Combined use of aortic dissection detection risk score and D-dimer in the diagnostic workup of suspected acute aortic dissection

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Peiman Nazeriana, Fulvio Morellob, Simone Vannia, Alessia Bonob, Matteo Castellia, Daniela Fornob, Chiara Giglia, Flavia Soardob, Federica Carboneb, Enrico Lupiab, Stefano Grifonia

Background

Acute aortic dissection (AD) represents a diagnostic conundrum. Validated algorithms are particularly needed to identify patients where AD could be ruled out without aortic imaging. We evaluated the diagnostic accuracy of a strategy combining the aortic dissection detection (ADD) risk score with D-dimer, a sensitive biomarker of AD.

Methods

Patients from two clinical centers with suspected AD were prospectively enrolled in a registry, from January 2008 to March 2013. The ADD risk score was calculated by retrospective blinded chart review. For D-dimer, a cutoff of 500 ng/ml was applied.

Results

AD was diagnosed in 233 of 1035 (22.5%) patients. The ADD risk score was 0 in 322 (31.1%), 1 in 508 (49.1%) and > 1 in 205 (19.8%) patients. The sensitivity and the failure rate of D-dimer were 100% and 0% in patients with ADD score 0, versus 97.5% (95% CI 91.4–99.6%) and 4.2% (95% CI 0.7–12.5%) in patients with ADD risk score > 1. In patients with ADD risk score ≤ 1, the sensitivity and the failure rate of D-dimer were 98.7% (95% CI 95.3–99.8%) and 0.8% (95% CI 0.1–2.6%). The diagnostic efficiency of D-dimer in patients with ADD risk score 0 and ≤ 1 was 8.9% (95% CI 7.2–10.7%) and 23.6% (95% CI 21.1–26.2%) respectively.

Conclusions

In a large cohort of patients with suspected AD, the presence of ADD risk score 0 or ≤ 1 combined with a negative D-dimer accurately and efficiently ruled out AD.

1. Introduction

Acute aortic dissection (AD) is a deadly, difficult to diagnose disease presenting with an array of common and unspecific symptoms [1], [2] and [3]. Currently, the diagnosis of AD is based on advanced aortic imaging studies such as computed tomographic angiography (CTA), transesophageal echocardiography or magnetic resonance imaging [4]. These exams are costly and frequently require patient transfer to specialized clinical centers. Furthermore, CTA, the most frequently used imaging exam for suspected AD, exposes patients to significant radiations and carries inherent risks of anaphylaxis and medium contrast nephropathy [5] and [6]. Hence, validated clinical strategies beyond subjective clinical judgment are needed to assist physicians in the approach to suspected AD, and in particular to limit the number of patients without AD undergoing urgent aortic imaging [7].

The 2010 guidelines for the diagnosis and management of thoracic aortic disease by the American Heart Association and other clinical societies proposed the aortic dissection detection (ADD) risk score as a bedside clinical tool to estimate the risk of AD [4]. We have recently shown that indeed, the ADD risk score can be used to estimate the clinical probability of AD in patients evaluated in the ED [8]. Nonetheless, additional evidence-based data is needed to guide further diagnostic workup in the different risk groups, especially in patients at non-high risk of AD.

Application of selected biomarkers in risk-stratified patients represents a well-established diagnostic strategy. In the workup of deep venous thrombosis and pulmonary embolism, for instance, low levels of D-dimer can be used to effectively rule out these conditions when applied to patients at non-high clinical risk [9] and [10]. Of note, D-dimer, a thrombosis/fibrinolytic by-product whose assay is relatively inexpensive and widely available worldwide to Emergency Departments (ED), has been evaluated in several studies also as a biomarker of AD, and has showed a pooled diagnostic sensitivity of 97% for AD in the latest meta-analysis [11], [12], [13], [14], [15], [16], [17], [18] and [19]. However, a negative D-dimer *per se* is considered insufficient to rule out AD in unselected patients [20]. The aim of the present study was therefore to evaluate the accuracy and the efficiency of a diagnostic strategy combining ADD risk score classification with D-dimer in a cohort of patients evaluated in the ED for suspected AD. In particular, we tested the hypothesis that a negative D-dimer test may allow safe rule-out of AD in patients at low or non-high risk of AD, without necessity to perform urgent aortic imaging.

2. Materials and methods

2.1. Setting and enrollment

This was a retrospective diagnostic accuracy study performed on a prospective registry of patients with suspected AD from two Emergency Departments (ED), enrolled at the time of initial medical evaluation and before the establishment of a final diagnosis, as previously described [8]. Participating hospitals are regional cardiothoracic surgery referral centers and each center evaluated in its ED > 100,000 patients/year in the study period.

