



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



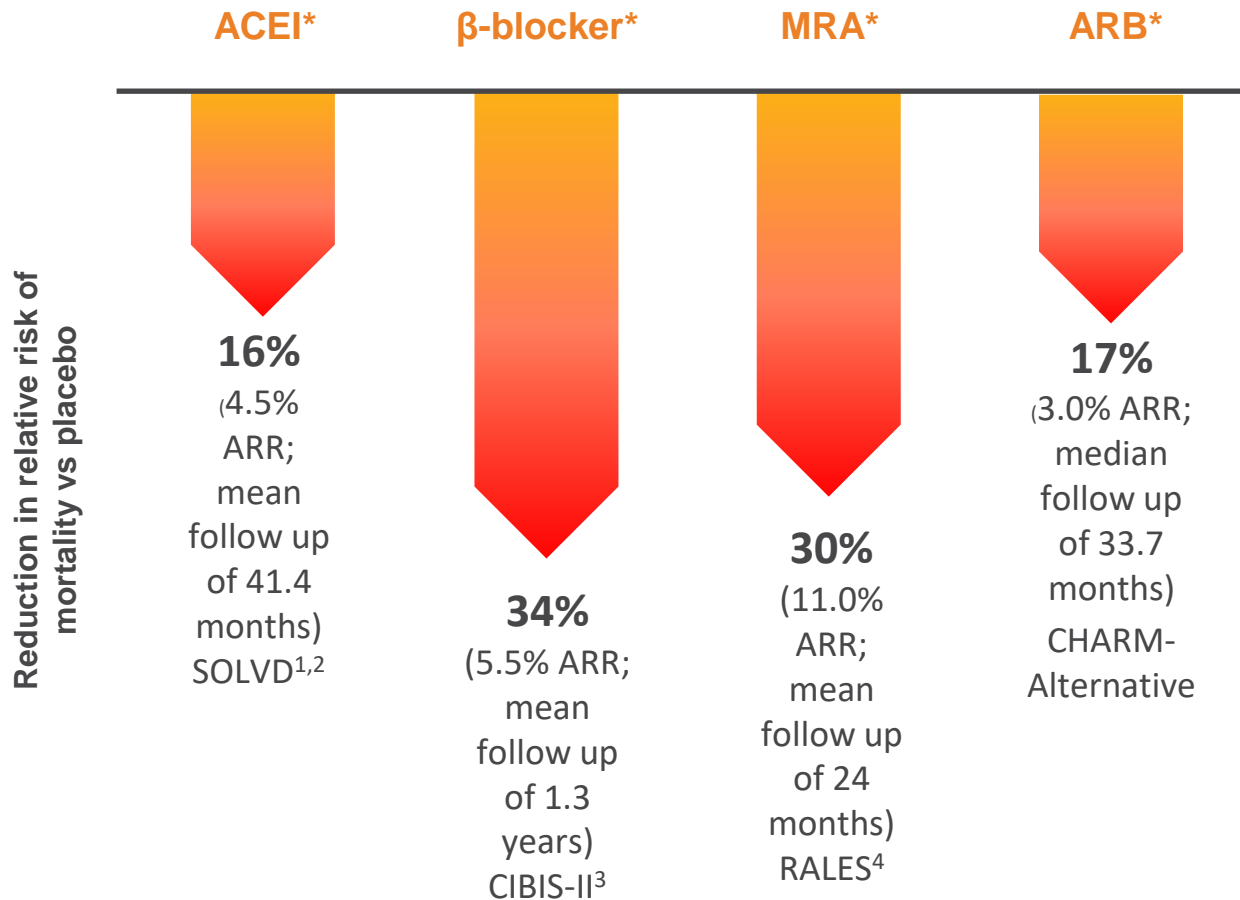
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49th Annual Scientific Meeting “Cardiology on the move”

CMU Heart Failure Clinic



Survival rates in chronic HF have improved with the introduction of new therapies

