The role of biomarkers in the setting of acute aortic syndrome?

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2014 ESC Guidelines on the diagnosis and treatment of aortic diseases

Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult

The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC)
**Figure 6** Flowchart for decision-making based on pre-test sensitivity of acute aortic syndrome. AAS = abdominal aortic aneurysm; AD = aortic dissection; CT = computed tomography; MRI = magnetic resonance imaging; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.
Diagnosis of Acute Aortic Dissection by D-Dimer

The International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) Experience

Toru Suzuki, MD; Alessandro Distante, MD; Antonella Zizza, MS; Santi Trimarchi, MD; Massimo Villani, MD; Jorge Antonio Salerno Uriarte, MD; Luigi De Luca Tupputi Schinosa, MD; Attilio Renzulli, MD; Federico Sabino, MD; Richard Nowak, MD; Robert Birkhahn, MD; Judd E. Hollander, MD; Francis Counselman, MD; Ravi Vijayendran, PhD; Eduardo Bossone, MD; Kim Eagle, MD; for the IRAD-Bio Investigators

From the University of Tokyo, Tokyo, Japan (T.S.); Istituto Scientifico Biomedico Euro Mediterraneo, Brindisi, Institute of Clinical Physiology, National Research Council, Lecce, and University Medical School, Pisa, Italy (A.D.); Institute of Clinical Physiology, National Research Council, Lecce, Italy (A.Z.); IRCCS Policlinico San Donato, Milan, Italy (S.T.); Vito Fazzi Hospital, Lecce, Italy (M.V.); Universita degli studi dell’Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Italy (J.A.S.U.); Policlinico Hospital, Bari, Italy (L.D.L.T.S.); UMG, Catanzaro, Italy (A.R.); ALIV Healthcare R&D, Forte dei Marmi, Italy (F.S.); Henry Ford Hospital, Detroit, Mich (R.N.); New York Methodist Hospital, Brooklyn (R.B.); University of Pennsylvania, Philadelphia (J.E.H.); Eastern Virginia Medical School, Norfolk (F.C.); Biosite, San Diego, Calif (R.V.); National Research Council, Lecce, Italy (E.B.); and University of Michigan, Ann Arbor (K.E.).

(Circulation. 2009;119:2702-2707.)
Patient demographics

- 220 cases initially suspected of having acute dissection
- largest sample size for aortic dissection biomarker study

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cases (males)</th>
<th>Age (yrs)</th>
<th>D-dimer (ng/ml)</th>
<th>25%ile</th>
<th>50%ile</th>
<th>75%ile</th>
<th>99%ile</th>
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<tbody>
<tr>
<td>Type A aortic dissection</td>
<td>64 (39)</td>
<td>60.6 ± 14.8</td>
<td>3213 ± 1465</td>
<td>2083</td>
<td>3310</td>
<td>5000</td>
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<tr>
<td>Type B aortic dissection</td>
<td>23 (14)</td>
<td>60.2 ± 12.4</td>
<td>3574 ± 1430</td>
<td>2265</td>
<td>3902</td>
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<tr>
<td>Myocardial infarction</td>
<td>46 (36)</td>
<td>65.2 ± 15.0</td>
<td>1459 ± 1650</td>
<td>325</td>
<td>694</td>
<td>2216</td>
<td>5000</td>
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<tr>
<td>Angina pectoris</td>
<td>37 (28)</td>
<td>61.7 ± 13.2</td>
<td>760 ± 974</td>
<td>250</td>
<td>319</td>
<td>250</td>
<td>4337</td>
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<tr>
<td>Pulmonary embolism</td>
<td>5 (2)</td>
<td>50.0 ± 32.0</td>
<td>2452 ± 1891</td>
<td>776</td>
<td>2765</td>
<td>3931</td>
<td>4515</td>
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<tr>
<td>Other uncertain diagnosis</td>
<td>45 (26)</td>
<td>62.2 ± 15.4</td>
<td>1399 ± 1511</td>
<td>250</td>
<td>676</td>
<td>2252</td>
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</table>

87 ADs

133 controls
### Diagnostic performance at cut-off of 500 ng/ml

- **500 ng/ml cut-off is commonly used for pulmonary embolism**

<table>
<thead>
<tr>
<th>AD</th>
<th>Control</th>
<th>Sens</th>
<th>95% CI</th>
<th>Spec</th>
<th>95% CI</th>
<th>PLR</th>
<th>NLR</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>A&amp;B</td>
<td>All</td>
<td>46.6</td>
<td>37.9 to 55.5</td>
<td>1.81</td>
<td>0.07</td>
<td>37.6</td>
<td>97.6</td>
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<tr>
<td></td>
<td>MI only</td>
<td>39.1</td>
<td>25.1 to 54.6</td>
<td>1.59</td>
<td>0.09</td>
<td>34.6</td>
<td>97.1</td>
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<td>62.2</td>
<td>44.8 to 77.5</td>
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<td>20.0</td>
<td>0.5 to 71.6</td>
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<td>28.7</td>
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<td>44.4</td>
<td>29.6 to 60.0</td>
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<td>36.7</td>
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<td>29.6 to 60.0</td>
<td>1.72</td>
<td>0.10</td>
<td>36.5</td>
<td>96.8</td>
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</table>