From 1st January 2008 to 30th March 2013, patients were included in a prospective registry of suspected AD if all the following criteria were satisfied: (1) presentation to the ED with any of the following symptoms: chest pain, back pain, abdominal pain, syncope or symptoms of perfusion deficit (central nervous system, mesenteric, myocardial, or limb ischemia), as suggested by clinical guidelines [4]; (2) an alternative diagnosis to AD could not be established by the attending physician after the initial medical evaluation; and (3) the clinical suspicion of AD by the attending physician was high enough to request an urgent aortic imaging exam (CTA) to explicitly identify or rule out AD, as previously performed in the IRAD-Bio study [18]. Enrollment in the registry was decided by the attending physician during evaluation in the ED and before the establishment of a final diagnosis by urgent aortic imaging. Only patients with an available D-dimer level at presentation were considered for data analysis. Informed consent was obtained from each patient or next of kin (if needed by clinical conditions) and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The institutional Review Boards approved the study.

2.2. ADD risk score classification

The ADD risk score was calculated retrospectively through independent physician review of medical charts, as previously performed [8] and [21]. In the participating centers, information relevant to the calculation of the ADD risk score was routinely registered by the attending physicians on the ED medical charts of all patients presenting with symptoms relevant to the present study (chest/back/abdominal pain, syncope, perfusion deficit). A team of researcher physicians blinded to the final diagnosis evaluated retrospectively the ED medical charts reporting all triage data, presenting symptoms, detailed medical history and physical examination. The reviewers collected from the charts the data relevant to the calculation of the ADD risk score on a standardized electronic form, which was then used to automatically input data into an electronic database. The data not reported in the charts were defaulted to negative, as previously performed in the IRAD [21].

The ADD risk score was calculated according to the presence or absence of 12 risk markers classified in three ADD risk categories (predisposing conditions, pain features and physical findings), as suggested by the 2010 AHA guidelines [4] and [21]. ADD predisposing conditions were: (1) history of Marfan syndrome or of

other connective tissue disease, (2) family history of aortic disease, (3) history of known aortic valve disease, (4) history of recent aortic manipulation, and (5) history of known thoracic aortic aneurysm. ADD pain features were: (6) abrupt onset of pain, (7) severe pain intensity, and (8) ripping or tearing quality of pain. For charts reporting a pain scale, severity of pain was defined as a numeric rating scale (NRS-11) of 7–10. For charts not reporting a pain scale, pain severity was defined by explicit definition of severity by the attending physician on the chart or by the administration of any opioid drug or ≥ 2 analgesic drugs. ADD physical findings were the following: (9) pulse asymmetry or systolic blood pressure differential (> 20 mm Hg) between extremities, (10) focal neurological deficit, (11) new murmur of aortic insufficiency, and (12) shock state or hypotension (systolic blood pressure ≤ 90 mm Hg). The ADD risk score was calculated based on the number of categories where at least one risk marker was present [4]. Patients were divided in low-risk (ADD risk score 0, 0 risk markers), intermediate-risk (ADD risk score 1, at least 1 risk marker in 1 ADD risk category) and high-risk (ADD risk > 1, at least 1 risk marker in > 1 ADD risk categories). For diagnostic accuracy analyses, a category of non-high-risk patients (ADD risk score ≤ 1) was also used.

2.3. D-dimer

D-dimer levels were assayed on venous samples drawn from patients at the time of initial medical evaluation in the ED, with automated latex agglutination tests (Hemosil D-dimer HS, Bedford or STA LIATEST® D-DI, DiagnosticaStago, Mannheim). The laboratory technicians were unaware of the clinical data. D-dimer was defined negative if lower than 500 ng/ml (Fibrinogen Equivalent Unit). This cutoff has been validated for D-dimer use in venous thromboembolic disease and has already been evaluated for the diagnosis of AD in previous studies [18], [19], [22] and [23].

2.4. Aortic imaging

The aortic imaging exam used to confirm or refuse the diagnosis of AD was chest and abdomen CTA, which was performed and interpreted by specialized radiologists not involved in the present study. CTA was performed with Lightspeed VCT 64 (GE, Piscataway NJ, USA) or Somatom Definition As4 and AS128 (Siemens, Erlangen, Germany).

