BIOMARKERS IN EMERGENCY MEDICINE

ESIM 2014

Nicola Montano
The Peppa Pig Talk
BIOMARKERS

• The use of biomarkers has changed approach of diagnosis and treatment procedures in emergency medicine, especially in the field of cardiovascular disorders.
THE IDEAL BIOMARKER

• High sensitivity → RULE OUT (SnOut)
• High specificity → RULE IN (SpIn)

• However in clinical practice rarely high sensitivity and specificity coexist in the same biomarker!
IDEAL TEST

Always negative in healthy pz

Always positive in affected pz

Not affected

affected

cut-off
REAL WORLD

Not affected

affected

cut-off
- True negative
- True positive
- False negative
- False positive
- Not affected
- Affected
- Cut-off
SE & SP

- The **sensitivity** describes the ability of a diagnostic test to identify true disease without missing anyone by leaving the disease undiagnosed. Thus, a high sensitivity test has few false negatives and is effective at ruling conditions “out” (SnOut).

- The **specificity** describes the ability of a diagnostic test to be correctly negative in the absence of disease without mislabeling anyone. Thus, a high specificity test has few false positives and is effective in ruling conditions “in” (SpIn).
THE REAL PRACTICE

• Rarely a single positive/negative value of a biomarker make or exclude a diagnosis
• The biomarker result should be inserted and interpreted in a diagnostic algorithm
NT-PROBNP
1. Male 72 years old; history of hypertension, myocardial infarction 5 years ago. Came to ER for dyspnea and dry cough. BP 140/85, HR 96 bpm, Sat. O2 93% on air. Temperature 38°C. No peripheral edema, plain jugulars. Lungs: Breath sounds are clear bilaterally, rales at the bases.

2. Male 83aa, years old, history oh hypertension, diabetes, chronic ischemic heart disease. Came to ER for worsening of dyspnea from the day before. BP 180/100, HR 108 bpm, Sat. O2 88% on air. Peripheral edema. Lung: basal crepitations.

3. Female, 63 years old, current smoker. Came to ER for worsening dyspnea an cough since one week. BP 160/90, HR 108 bpm, Sat. O2 88% on air. Mild peripheral edema. Lung: wheezes and ronchi.

Who is affected by acute heart failure? Who need NT-PROBNP dosage?
The regulation and actions of the natriuretic peptides

VOLUME CONTROL
- Neg feedback
  - ↓ Plasma Vol
    - ↓ BP
    - ↓ Aldo
    - ↓ Renin
    - ↑ FF (Na)
    - ↓ SNA
    - ↓ VSM cell growth

STRETCH
- Atrial receptor
- Ventricular receptor

ANP (BNP)
- BNP (ANP)

Clearance receptors
Endopeptidase E.C. 24.11
Bio receptors
↑ CNP
B NATRIURETIC PEPTIDES
## BNP vs. NT-proBNP

<table>
<thead>
<tr>
<th></th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HALF LIFE</strong></td>
<td>13-20 min</td>
<td>25-70 min</td>
</tr>
<tr>
<td><strong>KINETIC</strong></td>
<td>peak: 9 hours</td>
<td>peak: 6-9 hours</td>
</tr>
<tr>
<td><strong>CLEARANCE</strong></td>
<td>active+renal</td>
<td>Renal</td>
</tr>
</tbody>
</table>
POTENTIAL CLINICAL USE

• Differential diagnosis of acute dyspnea: acute heart failure vs other causes
• Prognostic stratification of chronic heart failure
• Prognostic stratification of acute cardiovascular events (acute myocardial infarction, pulmonary embolism)
• Monitoring and guiding heart failure treatment
• Screening population at heart failure risk
• Differential diagnosis of acute dyspnea: acute heart failure vs other causes
Maisel AS et al., NEJM 2002;347:161-7
WOW! Does NT proBNP solve our diagnostic dilemmas in ED!?
NT-proBNP: FALSE NEGATIVE results

• Obesity (BMI >30)

• “Flash” pulmonary edema

• Hypotiroidism
NT-proBNP: FALSE POSITIVE

- Chronic heart failure without re-exacerbation
- Acute coronary syndrome
- Arrhythmias (es. atrial fibrillation)
- Restrictive and hypertrophic heart disease
- Heart valve disease
- Amyloidosis
- Cardiac Graft Vs Host Disease
EXTRACARDIAC CAUSE OF NT-proBNP ELEVATION

- Age
- Renal failure
- Sepsis
- Lung disease (pulmonary embolism, COPD, pulmonary hypertension, ARDS)
- Stroke, cerebral hemorrhage
- BMI < 25
- Hypertyroidism
- Anemia
- Neoplasm
- Cushing, Hyperaldosteronism
CUT-OFF (for acute heart failure)

