Pharmacotherapy of Heart Failure (CHF)
Inotropics and Other Agents

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Congestive Heart Failure (CHF)
CO inadequate for body demand of oxygen (demand-supply)

6 million in USA
50% mortality @ 5 year
500,000 new cases each year

Adapted from The Heart, 8th Ed. Page 1093
Congestive Heart Failure (CHF) - Definition

**Compensated heart failure:**
- resting cardiac function, OK
- excessive stress or exercise, No

**Congestive heart failure:**
(CHF, Decompensated):
- resting cardiac function inadequate
- venous pooling $\rightarrow$ edema, esp. lungs
- shortness of breath, fatigue
- ejection fraction of less than 40%

**Causes**
- coronary artery disease (70%)
- hypertension
- primary cardiomyopathy
- toxic injury by chemicals
- congenital or genetic abnormalities
- drug: adriamycin (doxorubicin)

Hemodynamic Changes
“Hormonal Storm”

BP is well maintained in CHF:
- $\uparrow$ sympathetic tone (tachycardia)
- $\downarrow$ parasympathetic tone
- activation of renin-angiotensin system
- $\uparrow$ blood volume
- $\uparrow$ vasopressin release

Consequences:
- $\downarrow$ force of contraction
- $\downarrow$ CO, $\uparrow$ TPR, $\downarrow$ stroke volume
- $\uparrow$ venous pressure, $\downarrow$ tissue perfusion
- cardiac hypertrophy
- Na$^+$ & water retention
- edema
Heart failure: “Hormonal Storm”

Need to break the cycle

activation of sympathetic nerve system and of renin-angiotensin-aldosterone axis

additional neuro-humoral activation promoted

pumping function disrupted

heart tissue remodeling (hypertrophy)

CHF Therapy Overview

Non-Drug:  - exercise as tolerated
            - salt restriction

Drug Therapy:
A. Positive inotropic agents:
   - cardiac glycosides eg. digoxin
   - catecholamines eg. dobutamine
   - phosphodiesterase III inhibitors eg. inamrinone
B. Beta-blockers (caution) eg. metoprolol
C. Diuretics eg. thiazides, loop, K-sparing
D. ACE inhibitors / ARB eg. lisinopril / losartan
E. Vasodilators (non-inotropic) eg. hydralazine,
   beta-type natriuretic peptide (nesiritide)
Heart Physiology

Cardiac Glycosides inhibit Na+/K+-ATPase

<table>
<thead>
<tr>
<th>mM</th>
<th>Na+</th>
<th>K+</th>
<th>Ca++</th>
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<tbody>
<tr>
<td>Out</td>
<td>140</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>In</td>
<td>10</td>
<td>150</td>
<td>0.1</td>
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</table>

Cardiac Muscle Contraction

- **Voltage-sensitive slow Ca++ channel**
- **Na+/Ca++ Exchange**
- **Na++/K+ ATPase**

1. Ca++ entry from outside the cell triggers the release of a much larger quantity of Ca++ from the sarcoplasmic reticulum.
2. Increased Ca++ concentration initiates the contractile process.
3. Ca++ is removed by re-uptake into the sarcoplasmic reticulum and by extrusion from the cell by a Ca++/Na+ exchange.
4. Sodium balance is restored by Na+/K+ ATPase.

Figure 16.3 Ion movements during the contraction of cardiac muscle.
Cardiac Glycosides

Source:
- white and purple foxglove (Digitalis lanata and D. purpurea)
- Mediterranean sea onion (Strophantus gratus) - ouabain
- numerous other plants
- certain toads

History:
- Egyptians (3000 yr ago) - diuretic effect, tones the heart
- 1785, clinical effect of foxglove plant described (Digitalis purpurea)

Cardiac Glycosides Chemistry

Steroid nucleus:
- lipophilic
- essential for activity, OH is very reactive (synthesis)

Unsaturated five-membered lactone ring:
- hydrophilic, essential for activity
- opening the ring → loss of activity
- saturation → loss of activity

Series of sugars linked to C 3 of the steroid nucleus
- nonessential, hydrophilic

Digoxin
Kidney

Digitoxin
Liver
(-OH, C12)
Mechanism of Action

Cardiac glycosides (CG)
- Inhibition of Na⁺/K⁺ ATPase (Na⁺ pump)
- membrane bound transporter (3 Na⁺ / 2 K⁺)
- found all over the body, α/β-subunits
- 3 mammalian isoforms
- extracytoplasmic binding site for CG
- phosphorylation of cytosol α-subunit → stabilize CG binding
- ↑ [K⁺]EC → dephosphorylates α-subunit → ↓ CG binding
- ↓ [K⁺]EC → phosphorylates α-subunit → ↑ CG intoxication

