



Updates in Therapeutics® 2012:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Hypertension

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Conflict of Interest Disclosure

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No conflicts of interest to disclose

Learning Objectives

- Construct an appropriate pharmacologic and therapeutic monitoring plan for a patient with hypertension.
- Design an evidence-based hypertension medication regimen based on compelling indications

Learning Objectives (continued)

- Formulate appropriate pharmacotherapeutic regimens for patients with hypertension given unique case situations
- Develop a treatment strategy for patients who require combination antihypertensive therapy

HTN Guidelines

- JNC 7 (2002)
- AHA Update (2007)
- JNC 8 (due 2012)

Patient Case 1

- A 62-year-old man presents to your clinic for follow-up of his blood pressure.
- Last month he came to clinic for suturing of a laceration and his blood pressure was 152/85 mmHg.
- Today his blood pressure is 148/82, repeat 146/82.
- He is currently on no medications and his past medical history is unremarkable.

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Patient Case 1 continued...

- What stage of hypertension does this patient have?

☐ A. Pre-hypertension

☐ B. Stage 1

☐ C. Stage 2

☐ D. He does not have hypertension

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Classification

- **Pre-hypertension**

- SBP 120-139 mmHg and DBP 80-89 mmHg
 - Without compelling indication: No drug therapy indicated
 - With compelling indication: Drugs for compelling indications

Classification

- **Stage 1 hypertension**

- SBP 140-159 mmHg and DBP 90-99 mmHg
 - Without compelling indication: Thiazide-type diuretic, ACEI, ARB, DHP CCB
 - With compelling indication: Drugs for compelling indications. Other antihypertensives as needed.

Classification

- **Stage 2 hypertension**

- SBP ≥ 160 mmHg and DBP ≥ 100 mmHg
 - Without compelling indication: Two-drug combination for most (usually thiazide-type diuretic and ACEI, ARB, or CCB).
 - With compelling indication: Drugs for compelling indications. Other antihypertensives as needed.

Identifiable Causes of HTN

- | | |
|----------------------------------|---|
| ■ Sleep apnea | ■ Chronic steroid therapy or Cushing's syndrome |
| ■ Drug induced or related causes | |
| ■ Chronic kidney disease | ■ Pheochromocytoma |
| ■ Primary aldosteronism | ■ Coarctation of the aorta |
| ■ Renovascular disease | ■ Thyroid or parathyroid disease |

Risks of HTN

- For people 40 to 70 years of age
 - Each increment of 20 mmHg in systolic blood pressure OR
 - Each increment of 10 mmHg in diastolic blood pressure
 - Doubles the risk of CVD across the range of 115/75 to 185/115 mmHg.

Target Organ Damage

- Heart
 - ❑ Left ventricular hypertrophy
 - ❑ Angina or myocardial infarction
 - ❑ Coronary revascularization
 - ❑ Heart failure
- Brain
 - ❑ Stroke
 - ❑ Transient ischemic attack
- Chronic kidney disease
- Peripheral arterial disease
- Retinopathy

Benefits of Lowering BP

- Associated with reductions in incidence
 - ❑ Stroke – 35 to 40%
 - ❑ Myocardial infarction – 20 to 25%
 - ❑ Heart failure – >50%
- Achieving a sustained 12 mmHg reduction in SBP over 10 years prevents 1 death
 - ❑ CVD → NNT = 9
 - ❑ Stage 1 HTN → NNT = 11

BP Control Rates

- Current control rates (<140/90) at 47%
- Effective BP control can be achieved in most, but the majority will require 2 or more antihypertensive drugs

Patient Case 2

- MP is a 50-year-old woman presents for heartburn.
- Her primary care physician has been running late and she was just rushed back to her exam room.
- Her blood pressure is 151/84.
- She has no history of hypertension and the only medication she takes is OTC famotidine.

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Patient Case 2 continued...