- **ESCLUSION:**
  - BNP: 100 pg/ml
  - NT-proNP: 300 pg/ml

LR = 0.12
## AGE AND NTproBNP CUT OFF

The ICON Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Cut-off NT-proBNP</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>Acc</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>450 ng/L</td>
<td>97</td>
<td>93</td>
<td>76</td>
<td>99</td>
<td>94</td>
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<tr>
<td>50–75 years</td>
<td>900 ng/L</td>
<td>90</td>
<td>82</td>
<td>83</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>1800 ng/L</td>
<td>85</td>
<td>73</td>
<td>92</td>
<td>55</td>
<td>83</td>
</tr>
<tr>
<td>Rule in, overall</td>
<td></td>
<td>90</td>
<td>84</td>
<td>88</td>
<td>66</td>
<td>85</td>
</tr>
</tbody>
</table>

Januzzi JL et al., Eur Heart J 2006;27:330-37
Recommendations for the use of natriuretic peptides in acute cardiac care†

### BNP
- **<100 ng/L**
  - HF unlikely
- **100–500 ng/L**
  - Grey zone
  - HF confirmation by imaging (echocardiography)
- **>500 ng/L**
  - HF likely
  - Confirmation by imaging (echocardiography)

### NT-proBNP
- **<300 ng/L**
  - HF unlikely
- **Grey zone**
- **>75 y >1800 ng/L**
  - Grey zone
  - Diagnosis by imaging (echocardiography)
  - HF likely
  - Confirmation by imaging (echocardiography)

*Eur. Heart J. 2012; 33. 2001*
During ‘flash’ pulmonary oedema, BNP levels may remain normal at the time of admission. Otherwise, BNP has a good negative predictive value to exclude heart failure. Various clinical conditions may affect the BNP concentration [...]. If elevated concentrations are present, further diagnostic tests are required. If AHF is confirmed, increased levels of plasma BNP and NT-pro BNP carry important prognostic information. The exact role of BNP remains to be fully clarified.
Does this test really change the approach and outcome of my patients?
...in Emergency Department

*B-Type Natriuretic Peptide Testing and the Accuracy of Heart Failure Diagnosis in the Emergency Department*

Prospective randomized study, 2 centers, blind, 612 pazienti

Lokuge et al. Circulation 2010;3:104-110
...MEANTIME... WAITING FOR BPN RESULTS...

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
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<tbody>
<tr>
<td>pH</td>
<td>7.43</td>
<td>mmHg</td>
</tr>
<tr>
<td>pCO2</td>
<td>65</td>
<td>mmHg</td>
</tr>
<tr>
<td>pO2</td>
<td>69</td>
<td>mmHg</td>
</tr>
<tr>
<td>Na+</td>
<td>141</td>
<td>mmol/L</td>
</tr>
<tr>
<td>K+</td>
<td>2.9</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Ca++</td>
<td>1.03</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Glu</td>
<td>109</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Lat</td>
<td>1.1</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Hct</td>
<td>27</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Derived Parameters</th>
<th>Value</th>
<th>Unit</th>
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<tbody>
<tr>
<td>Ca++(7.4)</td>
<td>1.04</td>
<td>mmol/L</td>
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<tr>
<td>HCO3-</td>
<td>43.1</td>
<td>mmol/L</td>
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<td>HCO3std</td>
<td>37.9</td>
<td>mmol/L</td>
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<tr>
<td>TCO2</td>
<td>46.1</td>
<td>mmol/L</td>
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<tr>
<td>BEc</td>
<td>18.8</td>
<td>mmol/L</td>
</tr>
<tr>
<td>BET(B)</td>
<td>16.7</td>
<td>mmol/L</td>
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<tr>
<td>SO2c</td>
<td>94</td>
<td>%</td>
</tr>
<tr>
<td>THbc</td>
<td>8.4</td>
<td>g/dL</td>
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</table>

[Image of medical equipment]
PITFALLS

• FLASH PULMONARY OEDEMA
• RENAL FAILURE
• ATRIAL FIBRILLATION
• CONCOMITANT DISEASES (acute heart failure diagnosis doesn’t exclude a concomitant pulmonary embolism, COPD....)
TAKE-HOME MESSAGES

• Good rule out test
• Uncertainty as a rule in test
• Poor adjunctive information in presence of otherwise highly suggestive clinical picture

→ useful in intermediate probability patients
ASK YOURSELF

• Which is acute heart failure pretest probability in this patients?

• Does this patient has some characteristic that may preclude results reliability?

