CUTTING-EDGE DIAGNOSTICS FOR EVERYDAY PRACTICE: D-DIMER AND BNP

Maria Teresa B. Abola MD FPCP FPCC
D-Dimer
The Coagulation Cascade

Intrinsic Pathway (PTT)
- Factor XII
  - Factor XI
  - Factor IX
    - Factor IXa
      - Platelets
      - VIIIc
        - Ca²
      - Factor X
        - Factor Xa
          - Platelets
          - Va
            - Ca²
          - Prothrombin (II)
            - Thrombin (IIa)
              - Factor XIII
                - Factor XIIIa
                  - Fibrinogen
                    - Fibrin
                      - Thrombus
Dynamics of D-dimer Formation

Adam, et.al., Blood, March 2009
D-dimer

- unique marker of fibrin degradation that is formed by the sequential action of 3 enzymes: thrombin, factor XIIIa, and plasmin.
When are D-dimer levels raised?

- pulmonary embolism
- deep vein thrombosis
- disseminated intravascular coagulation
- Immediate postoperative state

Other conditions associated with elevated D-dimer level

• D-dimer levels are raised in many systemic illnesses associated with fibrin formation and degradation
  – elevated levels of D-dimers occur in most critically ill patients with severe infection, trauma, or inflammatory disorders

• Other conditions
  – acute cerebrovascular accident
  – acute myocardial infarction
  – unstable angina
  – Acute aortic dissection
  – atrial fibrillation
  – pneumonia
  – vasculitis
  – superficial phlebitis
  – many cancers including lung, prostate, cervical, and colorectal

* Only about 20% or less of patients admitted with these conditions will have a baseline D-dimer in the normal range

Sadosty AT, et.al. Emergency department D-dimer testing. J of Emergency Medicine, Dec 2001
Other factors affecting D-dimer levels

**INCREASED LEVELS**
- larger clots tend to produce **HIGHER levels** of circulating D-dimer
- Pregnancy
- Increasing age

**DECREASED LEVELS**
- impaired fibrinolytic activity
- D-dimer levels are **REDUCED** with initiation of heparin therapy, and may be lowered by two-thirds in patients on oral anticoagulants
- normalization of D-dimer levels with venous thromboembolism> 7 days duration

Sadosty AT, et.al. Emergency department D-dimer testing. J of Emergency Medicine, Dec 2001
Role of D-dimer measurement in the diagnosis of DVT or PE

1 CUS – compression ultrasonography
2 MSCT – multi-slice computed tomography
3 For negative CUS or MSCT and high PTP, consider venography or Lung VQ scan or pulmonary angiography

• D-dimer refers to highly sensitive assays; if less sensitive assay, use only in pts with low PTP

Righini, et.al., J ThrombHemostasis, 2008
Low Pretest Probability for DVT

DEEP VEIN THROMBOSIS DIAGNOSTIC ALGORITHM

High/Mod Sensitive D-dimer

Negative
- No DVT

Positive
- Proximal Ultrasound
  - Negative
    - No DVT
  - Positive
    - Whole leg Ultrasound
      - Negative
        - No DVT
      - Positive
        - Treat

Wells Model for DVT Assessment

<table>
<thead>
<tr>
<th>Clinical Parameter Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Paralysis or recent plaster immobilization of the lower extremities</td>
<td>+1</td>
</tr>
<tr>
<td>Recently bedridden for &gt;3 days or major surgery &lt;4 weeks</td>
<td>+1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>+1</td>
</tr>
<tr>
<td>Entire leg swelling</td>
<td>+1</td>
</tr>
<tr>
<td>Calf swelling &gt;3 cm compared with the asymptomatic leg</td>
<td>+1</td>
</tr>
<tr>
<td>Pitting edema (greater in the symptomatic leg)</td>
<td>+1</td>
</tr>
<tr>
<td>Previous DVT documented</td>
<td>+1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>+1</td>
</tr>
<tr>
<td>Alternative diagnosis (as likely or greater than that of DVT)</td>
<td>-2</td>
</tr>
</tbody>
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Total Score

<table>
<thead>
<tr>
<th>Score</th>
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<tbody>
<tr>
<td>&gt;3</td>
</tr>
<tr>
<td>1 or 2</td>
</tr>
<tr>
<td>&lt;0</td>
</tr>
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</table>