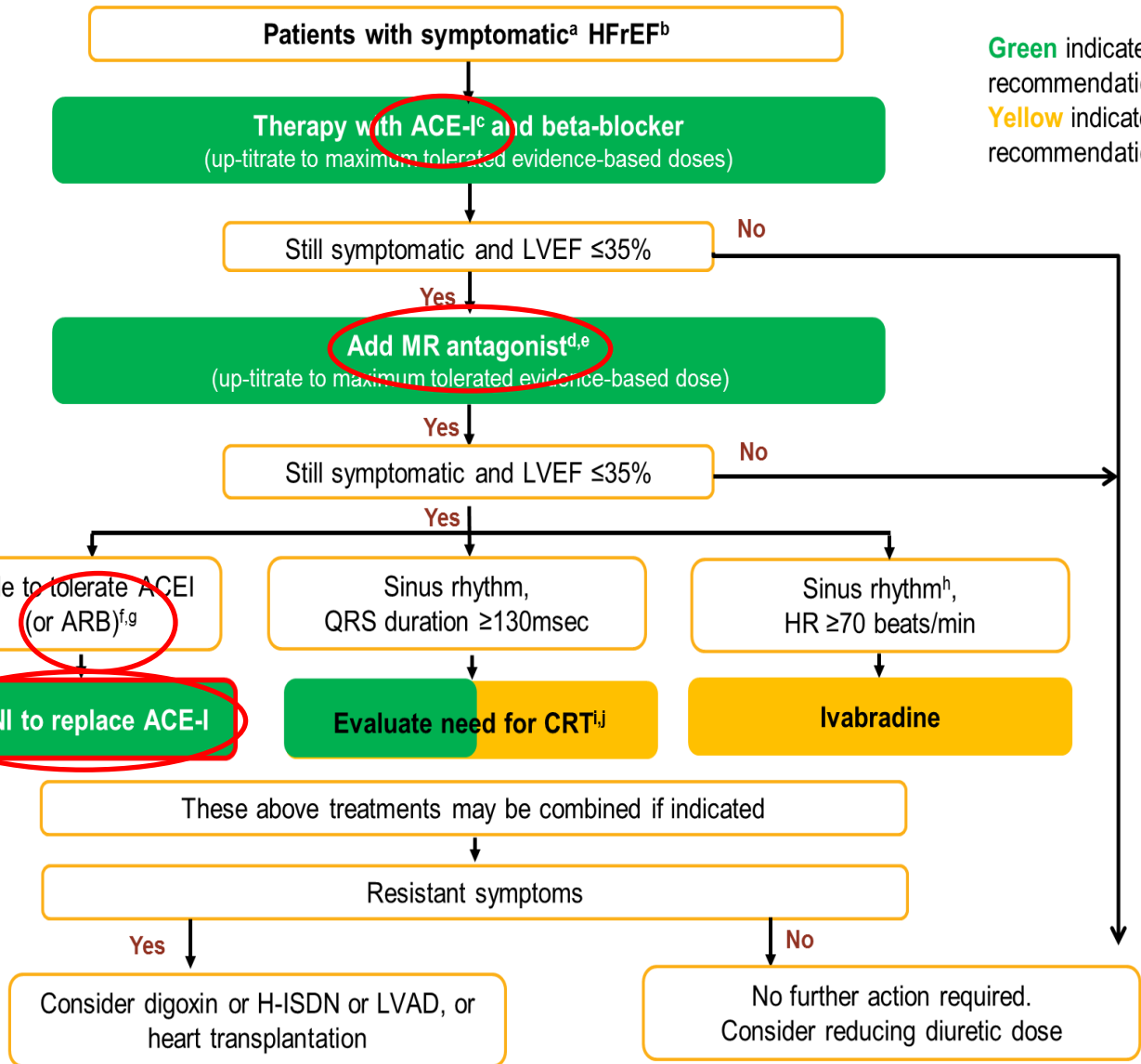


Renin Angiotensin Aldosterone System Blockade

- Angiotensin Converting Enzyme Inhibitor (ACEI)
 - Enalapril, lisinopril, Captopril etc.
- Angiotensin Receptor Blocker (ARB)
 - Lorsatan, valsatan, telmisatan etc.
- Aldosterone Antagonist
 - Spironolactone
- Angiotensin Receptor /Nepriylsin Inhibitor (ARNI)
 - Valsatan/ Sacubitril

Diuretics to relieve symptoms and signs of congestion

If LVEF \leq 35% despite OMT or a history of symptomatic VT/VF, implant ICD



Green indicates a **class I** recommendation;
Yellow indicates a **class IIa** recommendation.

ESC Guideline Treatment Algorithm

HF patient # 1

“รู้สึกโชคร้ายเหลือเกิน เป็นโรคหัวใจโต
แล้ว นี่ก็มีโรคหอบหืดเพิ่มขึ้นมาอีก กำลัง
คิดจะไปซื้อยาขยายหลอดลมมาพ่น เพื่อ
ว่าอาการจะดีขึ้น”