2.5. Final diagnosis

The final diagnosis (AD or alternative diagnosis) was established by two independent senior physicians, who reviewed all available clinical data aortic imaging studies, medical, surgical and autopsy records. Reviewers were blinded to D-dimer levels and to the ADD risk score. In case of discordant diagnosis, SG adjudicated the final diagnosis. Any of the following diagnoses were considered as AD: Stanford type A and type B AD, aortic intramural hematoma and penetrating aortic ulcer, regardless of dissection site.

2.6. Statistical analysis

Dichotomous data are expressed as proportions and continuous data as mean and standard deviation (SD). Fisher's exact test was used for the comparison of dichotomous data, and the unpaired Student's *t*-test was used to compare normally distributed data. The diagnostic performance of D-dimer (cutoff value 500 ng/ml) was assessed by computing sensitivity, specificity, negative and positive predictive values and negative and positive likelihood ratios with their 95% confident interval (95% CI) in all patients. As the study evaluated a diagnostic strategy rather than the characteristics of a specific test, the conventional accuracy measures as well as the failure rate and the efficiency of D-dimer were also calculated in high-risk patients (ADD score > 1), in low-risk patients (ADD risk score 0) and in the intermediate and low-risk patients combined (non-high-risk patients, ADD risk score ≤ 1). Failure rate (false negative proportion) was calculated as the number of patients with a negative D-dimer and a final diagnosis of AD divided by all patients with negative D-dimer in the same risk-group. The efficiency of the diagnostic strategy was calculated as the number of patients with a negative D-dimer within a risk-group divided by all included

patients. *P*-values were two-sided, and a *P*-value lower than 0.05 was considered as statistically significant. Analysis was performed with the SPSS statistical package (version 17.0, SPSS Inc., Chicago, Illinois).

3. Results

3.1. Characteristics of study population

During the study period, 1455 patients were evaluated for suspected AD and 1035 patients were enrolled in the study. Chief presenting symptoms were the following: chest pain (647, 62.5%), back pain (348, 33.6%), abdominal pain (200, 19.3%), syncope (148, 14.3%), and symptoms of perfusion deficit (133, 12.9%). AD was finally diagnosed in 233 (22.5%) patients: 148 (14.3%) patients had type A AD, 51 (4.9%) had type B AD, 31 (3%) had an aortic intramural hematoma and 3 (0.3%) had a penetrating aortic ulcer. AD was finally ruled out in 802 (77.5%) patients, and the alternative diagnoses were the following: acute coronary syndrome (94 patients, 11.7%), gastrointestinal disease (73, 9.1%), non-AD-related syncope (66, 8.2%), pericarditis (25, 3.1%), non-AD-related stroke (16, 2%), pulmonary embolism (13, 1.6%), non-AD-related limb or organ acute ischemia (12, 1.2%), musculoskeletal chest pain (302, 37.7%) and other diagnoses (201, 19.4%). The clinical characteristics and prevalence of ADD risk markers in patients with AD and in patients with alternative diagnoses are presented in Table 1. In *post-hoc* analysis (Supplementary Tables 1–2), the characteristics of study patients were similar to those of patients evaluated for suspected AD during the study period excluded from the present study due to the lack of D-dimer testing at presentation (N = 420). Only the rate of known aortic aneurysm was more prevalent in the study cohort than in excluded patients (20% vs. 15.2%, *P* = 0.04).

Table 1. Clinical characteristics and prevalence of aortic dissection detection (ADD) risk markers in study patients (N = 1035).

	AD (N = 233)	**AltD (N = 802)**	***P*-value**
Demographic and clinical characteristics			
Female gender	79 (33.9%)	277 (34.5%)	0.88
Age (years)	67.9 (SD 13.2)	67.3 (SD 14.3)	0.55
Systolic blood pressure (mm Hg)	132 (SD 37)	143 (SD 28)	< 0.001
Heart rate (bpm)	75 (SD 19)	78 (SD 16)	0.045
Arterial hypertension	158 (67.8%)	561 (70%)	0.57
Diabetes	20 (8.6%)	86 (10.7%)	0.39
Dyslipidemia	26 (11.1%)	156 (19.4%)	0.003
Smoke	76 (32.6%)	173 (21.6%)	0.001
Cocaine abuse	2 (0.9%)	6 (0.7%)	1.00
ADD risk markers			
Predisposing conditions			
Marfan/connective tissue disease	10 (4.3%)	19 (2.4%)	0.12
Family history of aortic disease	5 (2.1%)	10 (1.2%)	0.35
Known aortic valve disease	15 (6.4%)	68 (8.5%)	0.34
Recent aortic manipulation	6 (2.6%)	37 (4.6%)	0.19
Known thoracic aortic aneurysm	40 (17.2%)	167 (20.8%)	0.23
Pain features			
Abrupt onset of pain	84 (36.1%)	159 (19.8%)	< 0.001
Severe pain intensity	103 (44.2%)	164 (20.4%)	< 0.001
Ripping or tearing pain	6 (2.6%)	22 (2.7%)	1.00
Physical findings			
Pulse deficit or SBP differential	61 (26.2%)	83 (10.3%)	< 0.001
Focal neurological deficit	46 (19.7%)	59 (7.4%)	< 0.001