• Does the test really change clinical approach in this patient?
D-DIMMER
ER, 9 PM: on medical shift

1 → Female 41 years old. Medication: estroprogestinic. Came to medical attention for left chest pain, exacerbated by breathing; mild dyspnea and mild dry cough

2 → Female 85 years old; history of hypertension, diabetes, Horton. Came to medical attention for syncope with prodrome symptoms

3 → Female 27 years old, heavy smoker. Came to medical attention for throat constriction after a discussion with his husband

4 → Male 68 years old. History of atrial fibrillation, chronic heart failure (EF 35%), with many hospitalization for exacerbation, renal failure, poor compliance to medication. Came for worsening dyspnea

5 → Female 27 years old, pregnant III trimester. Obese. Came for asthenia, exertion and nocturnal dyspnea.

Who does need CT scan?
Tests types

• ELISA (enzyme-linked immunosorbent assays)

• LATEX AGGLUTINATION
clinical gestalt and probability scores present similar sensitivity when combined with high sensitivity d-dimer test in excluding pulmonary embolism
Which patient? Which dimer test?

- High sensitivity d-dimer (ELISA, quantitative latex) → a negative result allow PE exclusion in patients with low/intermediate pretest probability
- Intermediate sensitivity d-dimer (lattex) → a negative result allow PE exclusion only in patients with low pretest probability

ESC guidelines, European Heart J 2008
D-dimer and age

• D-dimer value increases with age
  - 16-40 years, 294 ng/mL
  - 40-60 years, 387 ng/mL
  - 60-80 years, 854 ng/mL
  - > 80 years, 1397 ng/mL

Harper 2007

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>51-60</th>
<th>61-70</th>
<th>71-80</th>
<th>&gt; 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP (%) traditional cut off</td>
<td>57.6</td>
<td>39.4</td>
<td>24.5</td>
<td>14.7</td>
</tr>
<tr>
<td>SP (%) cut off age adjusted (x 10)</td>
<td>62.3</td>
<td>49.5</td>
<td>44.2</td>
<td>35.2</td>
</tr>
</tbody>
</table>

Schouten BMJ 2013
Original Investigation

Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism
The ADJUST-PE Study

Marc Righini, MD; Josien Van Es, MD, PhD; Paul L. Den Exter, MD; Pierre-Marie Roy, MD, PhD; Franck Verschuren, MD; Alexandre Ghuysen, MD; Olivier T. Rutschmann, MD; Olivier Sanchez, MD; Morgan Jaffrelot, MD; Albert Trinh-Duc, MD; Catherine Le Gall, MD; Farès Moustafa, MD; Alessandra Principe, MD; Anja A. Van Houten, MD; Marije Ten Wolde, MD, PhD; Renée A. Douma, MD, PhD; Germa Hazelaar, MD; Petra M. G. Erkens, PhD; Klaas W. Van Kralingen, MD; Marco J. J. H. Grootenboers, MD, PhD; Marc F. Durian, MD; Y. Whitney Cheung, MD; Guy Meyer, MD; Henri Bounamaux, MD; Menno V. Huisman, MD, PhD; Pieter W. Kamphuisen, MD, PhD; Grégoire Le Gall, MD, PhD

IMPORTANCE  D-dimer measurement is an important step in the diagnostic strategy of clinically suspected acute pulmonary embolism (PE), but its clinical usefulness is limited in elderly patients.

OBJECTIVE  To prospectively validate whether an age-adjusted D-dimer cutoff, defined as age × 10 in patients 50 years or older, is associated with an increased diagnostic yield of D-dimer in elderly patients with suspected PE.
**INTERVENTIONS** All consecutive outpatients who presented to the emergency department with clinically suspected PE were assessed by a sequential diagnostic strategy based on the clinical probability assessed using either the simplified, revised Geneva score or the 2-level Wells score for PE; highly sensitive D-dimer measurement; and computed tomography pulmonary angiography (CTPA). Patients with a D-dimer value between the conventional cutoff of 500 μg/L and their age-adjusted cutoff did not undergo CTPA and were left untreated and formally followed-up for a 3-month period.