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

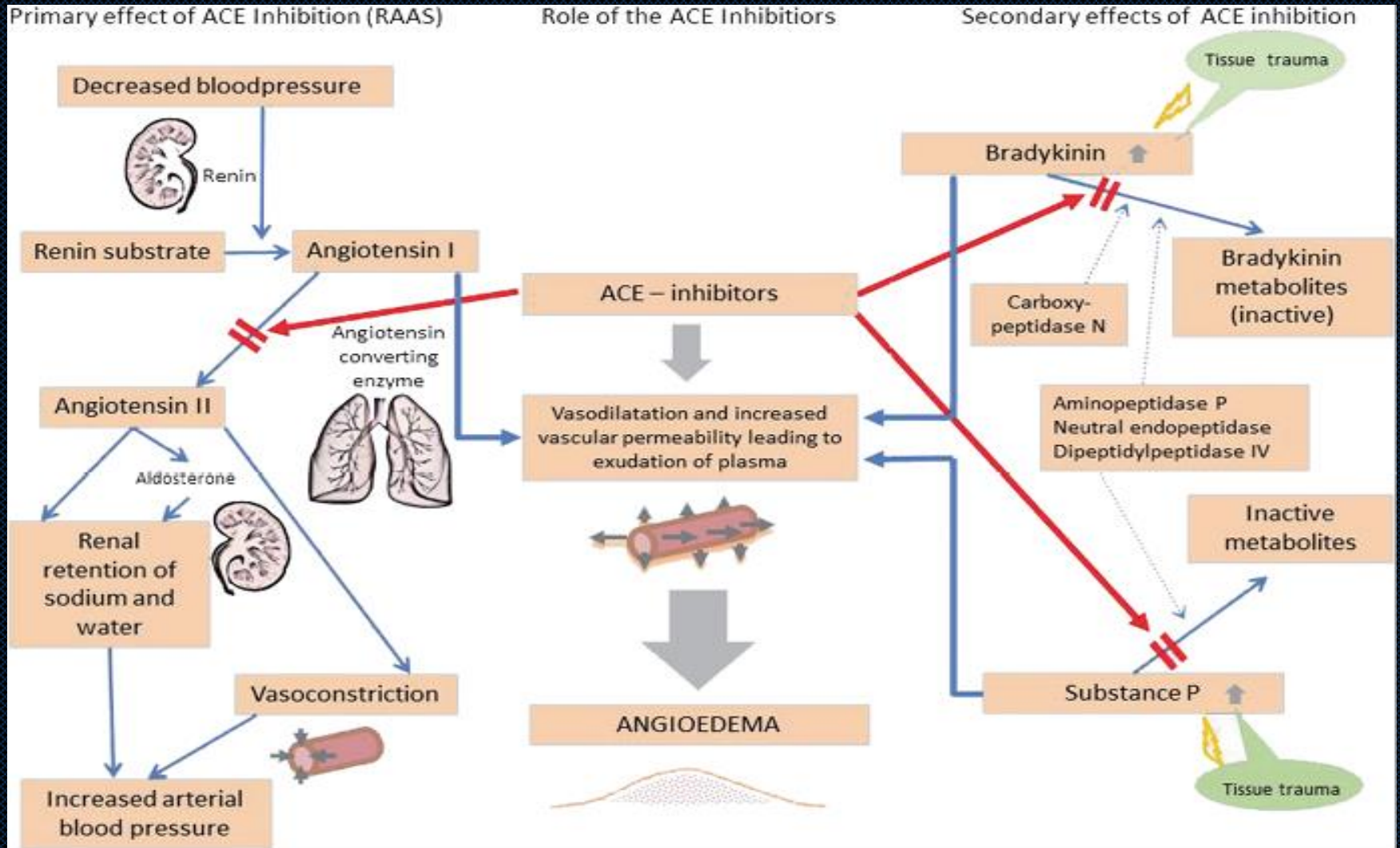
HF patient # 1

- Follow up 22/12/2016
- Medical therapy
 - Sacubitril/valsatan 200 mg 1 tab BID for 3 months
 - Changing from lorsatan 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

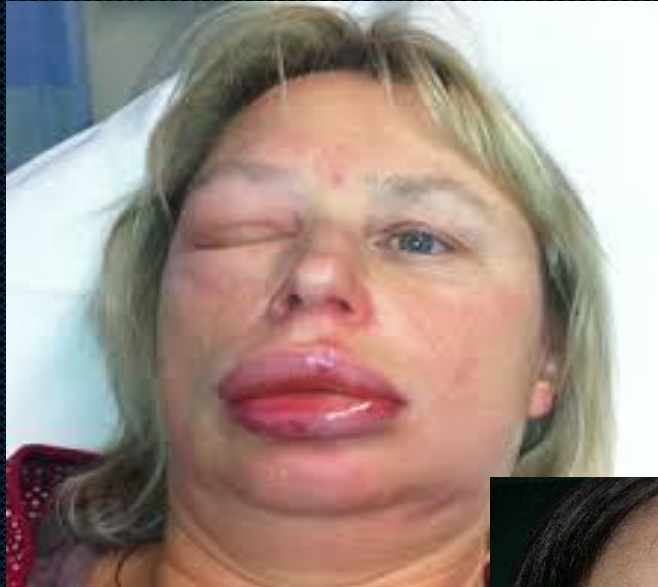
HF patient # 1

- **1 month PTA** รู้สึกมีอาการหน้าบวม ตาบวมหลังรับประทานยา โดยแต่ละครั้งเป็นนานประมาณ **1-2** ชั่วโมง
- มีเสียงหายใจวี๊ดเวลาหายใจออก รู้สึกเหมือนหายใจไม่สุด อาการมักเป็นตอนเช้า ภายหลังรับประทานยามื้อเช้า รู้สึกเหนื่อยเพิ่มมากขึ้น
- มีอาการประมาณ **4-5** ครั้งต่อสัปดาห์
- รับประทานขับปัสสาวะขึ้นจากครึ่งเม็ดเป็นหนึ่งเม็ด 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