- **NLR <0.1 against all controls in first 24 hrs after Sx onset**
Summary of findings

Patient presenting with chest pain

Rapid diagnostic test
Blood test (incl. D-dimer)
Chest X-ray, Electrocardiogram
Echocardiogram

D-dimer < 500 ng/ml
- Rule-out aortic dissection if within 24 hrs of onset and if no other signs of disease are seen on other tests

D-dimer > 1600 ng/ml
- Rule-in aortic dissection if within 6 hrs of onset and continue to further diagnostic test such as imaging procedure

Negative likelihood ratio <0.1  Positive likelihood ratio >10
Biomarkers of aortic diseases

Toru Suzuki, MD, a Eduardo Bossone, MD, b,c Daigo Sawaki, MD, c Rolf Alexander Jánosi, MD, d Raimund Erbel, MD, c Kim Eagle, MD, c and Ryozo Nagai, MD a Tokyo, Japan; Milan, and Salerno, Italy; Essen, Germany; and Ann Arbor, MI

The development of diagnostic biomarkers of acute cardiovascular disease remains an important topic of interest given potential use to aid in early diagnosis. Cardiac biomarkers of ischemia and heart failure have already proven to be clinically useful. Biomarkers of aortic diseases are also needed, especially for life-threatening conditions such as aortic dissection. In this review, we discuss the present status of the development of biomarkers of aortic diseases. Although aortic dissection has been most vigorously pursued, there has also been notable recent progress in biomarkers of aneurysms and inflammatory aortic disease. (Am Heart J 2013;165:15-25.)
High index of suspicion for AAS
Determine pre-test risk by combination of risk condition, history and exam

Intermediate Risk
Any single risk feature present

Low Risk
No high risk feature present

High Risk
Two or more risk features present

EKG, CXR
BLOOD TEST

D-dimer > 500 µg/L
PE?

D-dimer > 1600 µg/L
(within 6 hours Sx onset)
Very high suspicion of AAS

Initiate appropriate therapy

Identified

D-dimer < 500 µg/L
Consider alternate diagnosis

Immediate surgical consultation and expedited aortic imaging

TTE

If suspicion for AAS still remains (possible IMH-PAU-thrombosed false lumen)

TEE (preferred if clinically unstable)
CT (image entire aorta: chest to pelvis)

If AAS present proceed to treatment pathway

If suspicion for AAS still remains, consider secondary imaging study
Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes: The ADvISED Prospective Multicenter Study
Peiman Nazerian, Christian Mueller, Alexandre de Matos Soeiro, Bernd A. Leidel, Sibilla Anna Teresa Salvadeo, Francesca Giachino, Simone Vanni, Karin Grimm, Múcio Tavares Oliveira, Jr, Emanuele Pivetta, Enrico Lupia, Stefano Grifoni, Fulvio Morello and for the ADvISED Investigators

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doi: 10.1161/CIRCULATIONAHA.117.029457
Flow chart summarizing diagnostic workup

enrolled patients
(N=1850)

conclusive diagnostic data obtained during index ED visit?

Yes
(N=835)

- Conclusive imaging (N=831):
  - CTA (N=815)
  - CTA + TEE (N=3)
  - TEE (N=13)
- Surgery* (N=3)
- Autopsy (N=1)

- Angiography (N=35)

No
(N=1015)

14-day follow-up

lost at follow-up
(N=2)

- 14-day clinical follow-up + admission to hospital + conclusive imaging (N=30):
  - CTA (N=22)
  - CTA + TEE (N=1)
  - CTA + angiography (N=4)
  - TEE (N=2)
  - MRA (N=1)

- 14-day clinical follow-up + admission to hospital (N=179)

- 14-day clinical follow-up, outpatients after ED discharge (N=635)

AAS present
(N=234)

AAS absent
(N=601)

AAS present
(N=7)

AAS absent
(N=1006)
Table 3. Diagnostic Variables of the ADD-RS Integrated With DD Testing for Diagnosis or Rule Out of AAS in 1848 Included Patients