- What is the next best action to take for MP?
 - ☐ A. Recheck her blood pressure after she has been seated quietly for 5 minutes
 - ☐ B. Start HCTZ 12.5mg daily
 - ☐ C. Start lisinopril 10mg daily
 - ☐ D. No need to be concerned with her blood pressure as she does not have hypertension

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Accurate BP Measurement

- Seated quietly for 5" with feet on the floor and arms supported
- Use appropriate size cuff
- At least 2 measurements should be done
- BP readings and goals should be provided to patient

BP Self-Measurement

- Helpful for long-term BP monitoring and evaluating white coat HTN
- Check home devices for accuracy periodically
- Automatic inflating arm devices preferred over wrist or manual inflation devices

Patient Evaluation

- Assess lifestyle, CV risk factors and concomitant disorders that can affect prognosis or treatment
- Evaluate for identifiable causes of elevated BP
- Assess for target organ damage





Patient Case 3

- A 35-year-old man with diabetes who presents to your clinic for follow-up.
- Today his blood pressure is 138/78, with repeat of 135/76.
- He is currently taking metformin 1g bid, lisinopril 10mg daily and acetaminophen as needed.
- Laboratory results reveal: Cr 1.5, A1c 7.5%, K 4.5. His BMI is 32.5.

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Patient Case 3

How should you treat this patient?

-  A. Treat with education on diet and exercise, and weight loss only.
-  B. Treat with education on diet and exercise, and weight loss and increase his lisinopril dose to 20mg daily.
-  C. Treat with education on diet and exercise, and weight loss and lower his lisinopril dose to 5mg daily.
-  D. No further treatment needed.

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BP Goals

- JNC 7
 - Primary focus is systolic BP, especially for those over 50 years of age
 - Goal for most <140/90 mmHg
 - Goal for those with DM or CKD <130/80 mmHg

BP Goals (continued)

- 2007 AHA Update
 - Goal <130/80 mmHg (based on epidemiologic studies)
 - CAD or CAD equivalent (carotid artery disease, peripheral artery disease, abdominal aortic aneurysm)
 - Goal <120/80 mmHg (based on COPERNICUS trial)
 - Left ventricular dysfunction
 - Caution diastolic falling to < 60 mmHg
- The ACCORD Study
 - Questioned the utility of achieving more aggressive BP goals in DM patients
 - 2011 ADA guidelines recommend <130/80 mmHg

Patient Case 4

- A 50-year-old woman presents to your clinic for her BP
- She participated in a health fair last week and was told her blood pressure is “too high.” Today her blood pressure is 150/85, with repeat of 147/83. Her heart rate is 72 bpm.
- She is currently taking calcium and vitamin D supplementation daily and ibuprofen as needed.
- Laboratory results reveal: Cr 0.9, K 4.0, Na 141. Her BMI is 26.0.

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Patient Case 4 continued...

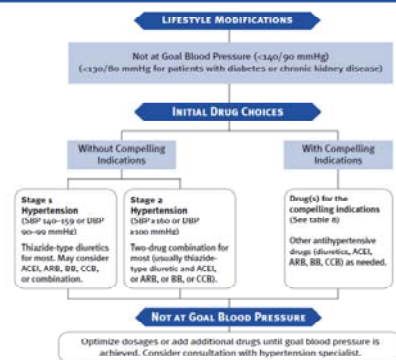
How should you treat this patient?

- ☐ A. Treat with education on diet and exercise only.
- ☐ B. Treat with education on diet and exercise and start verapamil 120mg daily.
- ☐ C. Treat with education on diet and exercise and start HCTZ 12.5mg daily.
- ☐ D. No treatment needed.

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JNC 7

Figure 1. Algorithm for treatment of hypertension



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DBP, diastolic blood pressure; SBP, systolic blood pressure.
Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker.