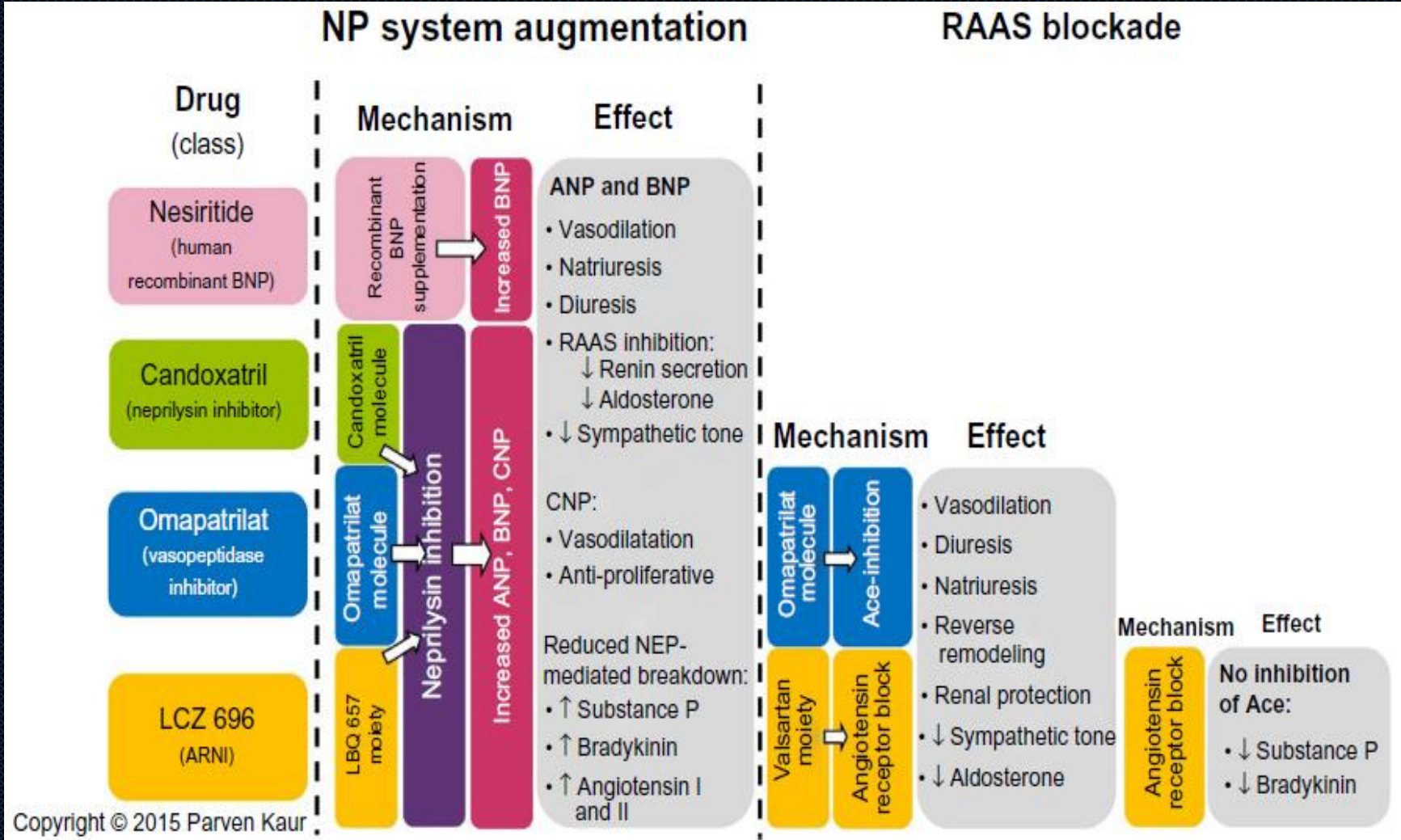
- Incidence of RASBA 0.25 – 2.5%
- Data from the national pharmacovigilance database of Thailand, total of 895 cases
- Age 59.9+12.8 YO and 66.5% female

Type of RAS blockers	n (%)
ACEI	785 (87.7%)
ARB	94 (10.5%)
spironolactone	19 (2.1%)
Direct renin inhibitor	2 (0.2%)