ACCP 2012 Guidelines, Chest Feb 2012
MODERATE PRETEST PROBABILITY FOR DVT

Highly sensitive D-dimer

Negative

No DVT

Negative

Repeat Proximal US in 1 week

Positive

Proximal Ultrasound

Whole leg Ultrasound

Positive

Treat

Treat

No DVT

Treat

ACCP 2012 Guidelines, Chest Feb 2012
## Kinds of D-dimer assays

<table>
<thead>
<tr>
<th>Type of Assay</th>
<th>Deep Vein Thrombosis</th>
<th>Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>ELISA microplate</td>
<td>94 (86-97)</td>
<td>53 (36-68)</td>
</tr>
<tr>
<td>ELFA (eg. Vidas)</td>
<td>96 (89-98)</td>
<td>46 (31-61)</td>
</tr>
<tr>
<td>LATEX quantitative (eg. Tinaquant)</td>
<td>93 (89-95)</td>
<td>53 (46-61)</td>
</tr>
<tr>
<td>Manual whole blood assay (eg. SimpliRed)</td>
<td>83 (67-93)</td>
<td>71 (57–82)</td>
</tr>
</tbody>
</table>

Righini, et.al., J ThrombHemostasis, 2008
Cost-effective Analysis

D-DIMER TESTING for ACUTE DVT/PE

• A diagnostic algorithm using CLINICAL PRETEST PROBABILITY FOLLOWED BY D-DIMER testing implies better use of resources for the health care sector as well as the society as a whole, compared to a traditional algorithm which involves diagnostic imaging for all patients.

Norlin, et.al., Thrombosis Research, 2010
Brain Natriuretic Peptides
Natriuretic Peptides

Atrial Natriuretic Peptide

Brain-type Natriuretic Peptide

C-type Natriuretic Peptide

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Cardiac distension
Sympathetic stimulation
Angiotensin II
Endothelin

1. ANP, BNP → Vasodilation
   → ↓ Ang II → ↓ Aldo
   → ↓ Blood Pressure
   → ↓ Blood Volume
   → Natriuresis Diuresis

2. ANP, BNP → ↓ Renin → GFR
BNP Metabolism

Stress/volume → Myocardial ischaemia

Increased BNP gene expression

COOH

Secretion 1:1

Proteolysis Furin

H2N

proBNP

Cardiomyocyte

NT-proBNP

H2N

COOH

Neutrale Endopeptidase

BNP

Proportion > 6:1

half-life: 120 min > half life: 20 min

Neurohumoral activation

COOH

NPR-A

Clearance receptor

Endocytosis

Regulated by proteolytic fragmentation

NEP

COOH

NPR-C

NH2

cGMP

Palazzuoli, et al., VHRM 2010
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologically active</td>
<td>Yes</td>
<td>no</td>
</tr>
<tr>
<td>Prohormone fragment</td>
<td>C-terminal</td>
<td>N-terminal</td>
</tr>
<tr>
<td>Half-life (min)</td>
<td>20</td>
<td>60-120</td>
</tr>
<tr>
<td>In vitro sample stability (room temperature)</td>
<td>4 hrs</td>
<td>&gt; 3 days</td>
</tr>
<tr>
<td>Sample type</td>
<td>Whole blood, plasma (EDTA)</td>
<td>Plasma (heparin) or serum</td>
</tr>
<tr>
<td>Assay measuring range (pg/ml)</td>
<td>5 – 5000</td>
<td>20 – 25,000*</td>
</tr>
</tbody>
</table>

* Vidas
When are BNP levels raised?

- Blood levels of BNP and proBNP are raised in patients with cardiac disease, particularly those with heart failure.
- Not merely a measure of systolic function, but may be raised in patients with elevated left ventricular (LV) filling pressure due to valve disease, diastolic dysfunction, and/or myocardial ischemia.
When is BNP indicated?

• may be used to help detect, diagnose, and evaluate the severity of heart failure
• may be done on patients who have symptoms such as edema, dyspnea, and fatigue
• Help differentiate between heart failure and other problems, such as lung disease/corpulmonale/pulmonary embolism
• may also be used to monitor the effects of treatment for heart failure and predict the cardiovascular prognosis in certain conditions other than heart failure, like acute coronary syndrome or cardiovascular surgery
Testing for BNP and NT-proBNP in the Diagnosis and Prognosis of Heart Failure


- **Diagnosis:** Pooled sensitivity and specificity values were 94 and 66% for BNP and 92 and 65% for NT-proBNP; there was minimal difference among settings (emergency, specialized clinics, and primary care). B-type natriuretic peptides also added independent diagnostic information above traditional measures for HF.
Testing for BNP and NT-proBNP in the Diagnosis and Prognosis of Heart Failure


• **Prognosis:** Both BNP and NT-proBNP were found to be independent predictors of mortality and other cardiac composite endpoints in patients:

  1) with risk of coronary artery disease (CAD) (risk estimate range = 1.10 to 5.40)
  2) diagnosed CAD (risk estimate range = 1.50 to 3.00)
  3) diagnosed HF patients (risk estimate range = 2.11 to 9.35)

• With respect to screening, the AUC values (range = 0.57 to 0.88) suggested poor performance.
• **Monitoring Treatment:** Studies showed therapy reduced BNP and NT-proBNP, however, relationship to outcome was limited and not consistent.