Inhibition of (Na⁺, K⁺-ATPase)
→ ↓ exchange Na⁺ - K⁺ (3:2)
→ ↑ [Na⁺]EC (8 → 9 - 9.5 mM)
→ ↑ Na⁺ - Ca⁺⁺ exchange (3:1) (depolarized)
→ ↑ [Ca⁺⁺]IC
→ ↑ SR uptake Ca⁺⁺ (↑ stores)
→ ↑ contractile force

Cardiac Muscle Contraction

Figure 16.3
Ion movements during the contraction of cardiac muscle.
Therapeutic consequence of Cardiac Gycosides

Moderate but persistent positive inotropic effect, ↑ sensitivity of the baroreceptor reflex

→ ↑ CO → ↓ sympathetic activity
→ ↓ HR and vascular tone
→ ↓ pre- and afterload to the heart
→ ↓ heart size
→ ↓ oxygen demand

→ ↑ CO → ↑ renal blood flow
→ improved GFR
→ ↓ renin-angiotensin activity level
→ ↑ Na⁺ excretion → ↓ body Na⁺
→ ↓ volume + vascular reactivity
→ ↓ pre- and afterload

Cardiac effects of Cardiac Gycosides

1. Increase in contractile force (inotropic effect)
2. Increase in vagal activity - cardiac slowing (chronotropic effect)
3. Major effects on electrophysiologic parameters
   a. decreased A-V conductivity due to decreased CV and an increase in the refractory period
   b. EKG changes
      1. T wave becomes inverted
      2. ST segment becomes depressed
      3. PR interval becomes prolonged
4. Heart size is decreased due to more complete ventricular emptying
### Summary of the Effects of CHF and the Results of Digitalis Administration

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure</th>
<th>Digitalis</th>
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<tbody>
<tr>
<td>Myocardial contractility</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>End diastolic and venous pressure</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Blood volume</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Heart size</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Frank-Starling Curve**

- **Normal Heart**
  - Within limits, when cardiac muscle is stretched, its force of contraction increases, and hence, cardiac output increases.
  - However, if the ventricle is overly stretched, the effect of ventricular contraction is diminished.
  - **B** is the normal operating point in the healthy heart.

- **Decompensated Heart Failure**
  - Initial reduction of contractility (A to B) due to CHF.
  - Symptoms of low cardiac output develop, for example, dyspnea and edema.

- **Compensated Heart Failure**
  - Ventricular end-diastolic pressure lowers (B to C) in an effort to maintain an adequate cardiac output.
  - The increased ventricular end-diastolic pressure causes symptoms of congestion, for example, dyspnea.

- **Digitalis Treatment**
  - Administration of digitalis shifts ventricular function curve toward normal.
  - Increased contractility (B to C) leads to increased cardiac output.
  - Decreased sympathetic reflexes and vascular tone cause decrease in ventricular end-diastolic pressure (B to C).

- **Frank-Starling Curve**
  - Need to bring curve towards normal without an increase in HR
Digitalis Glycosides

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Bioavail. %</th>
<th>Bound%</th>
<th>Peak effect</th>
<th>T1/2</th>
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<tr>
<td>Digoxin</td>
<td>oral, iv</td>
<td>45-85</td>
<td>25</td>
<td>6 hr</td>
<td>35 hr (kidney)</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>oral, iv</td>
<td>&gt;90</td>
<td>90</td>
<td>12 hr</td>
<td>6-7 day (liver)</td>
</tr>
</tbody>
</table>

Digoxin:
- water insoluble
- absorption by gut bacteria (10% resistant *Eubact. lentum*)
- unchanged excretion by kidney (85%), not removed by dialysis
- 15% liver metabolism, can crosses the placenta

Digitoxin:
- good oral absorption
- mainly metabolized by the liver (cardioactive metabolities)
- large interpatient variations (bacterial flora)
- enterohepatic recycling

Dosage & Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Digoxin</th>
<th>Digitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic [plasma]</td>
<td>0.5 –2 ng/ml</td>
<td>10 – 25 ng/ml</td>
</tr>
<tr>
<td>Toxic [plasma]</td>
<td>&gt; 2 ng/ml</td>
<td>&gt;35 ng/ml</td>
</tr>
</tbody>
</table>

Narrow therapeutic window (50%): → oscillatory afterdepolarization → ventricular tachycardia

Toxic effects:
tachycardia
delirium
dizziness
nausea
vomiting
vision disturbances
(halo effect, mostly yellow and green)
Therapeutic Index