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

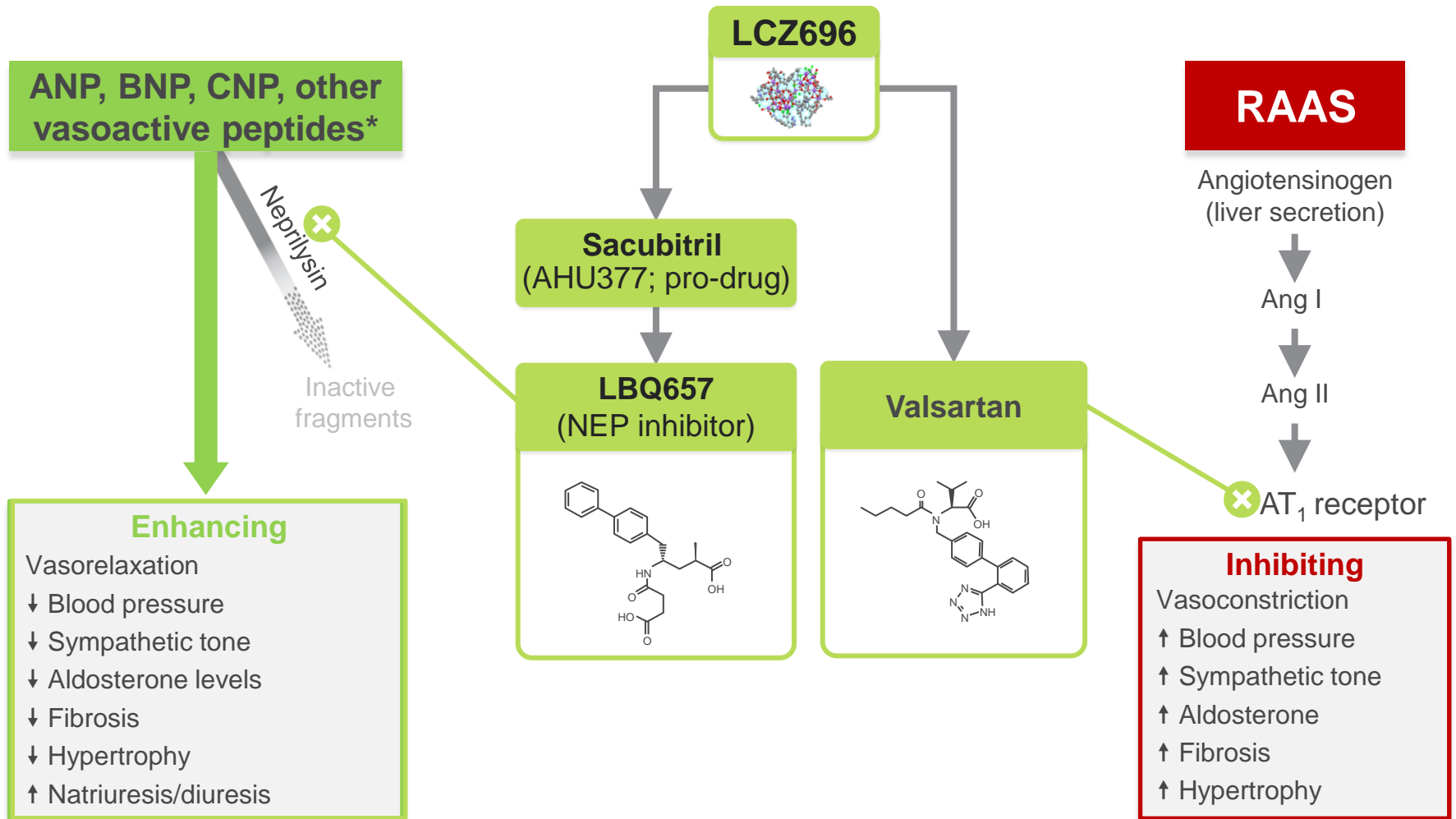
Time to event (Mean)	Number of reports (N=895)
1-7 days	435 (48.6 %)
8 days – 1 month	131 (14.6%)
1 – 6 months	94 (10.5%)
6 months – 1 year	21 (2.4%)
1 – 2 years	16 (1.8%)
2 – 3 years	22 (2.5%)

Natriuretic peptide system augmentation /RAAS blockade



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LCZ696 simultaneously inhibits neprilysin (via LBQ657) and blocks AT₁ 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

HF patient # 2

“ปัสสาวะดี อาการช่วงนี้ไม่มีอะไร (ขี้ม
หวาน) จะมีก็แต่เรื่องปวดหลังเหมือนเดิม ไม่
หายซักที เรื่องนี้มีหมอกระดูกดูแลอยู่”

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

Medications that could harm patients

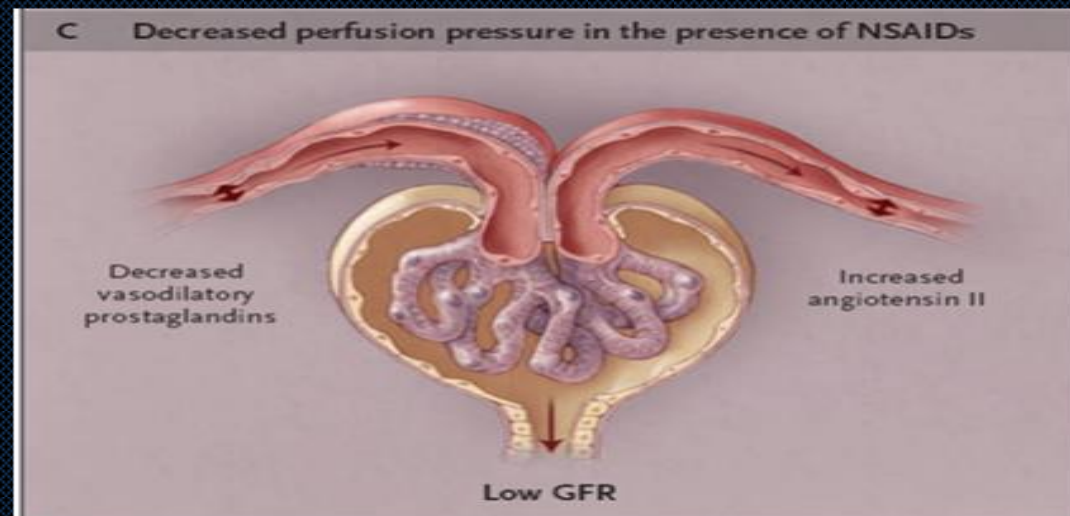
Recommendations	Class^a	Level^b	Ref^c
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B	211–213
Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.	III	C	214
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.	III	C	