ALLHAT (2002)

- 33,000+ people, 55 years or older, with HTN and additional risk factor
- Randomly assigned to receive chlorthalidone, amlodipine or lisinopril
- No difference found in primary CHD outcome or mortality
- Chlorthalidone found to be superior in preventing 1 or more major form of CVD
- Limitations may affect applicability

2007 AHA Update

- Amount of BP reduction major determinant of reduction in CV risk
- Clinical trials support ACE inhibitors, ARBs, DHP calcium channel blockers or thiazide diuretics as first line

Therapeutic Lifestyle Modifications

- Weight reduction
 - For every 10kg loss → reduce SBP by 5 – 20 mmHg
- Diet modification
 - DASH diet → reduce SBP by 8 – 14 mmHg
 - Na restriction → reduce SBP by 2 – 8 mmHg
- Exercise regularly
 - 30 min/day → reduce SBP by 4 – 9 mmHg
- Alcohol moderation
 - Limit 2 drinks/day (1 for women) → reduce SBP by 2 – 4 mmHg

Pharmacotherapy

- ACE inhibitors
- ARBs
- Renin inhibitor
- Beta blockers
- Diuretics
 - Thiazide
 - Loops
 - Potassium sparing
- Calcium channel blockers
 - Dihydropyridine
 - NonDihydropyridine
- Alpha-1 blockers
- Aldosterone receptor blockers
- Central alpha-2 agonists
- Vasodilators

ACE inhibitors

- Examples: lisinopril, enalapril, ramipril
- Mechanism of action – prevents conversion of angiotensin I to angiotensin II by inhibiting angiotensin-converting-enzyme (ACE)
- Evidence – HOPE, EUROPA, PEACE, PROGRESS, ANBP-2
- Clinical utilization
 - First line anti-hypertensive
 - Compelling indications: heart failure, post myocardial infarction, high CAD risk, diabetes, chronic kidney disease, stroke

ACE inhibitors

- Contraindications
 - Bilateral renal artery stenosis, pregnancy, angioedema
- Important adverse drug reactions
 - Increasing serum creatinine, hyperkalemia, angioedema, cough
- Dosing and monitoring
 - Consider avoiding in women during childbearing years
 - Monitor Scr and K 7 to 10 days after initiation or titration

Patient Case 5

A 60-year-old man with diabetes is new to your clinic.

- Today, his BP is 145/78 mm Hg, with repeat of 141/73 mm Hg. His HR is 80 beats/minute.
- He reports intolerance to two different ACEIs because of cough. He is currently taking metformin 850 mg 3 times/day, glipizide 10 mg 2 times/day, HCTZ 25 mg daily, and omeprazole as needed.
- Laboratory results reveal Cr 1.5 (CrCl [IBW] = 54 mL/minute), A1c 6.8%, K 4.0, and microalbumin/Cr 98.2. His BMI is 31.6.

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Patient Case 5 continued...

Which one of the following options is the best way to address his elevated BP?

- ☐ A. No further treatment is needed.
- ☐ B. Start amlodipine 2.5 mg daily.
- ☐ C. Start losartan 25 mg daily.
- ☐ D. Start atenolol 25 mg daily.

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Angiotensin Receptor Blocker

- Examples: losartan, candesartan, valsartan
- Mechanism of action – selective angiotensin II receptor antagonist
- Evidence – LIFE, VALIANT
- Clinical utilization
 - Recommended as first line, but generally reserved for patients with ACEI intolerances
 - Compelling indications (after ACE inhibitors)
 - Heart failure
 - Diabetes
 - Chronic kidney disease

Angiotensin Receptor Blocker

- Contraindications - Bilateral renal artery stenosis, pregnancy, angioedema
- Extreme caution recommended if substituting ARB in patient with ACEI-induced angioedema
- Important adverse drug reactions – Increasing serum creatinine, hyperkalemia, angioedema
- Dosing and monitoring
 - Consider avoiding in women during childbearing years
 - Monitor Scr and K 7 to 10 days after initiation or titration

Renin inhibitor (aliskiren)

- Mechanism of action – decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I
- ALTITUDE trial – terminated early
 - Aliskiren added to ACEI or ARB therapy in patients with type 2 diabetes mellitus and renal impairment compared with a placebo add-on
 - An increase in nonfatal stroke, renal complications, hyperkalemia, and hypotension and no apparent benefits among patients randomized to aliskiren group

Renin inhibitor (aliskiren)

- Contraindications – pregnancy
- Important adverse drug reactions
 - Angioedema
 - Hyperkalemia if used with ACEI
- Dosing and monitoring
 - Consider avoiding in women during childbearing years
 - High fat meal decrease absorption