![Therapeutic Index Chart](image)

Digoxin Drug Interactions

Many potential interactions:

- **Hypokalemia** → ↑ CG binding (esp. with diuretics)
- Hyperkalemia → ↓ CG binding (ACEI/ARB, K-sparing)
- Quinidine → displaces CG from plasma binding
- **Ca++-blockers** → enhance effect (eg. verapamil)
- Catecholamines → enhance toxicity
- **Amiodarone** → ↑ serum [CG] (↓ clearance)
- Cholestyramine → decrease CG absorption
- Thyroid function/disease
  - Hyperthyroidism - decreases digoxin levels
  - Hypothyroidism - increases digoxin levels
- **Antibiotics** → ↑ bioavailability (eg. erythromycin)
- **Altered renal function** and many other drugs
**Digoxin Treatment of Toxicity**

Digoxin increases quality of life but not survival. Patients must be closely monitored for signs of toxicity OR therapeutic failure (loss of effect).

a. discontinue agent (GC), lower dose  
b. discontinue K⁺ depleting diuretics  
c. K⁺ replacement → ↓ arrhythmias (esp. with diuretics)  
d. use of antiarrhythmic agent eg. lidocaine, phenytoin  
e. antidigoxin antibodies eg. digoxin immune FAB (used for high toxicities ie. suicide)

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**Catecholamines**

**Dobutamine (Dopamine)**
- short-acting, metabolism by COMT, MAO  
- acute, emergency treatment iv  
- ↑ cAMP → ↑ Ca²⁺ influx  
- can induce angina, arrhythmias (discontinue)  
- dopamine can activate renal D-receptors

**Phosphodiesterase III Inhibitors:**
- **Inamrinone (was Amrinone), Milrinone**  
- acute and chronic treatment  
- additional benefit → asthma  
- ↑ cAMP → ↑ Ca²⁺ influx (as per catecholamines)  
- reported to have less inotropic effect  
- long-term higher mortality than cardiac glycosides or other treatments
Catecholamines – Mechanism of Action in CHF

- Angiotensin converting enzyme (ACE) inhibitors / ARBs
  - Captopril, Lisinopril, Enalapril, Losartan (ARB)
  - Side benefit antihypertensive, decrease load
  - Frontline, cornerstone therapy, increasing in use, ↑ survival
  - Used in combination with CG, tissue remodeling
  - Hyperkalemia, dry cough (ACEI only), loss of taste (Zn loss), angioedema (<1%, less with ARBs), glossitis (<5%), tetrogenic
### Renin-Angiotensin System

- **Angiotensinogen**
- **Renin**
  - **Angiotensin I**
  - **ACE inhibitors** (Lisinopril)
    - **Angiotensin II**
    - **AT II**
    - **Bradykinin**
      - Inactive Peptides
      - **↑ Kinins**
      - **↑ NO**
        - Vasodilation
        - Anti-proliferation
        - ↑×
      - **↑ Nono**
      - **↑ SNS activation**
      - **↑ Aldosterone**
      - **↑ Antidiuretic hormone**
      - **↑ Enzymatic activity**
      - **Blockade**
    - **AT I**
      - **BK-R**
      - **Vasodilation**
      - **↓ Ischemia**
      - **↓ Platelet agg**
      - **⊕ Inotrope**
    - **Arterial baroreceptors**
      - **↓ TPR, CO unchanged, HR unchanged**
      - **↓ aldosterone production → ↓ Na/water retention**
      - **↑ bradykinin level (inhibit metabolism, only ACEIs)**
      - **improves intrarenal hemodynamics**
      - **less effective in elderly and Afro-Americans**

### Actions of Angiotensin-Converting Enzyme (ACE) Inhibitors/ARBs

- **decrease activity of sympathetic NS**
- **↓ TPR, CO unchanged, HR unchanged**
- **no reflex ↑ HR, probably due to resetting (↓) of baroreceptor reflex sensitivity**
- **↓ aldosterone production → ↓ Na/water retention**
- **↑ bradykinin level (inhibit metabolism, only ACEIs)**
- **improves intrarenal hemodynamics**
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Guidelines to ACE Inhibitor Therapy

- **Contraindications**
  - Pregnancy (C & D)
  - Renal artery stenosis
  - Renal insufficiency (relative)
  - Hyperkalemia
  - Arterial hypotension
  - Dry cough
  - Angioedema

- **Alternatives**
  - Hydralazine + ISDN ie Afro-Americans

ACEI – Angioedema; Glossitis

- Angioedema (<1%)
- Dry mouth
- Glossitis (<5%)
- Oral ulceration
- Oral bleeding

Angioedema

Glossitis

**Angioedema**

Often occurs in the deep layers of the skin, usually near the eyes and mouth.