HF patient # 2

- 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 $\frac{1}{2}$ x 2 , Carvedilol 6.25 $\frac{1}{2}$ x 2 and Digoxin 0.25 $\frac{1}{2}$ 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



HF patient # 3

“ มีสิ่งมหัศจรรย์เกิดขึ้นกับลุง ”

HF patient # 3



HF patient # 3

- 64 YO male
- Ischemic 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

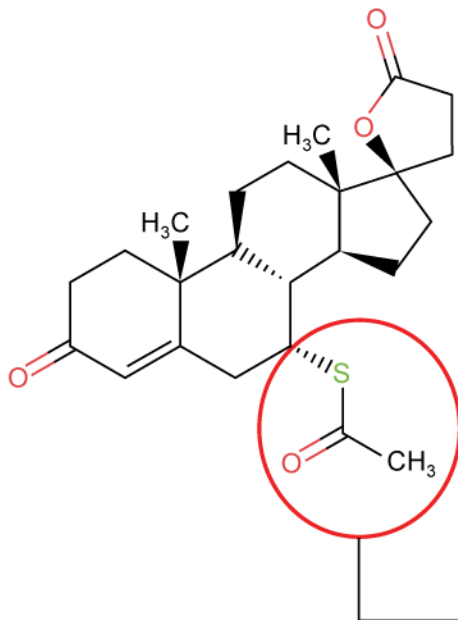
Mineralocorticoid antagonist

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

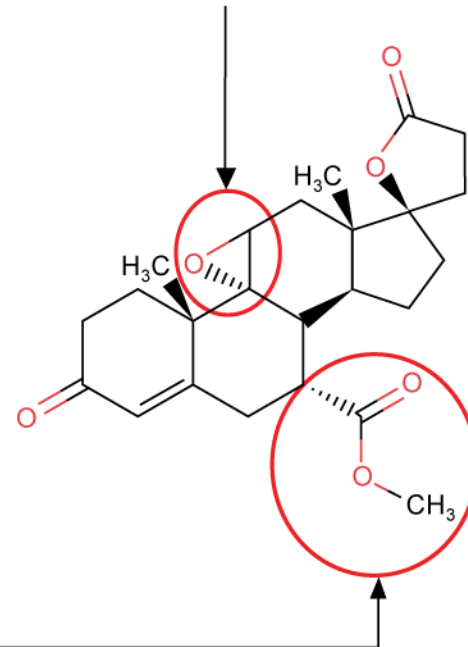
Spirolactone vs eplerenone

spironolactone



Inspra (eplerenone)