**RESULTS** Of the 3346 patients with suspected PE included, the prevalence of PE was 19%. Among the 2898 patients with a nonhigh or an unlikely clinical probability, 817 patients (28.2%) had a D-dimer level lower than 500 μg/L (95% CI, 26.6%-29.9%) and 337 patients (11.6%) had a D-dimer between 500 μg/L and their age-adjusted cutoff (95% CI, 10.5%-12.9%). The 3-month failure rate in patients with a D-dimer level higher than 500 μg/L but below the age-adjusted cutoff was 1 of 331 patients (0.3% [95% CI, 0.1%-1.7%]). Among the 766 patients 75 years or older, of whom 673 had a nonhigh clinical probability, using the age-adjusted cutoff instead of the 500 μg/L cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer from 43 of 673 patients (6.4% [95% CI, 4.8%-8.5%]) to 200 of 673 patients (29.7% [95% CI, 26.4%-33.3%]), without any additional false-negative findings.
CONCLUSIONS AND RELEVANCE  Compared with a fixed D-dimer cutoff of 500 μg/L, the combination of pretest clinical probability assessment with age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be considered ruled out with a low likelihood of subsequent clinical venous thromboembolism.
D-dimer and pregnancy

• D dimer value increase with gestational age
• In the II trimester only 22% present DD < 500
• In the II trimester 0% DD < 500

• In the I trimester 84% has normal DD
• In the II trimester 33% has normal DD
• In the II trimester 0%

50 pazienti
Kline 2005
89 pazienti
Kovac 2010
D-dimer and pregnancy

- D-dimer testing should not be performed to diagnose acute VTE in pregnancy (Grado C)
  
  Royal College of obstetrician and gynaecologist GUIDELINES, 2007

- In pregnant women with suspected PE, we suggest that D-dimer not be used to exclude PE (weak recommendation very low-quality evidence)
  
  ATS e STR Guidelines, Leung 2011

- D-dimer testing is not recommended for the evaluation of suspected DVT or PE in pregnancy or the early postpartum period. (Group Consensus Level 1)
  
  Australasian guidelines, Mclintock 2012
D-dimer kinetic

• One study analysed d-dimer kinetic after a surgical procedure in 154pz

• Peak: 7 days

• Return to normal values: 25 - 38 days

Dindo 2009
Das Leben (dimer) der Anderen

• Would I have asked d-dimer?
• Which is pretest probability in this pts?
• Other causes of positive results?
False positive causes

- Surgery
- Trauma
- Burns
- Infection
- Pregnancy and the puerperium
- Disseminated intravascular coagulation
- Cancer
- Myocardial infarction
- Stroke
- Atrial fibrillation
- Connective tissue disorders
- Inflammatory bowel disease
- Thrombolytic therapy
- Hemolysis
- Advanced age
D-dimer and aortic dissection

• SE 97%
• SP 56%
• LR- 0.06
• LR+ 2.43

Shimony, Am J Cardiol 2011

→ DD may be useful in excluding aortic dissection in low-intermediate probability
→ this strategy safety has not otherwise been properly evaluated in prospective study
Take home messages

➔ Test SnOUT
➔ Use caution in elderly patients, consider possibly cut-off adjusted for age
➔ There is no evidence of a safe use in pregnancy
➔ Serial measurements do not make sense
➔ Use caution to rule out an aortic dissection
➔ Someone else may have requested DD but now the patient is your!
TROPONIN
EMERGENCY ROOM

- 92 years old, history of dementia, hypertension. Came to ED for fever, vomiting, malaise. ECG→aspecific STchanges
- 60 years old, history of idiopathic cardiomyopathy, came to ED for epigastric discomfort, since 1 hour ECG→AF, 110 bpm, aspecific STchanges
- 48 years old, smoker, history of hypertension. Came to ED for typical chest pain lasted one hour (started 2 hours ago). ECG T negative inferior leads

WHO IS AFFECTED BY MYOCARDIAL INFARCTION???
Third Universal Definition of Myocardial Infarction

Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chatman and Harvey D. White: the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction

Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile limit (URL) and with at least one of the following:

- Symptoms of ischemia.
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.
High sensitive troponins

• The introduction of ultrasensitive troponin has greatly reduced the possibility to miss an acute coronary syndrome diagnosis
• The ultrasensitive troponin rise within 2-3 hours after cardiac damage, anticipating the time of diagnosis and then treatment
• However, with the introduction of ultrasensitive biomarkers, a reduction in specificity was observed
FALSE POSITIVE

• The troponins are specific markers for myocardial tissue, however, are not specific for ischemic damage
• They rise, therefore, in many non-ischemic heart disease or extracardiac disease that can cause stress myocardial
<table>
<thead>
<tr>
<th>Cardiac Causes</th>
<th>Noncardiac Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac contusion resulting from trauma</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Severe pulmonary hypertension</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
<td>Stroke, subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Acute and chronic heart failure</td>
<td>Infiltrative diseases, e.g., amyloidosis</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Cardiotoxic drugs</td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td>Critical illness</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Tachyarrhythmia</td>
<td>Extensive burns</td>
</tr>
<tr>
<td>Bradyarrhythmia, heart block</td>
<td>Extreme exertion</td>
</tr>
<tr>
<td>Apical ballooning syndrome</td>
<td></td>
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<tr>
<td>Post–percutaneous coronary intervention</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis with myocyte necrosis</td>
<td></td>
</tr>
<tr>
<td>Myocarditis or endocarditis/pericarditis</td>
<td></td>
</tr>
</tbody>
</table>
TROPONIN and AGE