Beta blockers

- Examples: metoprolol, carvedilol, nebivolol
- Mechanism of action – selective (β_1) and nonselective (β_1 and β_2) receptor antagonism
- Evidence – AHA/ACC guidelines since 1980s
- Clinical utilization
 - Compelling indications: heart failure, post myocardial infarction, high CAD risk, diabetes
 - Controversy over appropriateness as first line therapy if no compelling indication present

Beta blockers

- Contraindications (relative)
 - SA or AV node dysfunction, hypotension, decompensated heart failure, severe bronchospastic disease
- Important adverse drug reactions
 - Bradycardia, heart block, bronchospastic disease, exercise intolerance, sexual dysfunction
- Dosing and monitoring
 - Monitor heart rate regularly

Patient Case 6

- A 65-year-old woman with progressing renal insufficiency presents.
- Today, her BP is 128/65 mm Hg, with repeat of 127/66 mm Hg.
- She is currently taking HCTZ 25 mg daily, lisinopril 10 mg daily, amlodipine 5 mg daily, and a multivitamin daily.
- At her previous clinic visit 2 months ago, her Cr was 1.5 (CrCl [IBW] = 35 mL/minute). Today, laboratory results reveal Cr 1.8 (CrCl [IBW] = 29.2 mL/minute), K 4.3, and Na 139. Her BMI is 21.9.

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Patient Case 6 continued...

What changes, if any, should be made to her medication regimen?

- ☐ A. Discontinue HCTZ and lisinopril.
- ☐ B. Discontinue HCTZ only.
- ☐ C. Discontinue amlodipine only.
- ☐ D. No change in her current regimen is warranted.

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Thiazide diuretics

- Examples: HCTZ, chlorthalidone, metolazone
- Mechanism of action – reduces sodium absorption in the distal convoluted tubule
- Evidence – ALLHAT, SHEP, MRC
- Clinical utilization
 - First line anti-hypertensive
 - Enhances the efficacy of multi-drug regimens
 - Affordable

Thiazide diuretics

- Contraindications - Anuria
- Important adverse drug reactions
 - Electrolyte abnormalities (hypokalemia, hyponatremia)
 - Hyperuricemia
- Dosing and monitoring
 - Ineffective for patients with GFR <30 ml/min
 - Monitor Scr, Na and K 7 to 10 days after initiation or titration

Loop diuretics

- Mechanism of action – binds to the Na, K, Cl co-transport mechanism in the loop of Henle
- Clinical utilization
 - Utilize BID dosing for HTN
 - Useful in patients with HF and/or CKD
- Contraindications – anuria

Loop diuretics

- Important adverse drug reactions
 - Electrolyte abnormalities (Na, K, Mg)
 - Dehydration
- Dosing and monitoring
 - Monitor Scr, Na and K 7 to 10 days after initiation or titration
 - Approximate dose equivalence
 - Furosemide 40 mg ~ bumetanide 1 mg ~ torsemide 10 mg ~ ethacrynic acid 50 mg

Potassium sparing diuretics

- Examples: triamterene, amiloride
- Mechanism of action – blocks Na channel in the kidney collective tubule
- Clinical utilization
 - Typically used with thiazide diuretic for potassium balance
- Contraindications – anuria, hyperkalemia, severe renal or hepatic disease
- Important adverse drug reactions - hyperkalemia
- Dosing and monitoring
 - Avoid in patients with Clcr <10 ml/min
 - Monitor Scr and K 7 to 10 days after initiation or titration

DHP Calcium channel blockers

- Examples: felodipine, amlodipine, nifedipine
- Mechanism of action – relaxes smooth muscle in arterial wall
- Evidence – ACCOMPLISH, ASCOT, VALUE
- Clinical utilization
 - First line anti-hypertensive
 - Potent BP lowering
 - Improves anginal symptoms
- Important adverse drug reactions – peripheral edema
- Dosing and monitoring – start at low dose for elderly patients

NonDHP Calcium channel blockers

- Diltiazem and verapamil
- Mechanism of action – vasodilates coronary and peripheral vessels
- Evidence – CONVINCe, INVEST, NORDIL
- Clinical utilization – useful in patients with atrial fibrillation or angina