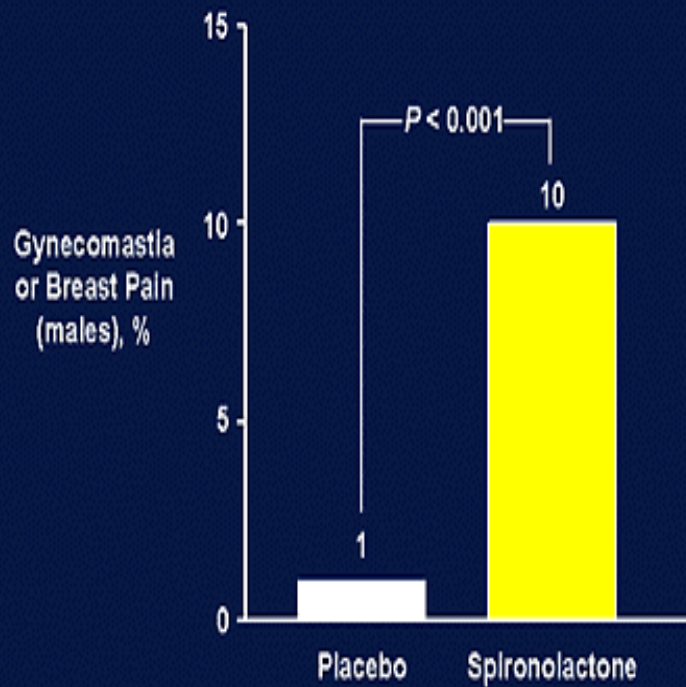
1. Add epoxy group



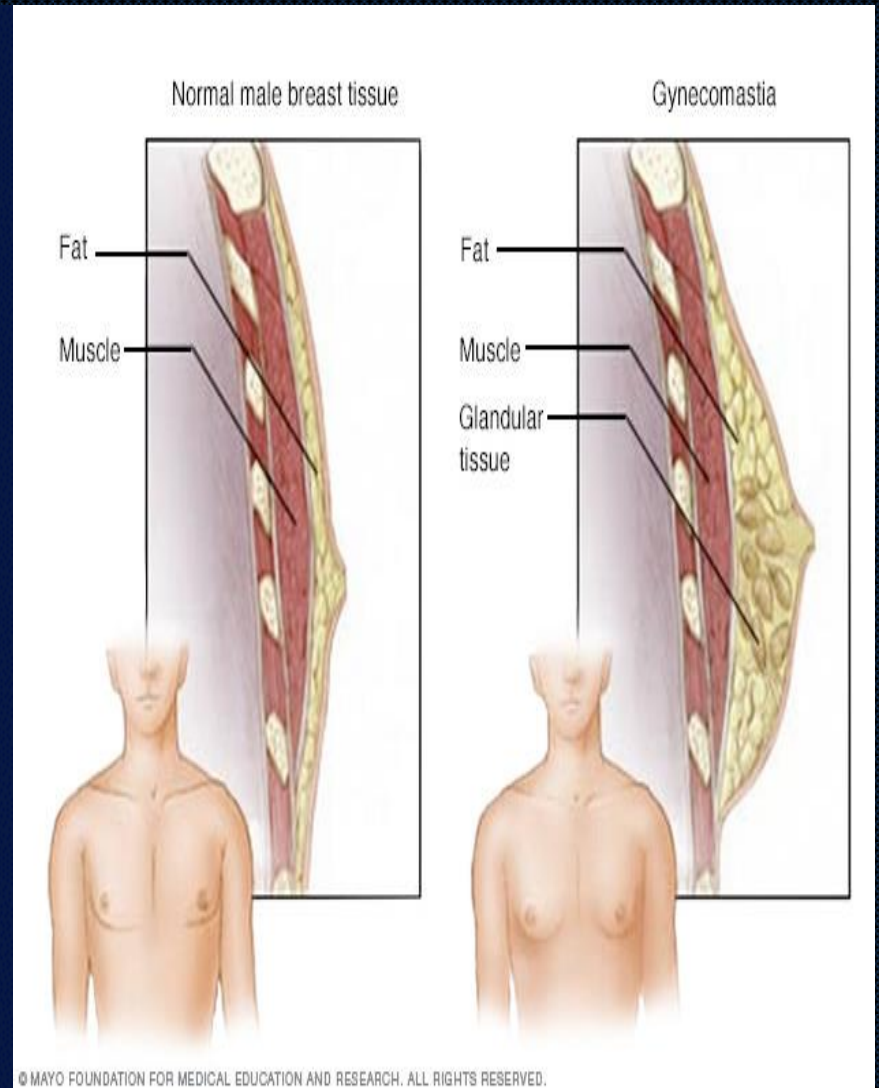
2. Replace thioacetyl group with carbomethoxy group

Gynecomastia

Spirolactone Induces Gynecomastia in Heart Failure Patients



Pitt B et al. *N Engl J Med.* 1999;341:709-17.



