Adverse drug reactions of CV drugs: What every healthcare personnel needs to know

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CMU Heart Failure Clinic
Survival rates in chronic HF have improved with the introduction of new therapies.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reduction in relative risk of mortality vs placebo</th>
<th>Follow-up Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI*</td>
<td>16% (4.5% ARR; mean follow up of 41.4 months)</td>
<td>SOLVD¹,²</td>
</tr>
<tr>
<td>β-blocker*</td>
<td>34% (5.5% ARR; mean follow up of 1.3 years)</td>
<td>CIBIS-II³</td>
</tr>
<tr>
<td>MRA*</td>
<td>30% (11.0% ARR; mean follow up of 24 months)</td>
<td>RALES⁴</td>
</tr>
<tr>
<td>ARB*</td>
<td>17% (3.0% ARR; median follow up of 33.7 months)</td>
<td>CHARM-Alternative</td>
</tr>
</tbody>
</table>
Renin Angiotensin Aldosterone System Blockade

- **Angiotensin Converting Enzyme Inhibitor (ACEI)**
  - Enalapril, lisinopril, Captopril etc.

- **Angiotensin Receptor Blocker (ARB)**
  - Lorsatan, valsatan, telmisatan etc.

- **Aldosterone Antagonist**
  - Spironolactone

- **Angiotensin Receptor / Neprilysin Inhibitor (ARNI)**
  - Valsatan/ Sacubitril
Patients with symptomatic\textsuperscript{a} HFrEF\textsuperscript{b}

- Therapy with ACE-I\textsuperscript{c} and beta-blocker
  (up-titrate to maximum tolerated evidence-based doses)

  - Still symptomatic and LVEF \lesssim 35%
    
    - Yes
      
      - Add MR antagonist\textsuperscript{d,e}
        (up-titrate to maximum tolerated evidence-based dose)
      
      - Yes
        
        - Still symptomatic and LVEF \lesssim 35%
          
          - No
            
            - Diuretics to relieve symptoms and signs of congestion
              
              - If LVEF \lesssim 35% despite OMT or a history of symptomatic VT/VF, implant ICD

          - Yes
            
            - Able to tolerate ACEI (or ARB)\textsuperscript{f,g}
              
              - ARNI to replace ACE-I

        - Sinus rhythm, QRS duration \geq 130msec
          
          - Evaluate need for CRT\textsuperscript{j}

    - No
      
      - Still symptomatic and LVEF \lesssim 35%
        
        - Sinus rhythm\textsuperscript{h}, HR \geq 70 beats/min
          
          - Ivabradine

  - No

- These above treatments may be combined if indicated

  - Resistant symptoms
    
    - Yes
      
      - Consider digoxin or H-ISDN or LVAD, or heart transplantation
    
    - No
      
      - No further action required. Consider reducing diuretic dose

\textbf{ESC Guideline}

\textbf{Treatment Algorithm}

Ponikowski P et al. Eur Heart J.
“รู้สึกโครงสร้างเหลือเกิน เเป็นโรคหัวใจโตแล้ว นี่ก็มีโรคหอบหิดเพิ่มขึ้นมาอีก กำลังคิดจะไปซื้อยาขยายหลอดลมมาพ่น เผื่อว่าอาการจะดีขึ้น”
HF patient # 1

- 33 yo male  wt. 90.3 kg
- Nonischemic DCM, frequent PVC, EF 24 %
- Enrolled in clinic since 18/9/2007
- No orthopnea, no PND, no readmission, functional class II
- BP 133/79 (supine), 134/60 (sitting), 159/97 (standing),
- RR 22 ,HR 77
- Na 140 K 4.0  BUN 10  SCr 1.19
HF patient # 1

• Follow up 22/12/2016
• Medical therapy
  – Sacubitril/valsatan 200 mg 1 tab  BID for 3 months
    ● Changing from lornesat 50 mg 1 ½ tab BID
  – Carvedilol 25 1 ½  BID
  – Spironolactone 25 mg 1 xOD
  – Furosemide 40 mg ½ x OD
  – Digoxin 0.25 mg ½ OD
1 month PTA รู้สึกมีอาการหน้าบวม ตาบวมหลังรับประทานยา โดยแต่ละครั้งเป็นนานประมาณ 1-2 ชั่วโมง
มีเสียงหายใจวีดเวลาหายใจออก รู้สึกเหมือนหายใจไม่สุด อาการมักเป็นตอนเช้า ภายหลังรับประทานยาเม shortcode รู้สึกเหนื่อยเพิ่มมากขึ้น
มีอาการประมาณ 4-5 ครั้งต่อสัปดาห์
ปรับยาขับปัสสาวะขึ้นจากครึ่งเม็ดเป็นหนึ่งเม็ด อาการไม่ดีขึ้น
PE: HR regular, angioedema both eyes, lung clear, no peripheral edema
Imp: likely angioedema from ARNI
Intervention after ADRs: plan switch back to ARB, follow up 1 month
Renin Angiotensin Aldosterone System Blockade
Angioedema
Angioedema