<table>
<thead>
<tr>
<th>Diagnostic Variable</th>
<th>Diagnostic Strategy (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ADD-RS=0 Plus DD &lt;500 ng/mL</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>99.6 (97.7–100)</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>18.2 (16.4–20.2)</td>
</tr>
<tr>
<td>PPV, %</td>
<td>15.4 (13.7–17.3)</td>
</tr>
<tr>
<td>LR+</td>
<td>1.22 (1.19–1.25)</td>
</tr>
<tr>
<td>NPV, %</td>
<td>99.7 (98.1–100)</td>
</tr>
<tr>
<td>LR−</td>
<td>0.02 (0.003–0.16)</td>
</tr>
</tbody>
</table>
Proposed diagnostic algorithm based on pretest probability assessment and D-dimer

1. Chest/abdominal/back pain syncope perfusion deficit
   
   - Pre-test probability assessment with ADD-RS
     
     a. ADD-RS ≤ 1
       
       i. D-dimer testing
         
         - D-dimer < 500 ng/ml
           
           AAS ruled out†
         
         - D-dimer ≥ 500 ng/ml
           
           CTA
     
     b. ADD-RS > 1
       
       CTA
Magnitude of Soluble ST2 as a Novel Biomarker for Acute Aortic Dissection
Yuan Wang, Xin Tan, Hai Gao, Hui Yuan, Rong Hu, Lixin Jia, Junming Zhu, Lizhong Sun, Hongjia Zhang, Lianjun Huang, Dong Zhao, Pei Gao and Jie Du

Circulation. 2018;137:259-269; originally published online November 16, 2017; doi: 10.1161/CIRCULATIONAHA.117.030469
## Overall study design

<table>
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<th>Study set</th>
<th>Discovery Set*</th>
<th>Validation cohort'</th>
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<tbody>
<tr>
<td></td>
<td>(n=1027: 677 AD + 234 AMI + 49 PE + 67 Healthy control)</td>
<td>(n=333)</td>
</tr>
<tr>
<td>Study population</td>
<td>AD cases</td>
<td>Non-AD controls</td>
</tr>
<tr>
<td>AAD vs AMI (Time onset ≤ 24 hours)</td>
<td>n=245</td>
<td>n=234</td>
</tr>
<tr>
<td>AAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAD vs PE (Time onset ≤ 14 days)</td>
<td>n=443</td>
<td>n=49</td>
</tr>
<tr>
<td>AAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td></td>
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<tr>
<td>Additional subjects for sST2 distribution</td>
<td>AD (time onset &gt; 14 days)</td>
<td>Healthy control</td>
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<tr>
<td>AD</td>
<td>n=234</td>
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<tr>
<td>Healthy control</td>
<td></td>
<td>n=67</td>
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<td>Study design</td>
<td>Retrospective</td>
<td>Prospective</td>
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</table>
Receiver operating characteristic curves of sST2 in the validation cohort

- sST2, 50 ng/mL
- sST2, 40 ng/mL
- sST2, 36 ng/mL
- sST2, 34.6 ng/mL
- D-dimer, 323 ng/mL
- D-dimer, 500 ng/mL

AUROC (95% CI)
- 333 patients (114 patients with AAD)
  - sST2: 0.97 (0.95, 0.98)
  - D-Dimer: 0.91 (0.88, 0.94)
  - cTnI: 0.50 (0.44, 0.56)

- 329 patients (113 patients with AAD)
<table>
<thead>
<tr>
<th>Threshold</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Accuracy, %</th>
<th>PLR</th>
<th>NLR</th>
<th>PPV, %†</th>
<th>NPV, %‡</th>
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<tbody>
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<td>Patients (n=333, with AAD n=114)</td>
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<tr>
<td>sST2, ng/mL</td>
<td>34.6*</td>
<td>99.1</td>
<td>84.9</td>
<td>89.8</td>
<td>6.6</td>
<td>0.01</td>
<td>68.7</td>
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<td>36</td>
<td>93.0</td>
<td>88.1</td>
<td>89.8</td>
<td>7.8</td>
<td>0.08</td>
<td>72.3</td>
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<td>40</td>
<td>87.7</td>
<td>91.3</td>
<td>90.1</td>
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<td>0.13</td>
<td>77.1</td>
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<td>50</td>
<td>74.6</td>
<td>95.0</td>
<td>88.0</td>
<td>16.3</td>
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<td>83.2</td>
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<td>D-dimer, ng/mL</td>
<td>323*</td>
<td>93.9</td>
<td>78.5</td>
<td>83.8</td>
<td>4.4</td>
<td>0.08</td>
<td>59.3</td>
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<td>500 (recommended)†</td>
<td>87.7</td>
<td>82.2</td>
<td>84.1</td>
<td>4.9</td>
<td>0.15</td>
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</tr>
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Summary

• Diagnostic biomarkers for aortic disease are needed.

• Development and implementation are ongoing. Initial markers are already used clinically.

• Guidelines recognize importance of biomarker-guided diagnosis.