostic and prognostic value of circulating D-dimers in patients with acute aortic dissection. *Crit Care Med*. 2006;34(5):1358–64.
26. Weber T, Rammer M, Auer J, Maurer E, Aspock G, Eber B. Plasma concentrations of D-dimer predict mortality in acute type A aortic dissection. *Heart*. 2006;92(6):836–7.
27. Gando S, Kameue T, Nanzaki S, Nakanishi Y. Massive fibrin formation with consecutive impairment of fibrinolysis in patients with out-of-hospital cardiac arrest. *Thromb Haemost*. 1997;77(2):278–82.
28. Szymanski FM, Karpinski G, Filipiak KJ, et al. Usefulness of the D-dimer concentration as a predictor of mortality in patients with out-of-hospital cardiac arrest. *Am J Cardiol*. 2013;112(4):467–71.
29. Goebel PJ, Williams JB, Gerhardt RT. A pilot study of the performance characteristics of the D-dimer in presumed sepsis. *West J Emerg Med*. 2010;11(2):173–9.
30. Levi M. The coagulant response in sepsis and inflammation. *Hamostaseologie*. 2010;30(1):10–2.
31. Giavarina D, Mezzena G, Dorizzi RM, Soffiati G. Reference interval of D-dimer in pregnant women. *Clin Biochem*. 2001;34(4):331–3.
32. Réger B, Péterfalvi A, Litter I, et al. Challenges in the evaluation of D-dimer and fibrinogen levels in pregnant women. *Thromb Res*. 2013;131(4):e183–7.
33. Ay C, Dunkler D, Pirker R, et al. High D-dimer levels are associated with poor prognosis in cancer patients. *Haematologica*. 2012;97(8):1158–64.
34. Dirix LY, Salgado R, Weytjens R, et al. Plasma fibrin D-dimer levels correlate with tumour volume, progression rate and survival in patients with metastatic breast cancer. *Br J Cancer*. 2002;86(3):389–95.
35. Favaloro EJ. Laboratory testing in disseminated intravascular coagulation. *Semin Thromb Hemost*. 2010;36(4):458–67.
36. Tian HL, Chen H, Wu BS, et al. D-dimer as a predictor of progressive hemorrhagic injury in patients with traumatic brain injury: Analysis of 194 cases. *Neurosurg Rev*. 2010;33(3):359–65;discussion365–6.
37. Schouten HJ, Geersing GJ, Koek HL, et al. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: Systematic review and meta-analysis. *BMJ*. 2013;346:f2492.

38. Verma N, Willeke P, Bicsan P, Lebiedz P, Pavenstadt H, Kumpers P. Age-adjusted D-dimer cut-offs to diagnose thromboembolic events: Validation in an emergency department. *Med Klin Intensivmed Notfmed*. 2014;109(2):121–8.
39. Polo Friz H, Pasciuti L, Meloni DF, et al. A higher D-dimer threshold safely rules-out pulmonary embolism in very elderly emergency department patients. *Thromb Res*. 2014;133(3):380–3.
40. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: The ADJUST-PE study. *JAMA*. 2014;311(11):1117–24.