• There is **insufficient evidence to demonstrate that** BNP and NT-proBNP levels show change in response to therapies to manage stable chronic HF patients.
CLASS I RECOMMENDATION FOR HOSPITALIZED PATIENTS

• Concentrations of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) should be measured in patients being evaluated for dyspnea in which the contribution of HF is not known. Final diagnosis requires interpreting these results in the context of all available clinical data and ought not to be considered a stand alone test. (Level of Evidence: A)
Class IIA RECOMMENDATION: INITIAL CLINICAL ASSESSMENT OF PATIENTS WITH HEART FAILURE

Measurement of natriuretic peptides (BNP and NT-proBNP) can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. Measurement of natriuretic peptides (BNP and NT-proBNP) can be useful in risk stratification. (Level of Evidence: A)
Decisional algorithm for HF diagnosis on the basis of BNP measurement:

1. Patients with acute dyspnea
2. Physical examination, chest x-ray, ECG, NP measurement
   - BNP < 100 pg/mL, NT-proBNP < 300 pg/mL: HF very improbable 2%
   - BNP 100–400 pg/mL, >300 NT-proBNP < 1800 pg/mL: ECHO (LV dimension and EF, diastolic filling, MR severity)
   - BNP > 500 pg/mL, NT-proBNP > 1800 pg/mL: HF very probable 95%

Palazzuoli, et.al., VHRM 2010
BNP and Outcome

• Predischarge BNP measurement appears a strong predictor for identifying subsequent death or hospital admission at 6 months.

• In patients with CAD and preserved ventricular function, BNP provides strong and incremental prognostic information to traditional risk factors.

• Morbidity and mortality in CHF appear to increase markedly with a proBNP concentration >500 pg/mL.

Palazzuoli, et.al., VHRM 2010
Role of serial BNP measurement

- Parallel the clinical severity of HF as assessed by NYHA class in broad populations.
- Levels higher in hospitalized patients and tend to decrease during aggressive therapy for HF.
- Cannot be assumed that BNP levels can be used effectively as targets for adjustment of therapy in individual patients. Many patients taking optimal doses of medications continue to show markedly elevated levels of BNP, and some patients demonstrate BNP levels within the normal range despite advanced HF.
- Use of BNP measurements to guide the titration of drug doses has not been shown conclusively to improve outcomes more effectively than achievement of the target doses of drugs shown in clinical trials to prolong life.

Jessup, et.al., 2009 focused update of ACC/AHA Guidelines on Management of Heart Failure. JACC 2009
Factors that may affect BNP levels

Increased levels:
• Increasing age
• Females
• African-American and Hispanics
• kidney disease
• Atrial fibrillation

Decreased levels
• therapies for heart failure such as ACE inhibitors, beta blockers, and diuretics
• obesity

* While both BNP and NT-proBNP will rise with left ventricle dysfunction and either can be measured, they are not interchangeable and the results cannot be directly compared.

Palazzuoli, et.al., VHRM 2010
BNP TESTING for the management of ACUTE dyspnea

• Analysis of incremental 180-day cost-effectiveness showed that BNP guidance resulted in lower mortality and lower cost in 80.6%
• Results were robust to changes in most variables
• Testing of BNP is cost-effective in patients with acute dyspnea.

Mueller, et.al, Archives of Internal Med, 2006
Summary: D-dimer

- generated as a result of fibrin formation and fibrinolysis
- formed during processes like hemostasis, thrombosis, and tissue repair
- serves as a clinically useful marker for exclusion of VTE, and evaluation of the risk of VTE recurrence in select populations, when combined with clinical probability and other imaging techniques
- Clinicians need to be aware of the conditions and factors that affect D-dimer levels and the different performance characteristics of the available assays, to make safe and timely therapeutic decisions
Summary: BNP

• Synthesized and released mainly by ventricular myocardial cells in response to myocyte stretch, i.e. pressure or volume overload, heart failure
• Affected by several factors and conditions
• BNP and NT pro-BNP have different cut-off levels
• Highly recommended to rule out heart failure in patients who present with acute dyspnea
• Not advised to test in asymptomatic patients
THANK YOU FOR YOUR ATTENTION!