HF patient # 4

มีโทรศัพท์สายด่วนมาจากห้องปฏิบัติการชั้น 1

รายงานว่ามีผู้ป่วย Serum potassium 6.7

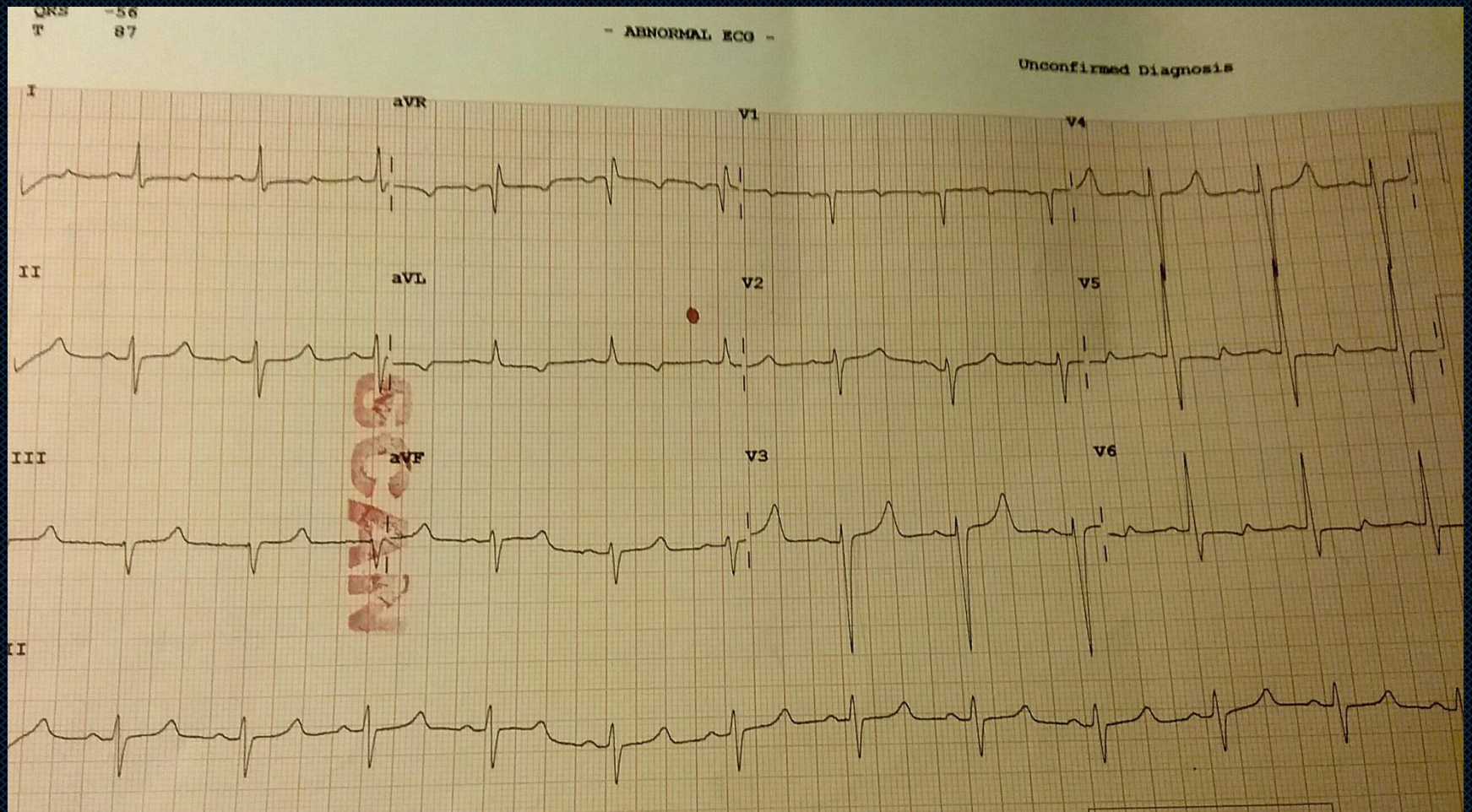
HF patient # 4

- 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)

HF patient # 4

- 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 Change in Hyperkalemia

ECG changes in hyperkalemia

QRS complex	Approximate serum potassium (mmol/L)	ECG change
P wave  T wave	~4	Normal
	6-7	Peaked T waves
	7-8	Flattened P wave, prolonged PR interval, depressed ST segment, peaked T wave
	8-9	Atrial standstill, prolonged QRS duration, further peaking T waves
	>9	Sine wave pattern

HF patient # 4

- 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

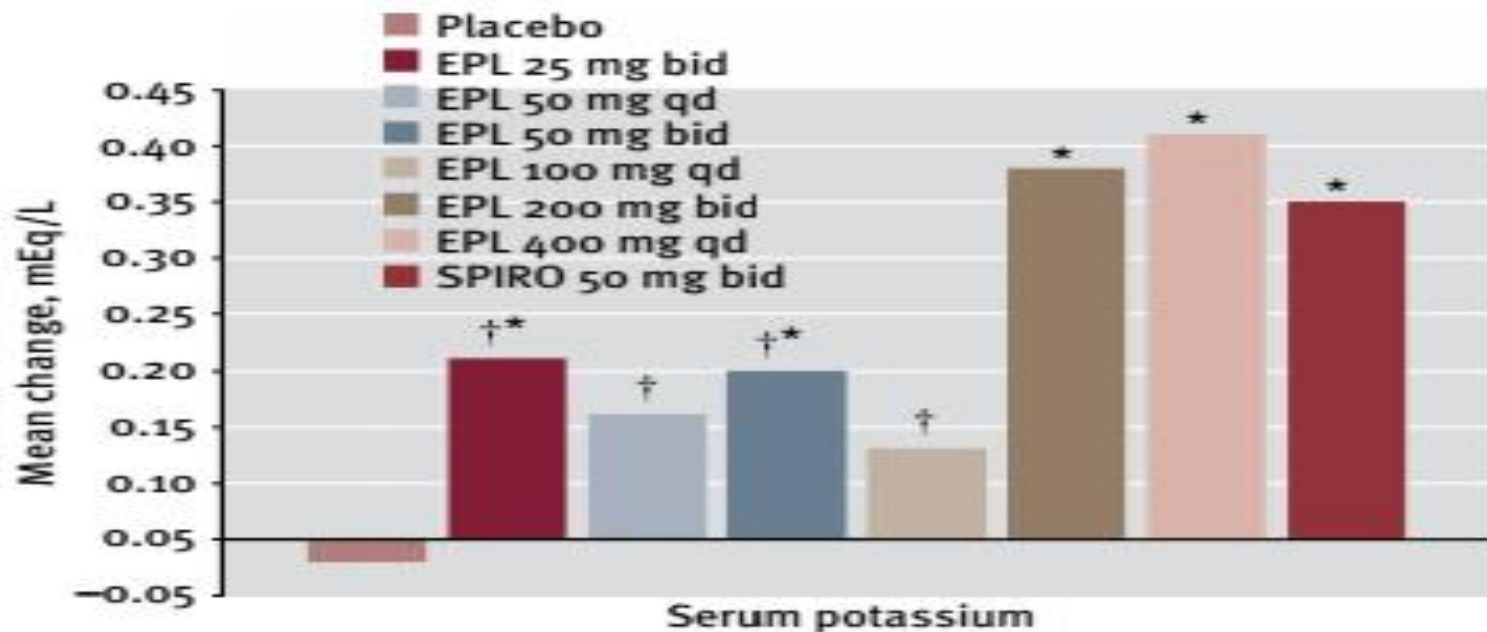


Figure 1: Mean change in serum potassium levels from baseline with eplerenone and spironolactone.¹⁸ * $p < 0.05$ versus placebo (Dunnett's test for eplerenone or contrast-based t test for spironolactone); † $p < 0.05$ versus spironolactone (Dunnett's test). *Abbreviations:* EPL = eplerenone; SPIRO = 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