NonDHP Calcium channel blockers

- Contraindications – heart block, sick sinus syndrome
- Important adverse drug reactions – bradycardia, heart block, constipation
- Dosing and monitoring
 - Potent CYP450 inhibitor (potentially serious drug-drug interactions)
 - Do not use with concomitant systolic HF
 - Use caution in patients on concomitant beta blockers

Alpha-1 blockers

- Mechanism of action – selective α_1 antagonist
- Evidence – ALLHAT showed 25% **higher** rate of combined CVD and 2x higher rate of HF compared to thiazide diuretic
- Clinical utilization
 - Generally reserved for men with concomitant BPH
 - Usually consider 4th or 5th line agent

Alpha-1 blockers

- Important adverse drug reactions – dizziness and orthostatic hypotension
- Dosing and monitoring
 - Start very low dose and titrate slowly
 - Patients could consider taking first dose in bed

Patient case 7

- A 58-year-old woman with CAD and diabetes presents to clinic with her home blood pressure readings, frustrated.
- She is currently taking HCTZ 25mg daily, lisinopril 40mg daily, amlodipine 10mg daily and metoprolol 25mg bid. She has tried terazosin, but had to discontinue it due to dizziness.
- Today her blood pressure is 138/79, with repeat of 135/81. Her heart rate is 58 bpm.
- Today, laboratory results reveal: Cr 1.2 (Clcr [ABW] = 51.8 ml/min), K 3.9, Na 142. Her BMI is 27.5. EF is 45%.

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Patient Case 7 continued...

Which of the following changes, if any, would be the best intervention for this patient?

- ☐ A. Start spironolactone 25mg daily
- ☐ B. Stop her HCTZ and start spironolactone 25mg daily
- ☐ C. Increase her metoprolol to 50mg bid
- ☐ D. No change in her current regimen is warranted

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Aldosterone receptor blockers

- Spironolactone and eplerenone
- Mechanism of action – inhibits aldosterone by competing for aldosterone receptors in the cortical collecting duct
- Evidence – Resistant HTN studies
- Clinical utilization
 - Resistant hypertension
 - Patients with HF and HTN

Aldosterone receptor blockers

- Contraindications – anuria, acute renal insufficiency, hyperkalemia
- Important adverse drug reactions
 - Hyperkalemia
 - Gynecomastia (spironolactone)
- Dosing and monitoring
 - Monitor Scr and K 7 to 10 days after initiation or titration

Central alpha-2 agonists

- Examples: clonidine, methyldopa, guanfacine
- Mechanism of action – stimulates α_2 receptors in brain which decreases sympathetic cardiac output and peripheral vascular resistance
- Clinical utilization
 - Resistant HTN
 - Hypertensive urgency

Central alpha-2 agonists

- Important adverse drug reactions
 - Dizziness and orthostatic hypotension
 - Dry mouth
- Dosing and monitoring
 - Rebound HTN possible if withdrawn too quickly, especially if on concomitant beta blocker (except carvedilol) due to unopposed α stimulation
 - Avoid in patients with HF

Vasodilators

- Mechanism of action – smooth muscle relaxant in arteries
- Clinical utilization
 - Resistant HTN
 - HTN + HF (hydralazine)
- Important adverse drug reactions
 - Hydralazine
 - Drug-induced lupus-like syndrome
 - Tachycardia (use with beta blocker)
 - Minoxidil
 - Fluid retention (use with diuretic)
 - Hirsutism
- Dosing and monitoring – can dose BID to QID

Patient Case 8

- A 72-year-old man is new to your clinic. He has not seen a healthcare provider for the last 7 years due to financial reasons.
- Today his blood pressure is 175/100, with repeat of 169/99.
- He takes no medications, although he reports he took medicine for his blood pressure “years ago”.
- He reports no symptoms of illness or feeling badly. Today, laboratory results reveal: Cr 1.6 (Clcr [ABW] = 46.5 ml/min), K 4.0, Na 142. His BMI is 29.6.

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Patient Case 8 continued...

Which of the following options would be the best intervention to treat this patient's hypertension?