- Angioedema is the swelling of deep dermis, subcutaneous, or submucosal tissue due to vascular leakage
- Acute episodes often involve the lip, eyes, and face
- Laryngeal swelling can be life-threatening

RAS blockers-associated angioedema (RASBA) in Thai patients 2015

- Incidence of RASBA 0.25 – 2.5%
- Data from the national pharmacovigilance database of Thailand, total of 895 cases
- Age 59.9+12.8 YO and 66.5% female

<table>
<thead>
<tr>
<th>Type of RAS blockers</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>785 (87.7%)</td>
</tr>
<tr>
<td>ARB</td>
<td>94 (10.5%)</td>
</tr>
<tr>
<td>spironolactone</td>
<td>19 (2.1%)</td>
</tr>
<tr>
<td>Direct renin inhibitor</td>
<td>2 (0.2%)</td>
</tr>
</tbody>
</table>

### RAS blockers-associated angioedema (RASBA) in Thai patients 2015

<table>
<thead>
<tr>
<th>Time to event (Mean)</th>
<th>Number of reports (N=895)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7 days</td>
<td>435 (48.6 %)</td>
</tr>
<tr>
<td>8 days – 1 month</td>
<td>131 (14.6%)</td>
</tr>
<tr>
<td>1 – 6 months</td>
<td>94 (10.5%)</td>
</tr>
<tr>
<td>6 months – 1 year</td>
<td>21 (2.4%)</td>
</tr>
<tr>
<td>1 – 2 years</td>
<td>16 (1.8%)</td>
</tr>
<tr>
<td>2 – 3 years</td>
<td>22 (2.5%)</td>
</tr>
</tbody>
</table>

Natriuretic peptide system augmentation /RAAS blockade
LCZ696 simultaneously inhibits neprilysin (via LBQ657) and blocks AT$_1$ receptors (via valsartan)

**Enhancing**
- Vasorelaxation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- ↑ Natriuresis/diuresis

**Inhibiting**
- Vasoconstriction
- ↑ Blood pressure
- ↑ Sympathetic tone
- ↑ Aldosterone
- ↑ Fibrosis
- ↑ Hypertrophy

**RAAS**
- Angiotensinogen (liver secretion)
  - Ang I
  - Ang II
  - ☓ AT$_1$ receptor

**ANP, BNP, CNP, other vasoactive peptides**

**Sacubitril** (AHU377; pro-drug)

**LBQ657** (NEP inhibitor)

**Valsartan**

**LCZ696**

Inhibiting: LCZ696 simultaneously inhibits neprilysin (via LBQ657) and blocks AT$_1$ receptors (via valsartan)
Prospectively defined safety events
Data from PARADIGM-HF study

- The LCZ696 group had a higher proportion of patients with non-serious angioedema, but LCZ696 was not associated with an increase in serious angioedema

"ป้าสบายดี อาการช่วงนี้ไม่มีอะไร (ยิ้มหวาน) จะมีก็แต่เรื่องปวดหลังเหมือนเดิม ไม่หายซักที เรื่องนี้หมอกระดูกดูแลอยู่"
HF patient # 2

- 49 YO female
- Ischemic DCM s/p CABG, MV repair  EF 35.4%
- No orthopnea, no PND, no readmission
- BP 73/47 (supine) , 82/50 (sitting) , 81/55 (standing), RR 18 , HR 49 (เดิม 62)
- Na 136, K 4.7  BUN 69 (เดิม 32) SCr 2.63 (เดิม 1.40)
- Last medication history
  - ASA 81 mg 1x1, Enalapril 5 mg ½ x 2, Carvedilol 6.25 ½ x 2, Lasix 40 mg ½ x 1, Spironolactone 25 mg 2x1, Digoxin 0.25 ½ x EOD
HF patient # 2

Received Diclofenac 50 mg # 100 tablets last two weeks, already took 20 tablets
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td>III</td>
<td>A</td>
<td>209, 210</td>
</tr>
<tr>
<td>NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td>III</td>
<td>B</td>
<td>211–213</td>
</tr>
<tr>
<td>Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td>III</td>
<td>C</td>
<td>214</td>
</tr>
<tr>
<td>The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.</td>
<td>III</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
• JV mildly raised, good perfusion
• Increasing SCr from 1.43 to 2.63
• Renal impairment due to NSAIDs, affected digoxin which is mainly eliminated by renal
• **Intervention after ADRs:**
  – Laboratory test for digoxin level
  – off Enalapril 5 mg ½ x 2, Carvedilol 6.25 ½ x 2 and Digoxin 0.25 ½ x EOD
Vasoregulation