	AD (N = 233)	AltD (N = 802)	*P*-value
Murmur of aortic insufficiency	12 (5.2%)	23 (2.9%)	0.10
Hypotension or shock state	51 (21.9%)	33 (4.1%)	< 0.001

Values are reported as mean and standard deviation (SD) for continuous variables or as absolute number and percent value (in brackets). AD: aortic dissection; AltD: alternative diagnosis; bpm: beats per minute; SD: standard deviation; ADD: aortic dissection detection.

The flow-diagram of the study is presented in Fig. 1. The prevalence of AD was 5.9% among patients at low-risk of AD (ADD risk score 0), 26.2% among patients at intermediate-risk of AD (ADD risk score 1) and 39.5% among patients at high-risk of AD (ADD risk score > 1). Presence of 1 or more ADD risk markers (ADD risk score ≥ 1) was associated with a sensitivity of 91.9% (95% CI 87.6–95) and a specificity of 37.8% (95% CI 34.4–41.2) for the diagnosis of AD. The negative and the positive predictive value were 94.1% (95% CI 90.9–96.4) and 30% (95% CI 26.7–33.5), while the negative and the positive likelihood ratio were 0.22 (95% CI 0.14–0.34) and 1.48 (CI 95% 1.38–1.58).

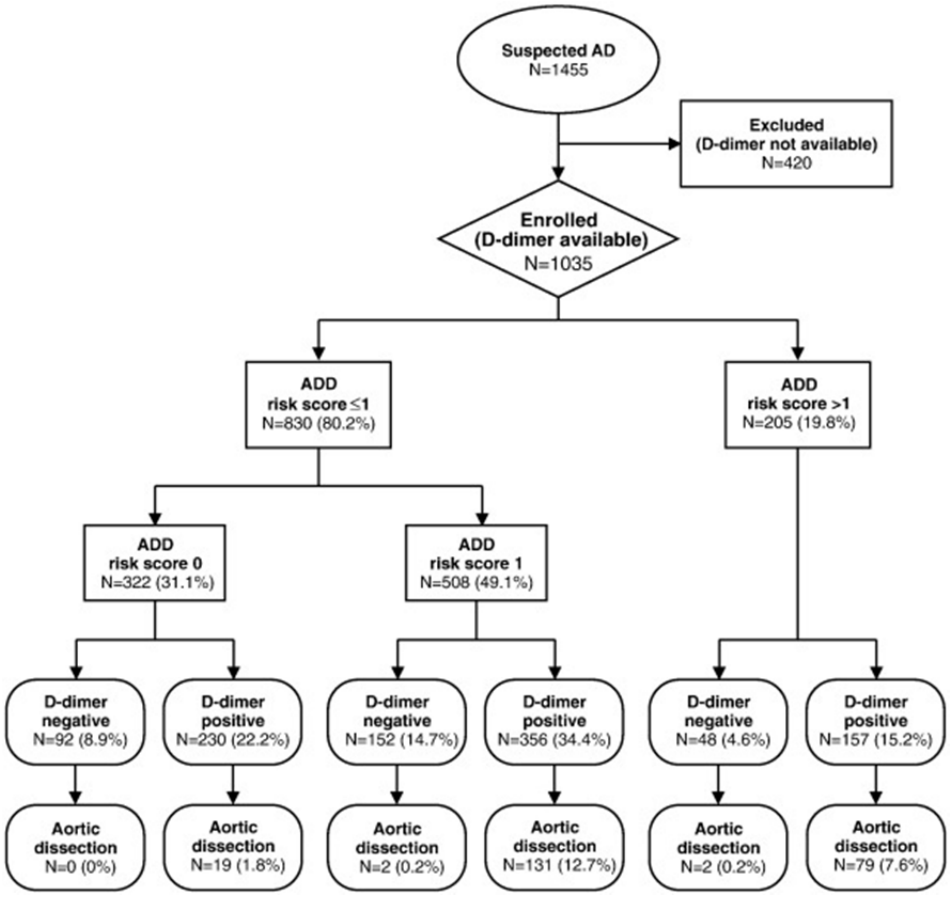

Fig. 1.