- ☐ A. Start lisinopril/hctz 10/12.5mg daily
- ☐ B. Start lisinopril 10mg daily.
- ☐ C. Start hctz 12.5mg/day
- ☐ D. Send him to the emergency room for hypertensive emergency.

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Achieving BP control (cont'd)

- Take the entire patient into consideration
- Most who are HTN will require 2 or more medications to achieve goals
- Addition of second drug from another class should be initiated when single drug in adequate doses fail to achieve goal
- When BP >20/10 mmHg above goal, consider starting with 2 drugs

Achieving BP control (cont'd)

- BP follow-up at monthly intervals until goal achieved; labs may be needed more frequently
- More frequent visits may be necessary for Stage 2 HTN or if compelling indications present

Compelling indications

Table 8. Clinical trial and guideline basis for compelling indications for individual drug classes

Compelling Indication*	Recommended Drugs [†]						Clinical Trial Basis [‡]
	Diuretic	BB	ACEI	ARB	CCB	Aldo/ANT	
Heart failure	+	+	+	+			ACC/AHA Heart Failure Guideline, ¹⁰ MERIT-HF, ¹¹ COPERNICUS, ¹² CIBIS, ¹³ SOLVD, ¹⁴ AIRE, ¹⁵ TRACE, ¹⁶ Val-HEFT, ¹⁷ RALES ¹⁸
Postmyocardial infarction		+	+				ACC/AHA Post-MI Guideline, ¹⁹ BHAT, ²⁰ SAVE, ²¹ Capricorn, ²² EPESUS ²³
High coronary disease risk	+	+	+		+		ALLHAT, ²⁴ HOPE, ²⁵ ANBP2, ²⁶ LIFE, ²⁷ CONVINCE ²⁸
Diabetes	+	+	+	+	+		NKF-ADA Guideline, ^{29,30} UKPDS, ³¹ ALLHAT ³²
Chronic kidney disease			+	+			NKF Guideline, ³³ Captopril Trial, ³⁴ RENAL, ³⁵ IDNT, ³⁶ REIN, ³⁷ AASK ³⁸
Recurrent stroke prevention	+		+				PROGRESS ³⁹

* Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

[†] Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Aldo, aldosterone; BB, beta-blocker; CCB, calcium channel blocker.

[‡] Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.

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Ischemic Heart Disease

- AHA Update: BP goal <130/80
- Most common form of target organ damage from HTN
- Stable angina: first drug choice is beta blocker, alternatively, a long acting nonDHP calcium channel blocker
- Acute coronary syndrome: initial tx should be beta blocker and ACE inhibitor
- Post MI: ACE inhibitors, beta blocker, aldosterone antagonist

Heart Failure (HF)

- AHA Update BP goal <120/80 mmHg
- Ventricular dysfunction with no symptoms: ACE inhibitors and beta blockers
- Ventricular dysfunction with symptoms or end stage HF: ACE inhibitors, beta blockers, ARBs, aldosterone antagonists (with loop diuretic)

Diabetic HTN

- Goal BP <130/80 mmHg
- CVD and stroke prevention: thiazide diuretics, beta blockers, ACE inhibitors, ARBs, DHP calcium channel blockers
- Slow progression of diabetic nephropathy and albuminuria: ACE inhibitors and ARBs

Chronic Kidney Disease

- GFR <60 ml/min or albuminuria
- Goal BP <130/80 mmHg – often 3 or more drugs required
- Slow progression of renal disease: ACE inhibitors and ARBs – limited rise of SCr up to 35% acceptable

Cerebrovascular Disease

- AHA Update BP goal <130/80 mmHg
- Reduce risk of recurrent CVA: ACE inhibitors and thiazide diuretics

Resistant Hypertension

- Failure to reach BP goal in patients who are prescribed full doses of appropriate three drug regimen that includes diuretic
- Improper BP measurement
- Volume overload
 - Excessive Na intake
 - Volume retention
 - Inadequate diuretic therapy

Resistant Hypertension

- Drug induced
 - Nonadherence
 - Educate on benefits of BP control; solicit buy-in
 - Ensure regimen is affordable and tolerable
 - Adjust based on cultural beliefs and attitudes
 - Utilize all members of healthcare team
 - Inadequate doses
 - Inappropriate combinations

Self-Assessment 6

P.T. is a 75-year-old woman with a history of CAD (stent placement 5 years ago) and osteoarthritis.