- **NSAIDs**
  - Blocked prostaglandin-mediated afferent arteriolar vasodilation resulting in compromised flow
- **ACE inhibitors and ARBs**
  - Blocked efferent arteriolar vasoconstriction
- **The combination of NSAIDs, ACE inhibitors and diuretics are particularly capable at causing kidney injury**
“มีสิ่งมหัศจรรย์เกิดขึ้นกับลุง”
HF patient # 3
64 YO male

Ishemic DCM, S/P CABG, MV repair, AF, EF=22%

Last admission from ADHF 10-13/3 2017

Medication history
- Bisoprolol 5 mg ¼ tab OD
- Furosemide 40 mg ½ tab EOD
- Spironolactone 25 mg 1 tab OD etc....

Intervention after ADRs:
- none, started enalapril 5 mg ½ tab OD
Mineralocorticoid antagonist

Spironolactone vs eplerenone

- Spironolactone, developed in the 1950s, is an antimineralocorticoid with structural elements of the progesterone molecule
  - associated with progestogenic and antiandrogenic adverse effects

- Eplerenone is a spironolactone derivative designed to enhance selective binding to receptor
  - minimizing binding to progesterone and androgen receptors
Spironolactone vs eplerenone

1. Add epoxy group

2. Replace thioacetyl group with carbomethoxy group
Spironolactone Induces Gynecomastia in Heart Failure Patients

Gynecomastia or Breast Pain (males), %

- Placebo: 1%
- Spironolactone: 10%

P < 0.001

HF patient # 4

มีโทรศัพท์สายด่วนมาจากห้องปฏิบัติการชั้น 1 รายงานว่ามีผู้ป่วย Serum potassium 6.7
HF patient # 4

- 64 yo female wt. 49.5 kg
- Nonischemic DCM, DM type II, HT, DLP, EF 38%
- Enrolled in clinic since 7/2/2017
- No orthopnea, no PND, no readmission, functional class I
- BP 147/82 (supine), 131/76 (sitting), 138/70 (standing),
- RR 20, HR 72
- Na 131 K 6.7 (เดิม 4.0) BUN 32 (เดิม 26) SCr 1.49 (เดิม 1.04)
Medical therapy

- Enalapril 5 mg 1 tab BID
- Carvedilol 25 mg ½ tab BID
- Furosemide 40 mg ½ tab OD
- Spironolactone 25 mg 1 tab OD (increase from last visit, 25 mg ½ tab OD)
- Atorvastatin 40 mg 1 tab OD
HF patient # 4

Nonspecific T abnormalities, lateral lead, prolong QT interval
### ECG Changes in Hyperkalemia

<table>
<thead>
<tr>
<th>QRS Complex</th>
<th>Approximate Serum Potassium (mmol/L)</th>
<th>ECG Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>P wave</td>
<td>~4</td>
<td>Normal</td>
</tr>
<tr>
<td>T wave</td>
<td>6-7</td>
<td>Peaked T waves</td>
</tr>
<tr>
<td></td>
<td>7-8</td>
<td>Flattened P wave, prolonged PR interval, depressed ST segment, peaked T wave</td>
</tr>
<tr>
<td></td>
<td>8-9</td>
<td>Atrial standstill, prolonged QRS duration, further peaking T waves</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>Sine wave pattern</td>
</tr>
</tbody>
</table>
• ช่วงหนึ่งสัปดาห์ที่ผ่านมา รับประทานกล้วยน้ำว้า 2 ลูกต่อวัน นอกจากนี้มีการรับประทานมะละกอสุก และส้มบ่อยๆ

• Imp: AKI from overdiuresis, hyperkalemia

• Medical adjustment
  – Off Enalapril for 3 days, then restart at 5 mg 1/2 tab OD
  – Decrease Furosemide to 40 mg ½ tab PRN
  – Off Spironolactone
  – Follow up in one week
Mean change in Serum potassium level from base line

Figure 1: Mean change in serum potassium levels from baseline with eplerenone and spironolactone.\(^*\) p<0.05 versus placebo (Dunnett’s test for eplerenone or contrast-based \(t\) test for spironolactone); \(^\dagger\) p<0.05 versus spironolactone (Dunnett’s test). Abbreviations: EPL = eplerenone; SPIRO = spironolactone; 1x/d, once daily; 2x/d, twice daily.
Take home message

• Adverse drug reaction of CVS drugs is common and need to be closely monitor

• ADRs from RAAS blockades can be found such as angioedema, renal impairment, gynecomastia, hyperkalemia

• Once the ADRs happened, an appropriated intervention should be made to maximized patients safety
Thank you for your attention