**Glossitis**
Drugs without Positive Inotropic Effects

Diuretics (frontline)
- loop (acute & chronic), thiazide diuretics (chronic)
- potassium-sparing used in combo Rx
- ↓ plasma volume → ↓ venous return (preload)
- relieve pulmonary congestion & peripheral edema
- K⁺ loss (loop, thiazides): interaction with CG

Direct Vasodilators
- not Ca⁺⁺ antagonists
- dilation of venous vessels → ↓ preload
- dilation of arterioles → ↓ afterload
- hydralazine → direct vasodilation → relaxation
- nitrates (NO): nitroglycerin, isosorbide dinitrate, nitroprusside
- beta-type natriuretic peptide (iv., severe CHF) → ↑ cGMP

Diuretics: Overview

• Loop diuretics (Furosemide)
  - Inhibit Na-K-2Cl ion cotransporter, ↓Na⁺, H₂O reabsorption: ascending loop of Henle
  - hypokalemia, hypomagnesemia, hypocalcemia ototoxicity, most potent

• Thiazides (Hydrochlorothiazide)
  - Inhibit Na-Cl symporter, ↓Na⁺, H₂O reabsorption in distal convoluted tube
  - hypokalemia, hypercalcemia, ↑uric acid→gout, DM-2

• K⁺-sparing (Spironolactone)
  - aldosterone antagonism at collecting tube
  - hyperkalemia, least potent, adjunct
  - decreases mortality
Diuretics: Reduction of volume overload

\( \downarrow \) plasma volume

\( \downarrow \) afterload

\( \downarrow \) preload

\( \downarrow \) peripheral edema

\( \downarrow \) pulmonary congestion

\( \downarrow \) HF symptoms

Drugs without Positive Inotropic Effects

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- hydralazine \( \rightarrow \) direct vasodilation \( \rightarrow \) relaxation
- nitrates (NO): nitroglycerin, isosorbide dinitrate, nitroprusside
- beta-type natriuretic peptide (iv., severe CHF) \( \rightarrow \) \( \uparrow \) cGMP
Actions of Vasodilators

**Ca**²⁺ Antagonists
- Verapamil
- Diltiazem
- Nifedipine

**Open K⁺ Channels**
- Minoxidil
- Diazoxide

**Nitric oxide (NO)**
- β-natriuretic peptide
- Nitroprusside
- Nitrates

**Direct Vasodilation**
- Hydralazine

**Vasodilators**
- relax smooth muscle of arterioles $\rightarrow$ ↓ TPR
- high clinical value (in combinations and hypertensive emergencies)

**Hydralazine**
- direct vasodilation
- dilate arterioles but not veins
- $\downarrow$ TPR $\rightarrow$ $\downarrow$ BP $\rightarrow$ reflex $\uparrow$ HR
- Lupus syndrome

**Adverse effects:**
- reflectory sympathetic activation
- headache, nausea, sweating, flushing
- palpitations, $\uparrow$ HR $\rightarrow$ angina
- lupus reaction (mainly in slow acetylators)
Bidil: Isosorbide-dinitrate (ISDN) & Hydralazine

- Approved 2005 for HF in Afro-Americans
- 1st race-based drug
- Blacks do not respond well to ACEIs/ARBs and beta-blockers
- Bidil was found to reduce mortality among blacks by 43%

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Bidil: Isosorbide-dinitrate & Hydralazine

- Isosorbide-dinitrate
  - Conversion to NO
  - ↓ vascular tone
  - ↑ venous filling

- Hydralazine
  - Direct ↓ arterial tone
  - ↓ arterial resistance
  - ↓ cardiovascular load
Lupus erythematosus

- Chronic inflammatory disease
- Autoimmune disease

Drug induced: Procainamide, Hydralazine, Isoniazid

Beta-Blockers

**Metoprolol, Carvedilol, Bisoprolol (EBM)**

Main action to decrease HR and catecholamine action on the heart

**Positive Actions**
- ↓myocardial O₂ consumption (demand) by ↓HR and ↓force contraction
- ↓BP → ↓afterload, ↓preload (less)

**Negative Actions**
- remove positive sympathetic activity
- decrease cardiac contractility
### Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
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<td><strong>Non-selective β₁/β₂</strong></td>
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<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
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</tbody>
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### MERIT-HF : Use of Metoprolol in CHF