Flow diagram of the study. Percentages are referred to included patients. ADD: aortic dissection detection.

3.2. Diagnostic performance of D-dimer in ADD-classified patients

The sensitivity and the specificity of D-dimer (cutoff 500 ng/ml) in the general study population were 98.3% (95% CI 95.7–99.5) and 35.9% (95% CI 32.6–39.3) respectively. The negative and positive predictive values of D-dimer for AD were 98.6% (95% CI 96.5–99.6) and 30.8% (95% CI 27.5–34.3), while the negative and positive likelihood ratios of D-dimer were 0.05 (95% CI 0.02–0.13) and 1.53 (95% CI 1.45–1.62) respectively. The clinical characteristics of patients with a final diagnosis of AD and a negative D-dimer (N = 4) are

summarized in Table 2. There were 0 patients with AD and a negative D-dimer in the low-risk group (ADD risk score 0), 2 patients with AD (1 Stanford type B and 1 intramural hematoma) and a negative D-dimer in the intermediate-risk group (ADD risk score 1) and 2 patients with AD (both Stanford type A AD) in the high-risk group (ADD risk score > 1). The rate of false negative Stanford type A ADs was significantly higher among high-risk patients (P = 0.04 vs. non-high-risk patients).

Table 2. Clinical description of patients (N = 4) affected by acute aortic dissection presenting a negative D-dimer level (< 500 ng/ml).

Patient	Description	Final diagnosis
1	64 year-old man presenting with severe chest and abdominal pain, ADD risk score 1	Stanford type B AD
2	58 year-old man presenting with severe chest pain, ADD risk score 1	Intramural hematoma of the ascending aorta
3	73 year-old man with known thoracic aortic aneurysm, presenting severe chest pain, associated with pulse deficit, ADD risk score 3	Stanford type A AD
4	63 year-old woman with family history of aortic disease, presenting with chest pain, associated with a new murmur of aortic insufficiency, ADD risk score 2	Stanford type A AD

ADD: aortic dissection detection.

We next evaluated the accuracy and the efficiency of a diagnostic strategy combining ADD risk score classification with D-dimer for rule-out of AD (Table 3). In patients with ADD risk score > 1 (high-risk group), D-dimer had a sensitivity of 97.5% and a failure rate of 4.2% for presence of AD. In patients with ADD risk score < 1 (low-risk group), D-dimer had a sensitivity of 100% and a failure rate of 0% for presence of AD. The efficiency of a diagnostic strategy combining ADD risk score < 1 with a negative D-dimer was 8.9%. In patients with ADD risk score ≤ 1 (non-high risk group), D-dimer had a sensitivity of 98.7% and a failure rate of 0.8% for presence of any type of AD. For Stanford type A AD, the sensitivity and the failure rate of D-dimer were 100% and 0% respectively. The efficiency of a diagnostic strategy combining ADD risk score ≤ 1 with a negative D-dimer was 23.6%.

Table 3. Diagnostic accuracy of D-dimer (cutoff 500 ng/ml) in patient groups according to aortic dissection detection (ADD) risk score classification.

	ADD risk score group		
	0, low-risk (N = 322)	**≤ 1, non-high-risk (N = 830)**	**> 1, high-risk (N = 205)**
Sensitivity	100%	98.7% (95.3–99.8)	97.5% (91.4–99.6)
Specificity	30.4% (25.2–35.9)	35.7% (32.1–39.4)	37.1% (28.6–46.2)
NPV	100%	99.2% (97.1–99.9)	95.8% (85.7–99.4)
PPV	8.26% (5.1–12.6)	25.6% (22.1–29.3)	50.3% (42.2–58.4)
− LR	0	0.04 (0.01–0.15)	0.07 (0.02–0.27)
+ LR	1.44 (1.33–1.55)	1.53 (1.45–1.63)	1.55 (1.35–1.78)
Failure rate[a]	0%	0.8% (0.1–2.6)	4.2% (0.7–12.5)
Efficiency[b]	8.9% (7.2–10.7)	23.6% (21.1–26.2)	4.6% (3.5–6)

Data are presented as percent and 95% confidence interval (in brackets). ADD = aortic dissection detection; PPV = positive predictive value; NPV = negative predictive value; + LR = positive likelihood ratio; − LR = negative likelihood ratio. A: Number of patients with a negative D-dimer and a final diagnosis of AD divided by all patients with negative D-dimer in the same risk-group. B: Number of patients with a negative D-dimer within a risk-group divided by the number of study patients.