- She has been checking her BP at home, and it has been steadily increasing (range during the past 2 weeks: 140s–150s/80s–90s).
- She had been on her medication regimen since her stent placement without problem. Her medication regimen includes carvedilol 25 mg BID, ramipril 5 mg daily, atorvastatin 40 mg daily, ASA 81 mg daily, and ibuprofen 600 mg twice daily.
- Her laboratory results reveal Cr 1.7 (CrCl [IBW] = 24.7 mL/minute), BMI 22.4, and TSH 1.56.

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Self-Assessment 6 continued...

Which one of the following options is the most likely cause of her increasing BP?

- ☐ A. Medication nonadherence.
- ☐ B. Poor diet and lack of exercise.
- ☐ C. Nonsteroidal anti-inflammatory drug (NSAID) use and renal function.
- ☐ D. Thyroid disorder

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Resistant Hypertension

- Specific drugs
 - ☐ NSAIDs
 - ☐ Cocaine, amphetamines
 - ☐ Sympathomimetics
 - ☐ Oral contraceptives
 - ☐ Adrenal steroids
 - ☐ Cyclosporin or tacrolimus
 - ☐ Erythropoietin
 - ☐ Licorice
 - ☐ Dietary supplements

Resistant Hypertension

- Associated conditions
 - ☐ Obesity
 - ☐ Alcoholism
- Identifiable causes of HTN
- Clinical inertia
 - ☐ Failure to initiate or titrate combination meds
 - ☐ Decision support and involving nurse and pharmacist clinicians can be helpful

Special Case Situations

- Minorities
 - ☐ Mexican and Native Americans have lower BP control rates
 - ☐ Socioeconomic and lifestyle factors may be barriers
 - ☐ African Americans
 - Increased severity, prevalence and impact of HTN
 - Demonstrate reduced response to some therapies (beta blockers, ACE inhibitors, ARBs)
 - Start with thiazide diuretic or DHP calcium channel blocker

Special Case Situations

- Obesity (BMI ≥ 30 kg/m²)
 - ☐ Prevalent risk factor for HTN and CVD
 - ☐ Intensive lifestyle modification recommended
- Left ventricular hypertrophy
 - ☐ Independent risk factor for CVD
 - ☐ Regression with aggressive management

Special Case Situations

- People over age 65 years
 - HTN occurs in 2/3 of population
 - Lowest rate of BP control
 - Consider initiating lower doses, but titrating to standard doses to reach goals
- Postural HTN
 - Decrease in standing BP >10 mmHg, when associated with dizziness
 - Avoid volume depletion and rapid dose titration

Self-Assessment 4

- A.M. is a 32-year-old woman with diabetes and HTN.
- Her current medication regimen is as follows: ramipril 10 mg daily, chlorthalidone 25 mg daily, amlodipine 10 mg daily, oral contraception (for the past 12 years), and insulin as directed.
- Her vital signs today include BP 141/83 mm Hg, repeat 140/79 mm Hg; HR 82 beats/minute; height 5'6"; weight 155 lb; and body mass index (BMI) 25.

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Self-Assessment 4 continued...

She would prefer not to take any more drugs, if possible. Which one of the following options is the best clinical plan for A.M.?

- ☐ A. No change in therapy is warranted at this time.
- ☐ B. Advise weight loss and recheck her BP in 3 months.
- ☐ C. Change chlorthalidone to HCTZ.
- ☐ D. Change her contraceptive method.

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Special Case Situations

- Women
 - Oral contraception can increase BP, with risk increasing over time
 - HTN increases risk to mother and fetus. Preferred medications include methyldopa, beta blockers and vasodilators.
 - Drugs that affect RAAS should not be used in women during child bearing years, especially during pregnancy

Self-Assessment 5

- A.M. and her husband have decided to have children.
- Her current medication regimen is as follows: ramipril 10 mg daily, chlorthalidone 25 mg daily, amlodipine 10 mg daily, and insulin as directed.