Diagnostic accuracy for NSTEMI
(measurement at presentation in ED)

< 70 YEARS OLD
- SE 91%
- SP 88%

≥70 anni YEARS OLD
- SE 96%
- SP 51%

Am J Card 2013;111(12):1701
BACKGROUND TO INTERPRETATION

- kinetic
- Pretest probability
kinetic hs-TN IN INFARCTION

Start to rise 3-6 h

Peak 12-96 h

Return to normal 7-14 days

Start to rise 3-6 h
USEFULNESS OF A NEGATIVE TEST (RULE OUT)

<table>
<thead>
<tr>
<th>Time of Testing</th>
<th>Detection of Myocardial Infarction % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td></td>
</tr>
<tr>
<td>0 to &lt;6 hr after chest-pain onset</td>
<td>87.7</td>
</tr>
<tr>
<td>6 to 12 hr after chest-pain onset</td>
<td>94.5</td>
</tr>
<tr>
<td>&gt;12 hr after chest-pain onset</td>
<td>100</td>
</tr>
<tr>
<td>After admission</td>
<td></td>
</tr>
<tr>
<td>At 3 hr</td>
<td>100</td>
</tr>
<tr>
<td>At 6 hr</td>
<td>100</td>
</tr>
</tbody>
</table>

* The diagnostic criteria for acute myocardial infarction were a troponin I level (as measured by sensitive assay) above the 99th percentile of 0.04 ng per milliliter in at least one measurement and a rise or fall in the level of at least 30%.

Keller NEJM 2009
USEFULNESS OF A POSITIVE TEST

• If high clinical (symptoms-ECG) probability of myocardial infarction → only a single positive value make diagnosis

• Otherwise, a curve of ascent / descent value (depending on the timing of the pain) suggests infarction
Kinetic in other cardiac disease

1. Myocarditis
2. CHF
3. Myocardial infarction

DELTA TROPONIN
OPEN ISSUES: DELTA hs-Tn

• It is not yet clear the ideal threshold of troponine variation from baseline (delta) indicative of myocardial infarction

• The literature often suggest a 20% variation from baseline as indicative infarction (National Academy of Clinical Biochemistry laboratorymedicine practice guidelines in 2007)

• Other evidences recommend to indicative of infarction an absolute delta of 7-9 ng / L (Delta Cardiac Troponin Values in Practice: Are We Ready to Move Absolutely Forward to Clinical Routine? Clinical Chemistry 58:1; 8–10 (2012))
TAKE HOME MESSAGE
Hs-troponins

- Very sensitive biomarker: useful for **RULE OUT** → if the curve of troponin is negative, the probability that patients is affected by infarction is extremely low (NB some exception → unstable angina ... still exists)

- New generation troponins start to rise after myocardial damage earlier than conventional troponins: a second negative control at 3-6 h is sufficient to rule out myocardial infarction (if time of symptoms onset is certain and if the patient has remained asymptomatic)

- Although specific for cardiac tissue are not ischemic-specific, so they are less useful for the **RULE IN** → Positives values need to be interpreted in the the clinical picture and kinetics of biomarker must be evaluated
D dimer and hospitalized patients

- Both SE and SP are reduced
- DDimer evaluation in 234 out- vs 233 in-patients with suspected PE

<table>
<thead>
<tr>
<th></th>
<th>ELISA</th>
<th>SE (%)</th>
<th>SP (%)</th>
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<tbody>
<tr>
<td>outpatient</td>
<td>95</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>microlattex</td>
<td>90</td>
<td>48</td>
<td></td>
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<tr>
<td>inpatients</td>
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<td>20</td>
<td></td>
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<tr>
<td>microlattex</td>
<td>86</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Schrecengost 2003
Elevated troponin

- No
  - Pretest probability of ACS (risk factors, symptoms, ECG)
    - Low: ACS unlikely
    - High: Global risk
      - Low: Early conservative or invasive strategy
      - High: Early invasive strategy

- Yes
  - Pretest probability of ACS (risk factors, symptoms, ECG)
    - Low: ACS unlikely
      - Search for other causes
      - Early conservative or invasive strategy
    - High: Global risk
      - Early invasive strategy