4. Discussion

This is to our knowledge the first study evaluating the performance of a diagnostic strategy combining standardized clinical risk stratification with a highly sensitive blood biomarker (D-dimer) in the diagnostic

approach to suspected AD. A similar approach is currently recommended in the workup of deep vein thrombosis and pulmonary embolism, where evidence has been provided that non-high clinical risk combined with a negative D-dimer provides optimal negative predictive value [9] and [10]. As the presenting symptoms of AD account for large proportions of ED visits worldwide (e.g. ~ 18% of total visits in the participating centers during the study period), large-scale implementation of a similar strategy could substantially reduce the burden of unnecessary aortic imaging exams performed in EDs [24].

The accuracy of D-dimer testing *per se* for the diagnosis of AD has been previously evaluated in several studies [12], [13], [14], [15], [16], [17], [18], [19] and [25]. Limited sample size, inclusion of healthy volunteers or patients with other established conditions instead of cohort of patients with suspected AD, and use of different diagnostic cutoff values for D-dimer constitute inherent limitations of several studies. Nonetheless, the latest meta-analysis involving 734 patients (298 patients with AD) has shown for D-dimer (cutoff value 500 ng/ml) a sensitivity of 97% (95% CI 94–99) and a negative predictive value of 96% (95% CI 93–98) for AD [11]. The present study is, to our knowledge, the largest available study assessing the diagnostic performance of D-dimer in suspected AD, both in terms of general study size and of patients with final diagnosis of AD. The previous largest prospective study evaluating D-dimer performance in suspected AD was conducted by Suzuki et al. [18]. In this multicenter study enrolling 220 patients (87 with AD), D-dimer (cutoff value 500 ng/ml) showed a sensitivity of 96.6% (95% CI 90.3–99.3) and a specificity of 46.6% (95% CI 37.9–55.5). In our study, the sensitivity of D-dimer was similar (98.3%, 95% CI 95.7–99.5), confirming that D-dimer indeed represent a highly sensitive biomarker suitable for the development of efficient rule-out diagnostic algorithms for AD. Instead, the specificity of D-dimer in our population was substantially lower (35.9%, 95% CI 32.6–39.3) than the specificity reported by Suzuki et al. As the recruitment rate of the present study was high (71% of all patients evaluated for suspected AD) and no substantial differences were found by *post-hoc* comparison of included and excluded patients, such discrepancy may not be attributed to selection bias. Instead, the higher incidence of increased D-dimer in patients without AD in our study may be caused by the older age of our population (67 vs. 61 years) leading to more frequent comorbidities, and to a broader case-mix. For instance, the rate of patients affected by acute coronary syndrome was 11.7%, compared to 33.1% in Suzuki et al., indicating that a more clinically heterogeneous population was enrolled in our study.

In the present study, the accuracy of D-dimer for rule-out of AD was lowest (failure rate 4.2%, 95% CI upper limit of 12.5%) in patients at high-risk of AD (ADD risk score > 1), which may be hardly acceptable to rule out a deadly disease. Instead, in the low-risk group (ADD risk score 0), no patient with a negative D-dimer was finally diagnosed with AD. In this group, the sensitivity and the negative predictive value of D-dimer were therefore 100%, with a failure rate of 0%. When low and intermediate ADD risk groups were considered together as a non-high-risk group (ADD risk score ≤ 1), D-dimer showed a sensitivity of 98.7% and a negative predictive value of 99.2% for all types of AD, and 100% for Stanford type A AD. Of note, the two false negative cases in this group were one Stanford type B AD and one intramural aortic hematoma, which have a better prognosis and do not routinely require immediate surgical intervention [26] and [27]. A lower sensitivity of D-dimer for intramural aortic hematomas has been reported previously [28].

Sarasin et al. have estimated the threshold clinical probability of AD above which the benefits of testing outweigh its risks, and found that such threshold is 2% for magnetic resonance, 3% for CTA and 9% for transthoracic echocardiography [29]. Indeed, in our study ADD risk score ≤ 1 associated with a negative D-dimer lead to a failure rate of 0.8% (0% for Stanford type A AD), which is substantially inferior to the lowest testing threshold calculated by Sarasin et al. As the upper limit of the 95% CI for failure rate was 2.6% in this study, increased sample size would be expected to narrow the confidence interval without affecting the point estimate.