- Metoprolol vs Placebo, USA & 13 other countries
- β₁-selective, no ISA, LA-action
- LVEF <0.40 and NYHA class II-IV heart failure
- Stabilized by optimum standard therapy (diuretics/ACEI)
- 2.4 years, terminated early after 1 year

- Mortality ↓34%
- Risk ↓39%
- Hospitalization ↓29%
- Felt better ↑25%
- Prevent 1 death per 27 patients treated per year
Multiplas possible mechanisms of action:

i. CNS effect to decrease sympathetic NS tone

ii. ↓ renin secretion: beta1-receptors mediate renin release

iii. block cardiac beta1-receptors: ↓ HR → ↓ CO → ↓ BP

\[ \text{Beta-Adrenoceptor Antagonists} \]

\[ \text{US carvedilol study} \]

\[ \text{CIBIS II} \]

\[ \text{MERIT-HF} \]

\[ \text{COPERNICUS} \]
Beta-type Natriuretic peptide - Nesiritide (Natrecor)

- binds to A-type receptor on vascular smooth muscle cell
- activates cGMP $\rightarrow$ muscle relaxation and vasodilation
- arterial & venous dilation $\rightarrow$ ↓ preload & afterload
- dilation of afferent renal arterioles leads to increased GFR and decreased sodium reabsorption, causing a diuresis
- SNS and RAA systems are also suppressed
  - acute decompensated heart failure
  - use - severe (Class IV) CHF
  - iv administration (T$_{1/2}$: 20 mins, duration: 2 hrs))
  - Main adverse effect - hypotension

Natriuretic peptides: ANP, BNP, CNP

- atrial natriuretic peptide (ANP, 28 aa), brain natriuretic peptide (BNP, 32 aa) and C-type natriuretic peptide (CNP, 22 aa) are peptides released in response to atrial and ventricular volume/pressure expansion.

- ANP and BNP are released from the atria and ventricles, respectively, and both promote vasodilation and natriuresis.

- BNP, in particular, produces selective afferent arteriolar vasodilation and inhibits sodium reabsorption in the proximal convoluted tubule.

- BNP inhibits renin and aldosterone release and, possibly, adrenergic activation as well.

- ANP and BNP are elevated in chronic heart failure.

- BNP, in particular, has potentially important diagnostic, therapeutic, and prognostic implications: Nesiritide, a recombinant BNP
Type-A natriuretic peptide receptor

Binding of atrial natriuretic peptide, brain natriuretic peptide, or nesiritide to ligand binding domain results in ATP binding, and conformational change in the hinge region allows for activation of the guanylyl cyclase domain and biologic effects.

### Pharmacotherapy of Congestive Heart Failure: 2004

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong> (no limitations on activity)</td>
<td>ACE Inhibitor/AT₁ - RB</td>
</tr>
<tr>
<td><strong>Class II</strong> (slight, mild limitation of activity, comfortable at rest)</td>
<td>Digoxin*, Furosemide, ACE Inhibitor/AT₁ - RB, Beta-blocker</td>
</tr>
<tr>
<td><strong>Class III</strong> (marked limitation of activity, only comfortable at rest)</td>
<td>Bi-Ventricle pacing, Bidil</td>
</tr>
<tr>
<td><strong>Class IV</strong> (complete rest, confined to bed or chair)</td>
<td>Bi-Ventricle pacing, Bidil, Digoxin*, Furosemide (IV), Thiazide, ACE Inhibitor/AT₁ - Receptor blocker, K⁺-sparing/Inotropic therapy/ Beta-type Natriuretic peptide</td>
</tr>
</tbody>
</table>

Recommended Digoxin* not be used in females for routine CHF. 8/10/04
Recommended Pharmacotherapy of CHF requires 4 or more agents
Bidil: (isosorbide dinitrate (ISDN) and hydralazine) African Americans very effective
Summary: Pharmacotherapy of Heart Failure

• Improved survival
  – ACE inhibitors/ARBs, β-blockers, K-sparing
• Increased mortality
  – Phosphodiesterase III inhibitors (chronic)
• Neutral on survival
  – Digoxin, Loop diuretics, Thiazides
• Quality of life
  – Digoxin, Loop diuretics, Thiazides, β-blockers
• Reduction of edema
  – Loop diuretics, Thiazides
• Tissue Remodeling
  – ACE inhibitors/ARBs, K-sparing
• Prevention of ischemia
  – β-blockers, Anticoagulant therapy
• Hemodynamic improvement: All agents
  – ACEI, ARBs, Digoxin, Diuretics, β-blockers, K-sparing