5. Study limitations

A number of limitations apply to the present study. Most importantly, patients where AD was not suspected in the ED were not included in the study, which could bias against atypical presentations of AD. *Post-hoc* analysis of institutional databases identified N = 10 missed diagnoses of AD in the participating centers in the study period (all Stanford type A AD, N = 6 classified as ADD risk score 1, and N = 4 classified as ADD risk score > 1). D-dimer dosage at presentation was available in N = 5 patients (all > 500 ng/ml), and not available in N = 5 patients. Hence, inclusion of these patients in the study would not have modified our findings.

An important limitation of the present study is represented by the retrospective nature of ADD scoring. Compared with the IRAD database, the present study indeed overestimated the percent of AD patients at non-high-risk (ADD risk score 0: 8.2% vs. 4.3%; ADD risk score 1: 57.1% vs. 36.5%), while proportionally less AD patients were classified at high-risk (ADD risk score > 1: 34.8% vs. 59.2%) [8] and [21]. However, this bias corroborates our finding that the association of non-high-risk of AD with a negative D-dimer accurately rules out AD, as reclassification of AD patients with ADD risk score 1 and a negative D-dimer in the high-risk group would further increase the sensitivity and efficiency obtained in non-high-risk patients.

As a gold standard defining a justified clinical suspicion of AD is presently lacking, patient inclusion in the study was largely based on clinical judgment by the treating physician. Physician-based selection of patients is commonly applied in diagnostic studies of AD in order to obtain sufficient statistical power, but clinical judgment may significantly vary [8], [15], [18], [25] and [30]. Hence, the present results essentially apply to patients where AD appears as a reasonable diagnosis to the treating physician and where alternative diagnoses are not evident, and not to unselected patients with chest pain or any other symptom compatible with AD. Furthermore, treating physicians were not blinded to D-dimer, which could have influenced in some cases their decision to perform CTA. However, *post-hoc* comparison of study patients with patients where D-dimer was not performed did not show significant differences, thus excluding a systematic bias in patient enrolment.

6. Conclusions

The present study provides proof-of-concept that the absence of ADD risk markers (ADD risk score 0) combined with a negative D-dimer strongly argues against a diagnosis of AD. Also in the larger group of patients with up to one ADD risk marker (ADD risk score ≤ 1), a negative D-dimer accurately rules out AD, with a minor increase in false negatives. Rule-out of AD by combination of ADD risk score 0 or ≤ 1 with a negative D-dimer could lead to a reduction of 7–10% and 21–36% respectively in the number of urgent aortic imaging exams performed in EDs for suspected AD. Although careful and three-dimensional case-by-case judgment beyond standardized scoring and biomarker testing remains paramount in approaching patients potentially affected by this life-threatening disease, our study provides preliminary evidence that low or non-high clinical probability of AD combined with a negative D-dimer could be used to safely and efficiently rule out AD without performing further diagnostic steps. Prospective validation of this strategy is warranted to confirm our findings.

References

[1]

P.G. Hagan, C.A. Nienaber, E.M. Isselbacher, et al.

The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease

JAMA, 283 (7) (2000), pp. 897–903

[2]

P.R. Sullivan, A.B.. Wolfson, R.D. Leckey, et al.

Diagnosis of acute thoracic aortic dissection in the emergency department

Am J Emerg Med, 18 (1) (2000), pp. 46–50

[3]

M.S. Hansen, G.J. Nogareda, S.J. Hutchison

Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection

Am J Cardiol, 99 (6) (2007), pp. 852–856

[4]

L.F. Hiratzka, G.L. Bakris, J.A. Beckman, et al.

2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine

Circulation, 121 (13) (2010), pp. e266–e369

[5]

D.J. Brenner, E.J. Hall

Computed tomography — an increasing source of radiation exposure

N Engl J Med, 357 (22) (2007), pp. 2277–2284

[6]

S.T. Cochran

Anaphylactoid reactions to radiocontrast media

Curr Allergy Asthma Rep, 5 (1) (2005), pp. 28–31

[7]

R.A. Taylor, N.S. Iyer

A decision analysis to determine a testing threshold for computed tomographic angiography and D-dimer in the evaluation of aortic dissection

Am J Emerg Med, 31 (7) (2013), pp. 1047–1055

[8]

P. Nazerian, F. Giachino, S. Vanni, et al.

Diagnostic performance of the aortic dissection detection (ADD) risk score in patients with suspected acute aortic dissection

Eur Heart J Acute Cardiovasc Care (Mar 6 2014)

[9]

G.H. Guyatt, E.A. Akl, M. Crowther, et al.

Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines

Chest, 141 (2_suppl.) (2012), pp. 7S–47S

[10]

A. Torbicki, A. Perrier, S. Konstantinides, 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, 29 (18) (2008), pp. 2276–2315

[11]

A. Shimony, K.B. Filion, S. Mottillo, et al.

Meta-analysis of usefulness of D-dimer to diagnose acute aortic dissection

Am J Cardiol, 107 (8) (2011), pp. 1227–1234

[12]

K. Akutsu, N. Sato, T. Yamamoto, et al.

A rapid bedside D-dimer assay (cardiac D-dimer) for screening of clinically suspected acute aortic dissection

Circ J, 69 (4) (2005), pp. 397–403

[13]

H. Eggebrecht, C.K. Naber, C. Bruch, et al.

Value of plasma fibrin D-dimers for detection of acute aortic dissection

J Am Coll Cardiol, 44 (4) (2004), pp. 804–809

[14]

H. Hazui, H. Fukumoto, N. Negoro, et al.

Simple and useful tests for discriminating between acute aortic dissection of the ascending aorta and acute myocardial infarction in the emergency setting

Circ J, 69 (6) (2005), pp. 677–682

[15]

P. Ohlmann, A. Faure, O. Morel, et al.

Diagnostic and prognostic value of circulating D-dimers in patients with acute aortic dissection

Crit Care Med, 34 (5) (2006), pp. 1358–1364

[16]

A. Perez, P. Abbet, M.J. Drescher

D-dimers in the emergency department evaluation of aortic dissection

Acad Emerg Med, 11 (4) (2004), pp. 397–400

[17]

G. Sodeck, H. Domanovits, M. Schillinger, et al.

D-dimer in ruling out acute aortic dissection: a systematic review and prospective cohort study

Eur Heart J, 28 (24) (2007), pp. 3067–3075

[18]

T. Suzuki, A. Distante, A. Zizza, et al.

Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience

Circulation, 119 (20) (2009), pp. 2702–2707

[19]

T. Weber, S. Hogler, J. Auer, et al.

D-dimer in acute aortic dissection

Chest, 123 (5) (2003), pp. 1375–1378

[20]

M.D. Brown, D.H. Newman

Can a negative D-dimer result rule out acute aortic dissection?

Ann Emerg Med, 58 (4) (2011), pp. 375–376

[21]

A.M. Rogers, L.K. Hermann, A.M. Booher, et al.

Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the International Registry of Acute Aortic Dissection

Circulation, 123 (20) (2011), pp. 2213–2218

[22]

A. van Belle, H.R. Buller, M.V. Huisman, et al.

Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography

JAMA, 295 (2) (2006), pp. 172–179

[23]

P.S. Wells, D.R. Anderson, M. Rodger, et al.

Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer

Ann Intern Med, 135 (2) (2001), pp. 98–107

[24]

R. Niska, F. Bhuiya, J. Xu

National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary

Natl Health Stat Report, 26 (2010), pp. 1–31

[25]

F. Giachino, M. Loiacono, M. Lucchiari, et al.

Rule out of acute aortic dissection with plasma matrix metalloproteinase 8 in the Emergency Department

Crit Care, 17 (1) (2013), p. R33

[26]

A.M. Booher, E.M. Isselbacher, C.A. Nienaber, et al.

The IRAD classification system for characterizing survival after aortic dissection

Am J Med, 126 (8) (2013), p. 730 [e719-724]

[27]

T.T. Tsai, R. Fattori, S. Trimarchi, et al.

Long-term survival in patients presenting with type B acute aortic dissection: insights from the International Registry of Acute Aortic Dissection

Circulation, 114 (21) (2006), pp. 2226–2231

[28]

P. Ohlmann, A. Faure, O. Morel, et al.

Lower circulating Sta-Liatest D-Di levels in patients with aortic intramural hematoma compared with classical aortic dissection

Crit Care Med, 37 (3) (2009), pp. 899–901

[29]

F.P. Sarasin, M. Louis-Simonet, J.M. Gaspoz, et al.

Detecting acute thoracic aortic dissection in the emergency department: time constraints and choice of the optimal diagnostic test

Ann Emerg Med, 28 (3) (1996), pp. 278–288

[30]

T. Suzuki, A. Distante, A. Zizza, et al.

Preliminary experience with the smooth muscle troponin-like protein, calponin, as a novel biomarker for diagnosing acute aortic dissection

Eur Heart J, 29 (11) (2008), pp. 1439–1445