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Self-Assessment 5 continued...

Which one of the following medication changes, if any, needs to be made?

- ☐ A. No change in therapy is warranted at this time.
- ☐ B. Discontinue ramipril and replace with labetalol.
- ☐ C. Increase chlorthalidone to 50 mg daily.
- ☐ D. Discontinue all antihypertensive therapy.

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Special Case Situations

- Hypertensive urgencies
 - BP >180/>120 mmHg without acute target damage
 - Does not require hospitalization
 - Should receive immediate combination oral therapy
 - Agents typically used include captopril, clonidine and labetalol

Other effects of antihypertensives

- Favorable
 - Thiazides – slow demineralization in osteoporosis
 - Beta blockers – treat atrial fibrillation, tachyarrhythmias, angina and essential tremor; migraine prophylaxis
 - Calcium channel blockers – treat Raynaud's syndrome and certain arrhythmias; migraine prophylaxis
 - Alpha blockers – treats prostatism
 - ACE inhibitors – favorable affects on blood glucose

Other effects of antihypertensives

- Unfavorable
 - Thiazides – caution with gout or hyponatremia; may negatively affect blood glucose
 - Beta blockers – caution with asthma or heart blocker; may negatively affect blood glucose
 - ACE inhibitors or ARBs – avoid in women with child bearing potential
 - Aldosterone antagonists and potassium sparing diuretics – avoid in patients with K >5.0 mEq/L or CrCl <30 ml/min

Pharmacy Practice and HTN

- Role of the pharmacist
 - Community
 - Medication adherence
 - Medication counseling
 - Treatment recommendations to providers
 - Primary care
 - Patient interview
 - Treatment recommendations to providers
 - Implement therapy changes based on collaborative practice agreements (see KPCO example)
 - Follow-up

Conclusion

- ACE inhibitors, ARBs, DHP-CCB and thiazide diuretics first line therapy for HTN
- If present, base therapy on compelling indications. Special case situations may dictate therapy or therapy change
- Achieve and maintain determined BP goals to reduce risk of CVD and other target organ damage.
- Pharmacists can play key roles in hypertension management.



Updates in Therapeutics® 2012:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

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Conflict of Interest Disclosures

**Employed by Kaiser Permanente Colorado,
a non-profit integrated healthcare delivery
system**

Learning Objectives

Detect care delivery
gaps to ensure
optimal heart failure
(HF) treatment
according to
published evidence-
based guidelines

Develop patient-
specific treatment,
monitoring, and
follow-up plans for
patients with HF

Detail the role of the
clinical pharmacist in
HF management

Page Number 2-232

Patient Case Question 1

- M.J. is a 55-year-old white man who presents for an evaluation of symptoms of fatigue and SOB. He was walking 2 miles 3 times/week without difficulty, but now has limiting SOB after 1 mile. He denies recent CP, but he has a history of MI 2 years ago. Current medications include ASA 325 mg once daily, nabumetone 500 mg 2 times/day, and simvastatin 10 mg/day. His BP is 130/85 mm Hg and HR 75 beats/minute, regular. Other pertinent clinical data include Na 140 mEq/L, K 3.8 mEq/L, BUN 12 mg/dL, and SCr 0.7 mg/dL. During the examination, the physician notes bilateral rales, 2+ pretibial edema, S1, S2, and auditory S3. Medical history is significant for MI, hyperlipidemia, and osteoarthritis. His LVEF is 25%–35%.

Page Number 2-239

Morbidity and Mortality

- Total mortality (2008): 281,437
- Hospital discharges (2009): 1,094,000
- 1- and 5-year risk adjusted mortality in Medicare population: 27.5% and 62.2%
- Estimated direct and indirect cost (2010): \$39.2 billion

Page Number 2-234

Patient Case Question 1

Which one of the following is the best recommendation for this patient?

- ☐ A. Add digoxin 0.25 mg/day and continue current regimen.
- ☐ B. Add carvedilol 3.125 mg 2 times/day to current regimen.
- ☐ C. Add enalapril 2.5 mg 2 times/day and furosemide 40 mg/day, and discontinue nabumetone.
- ☐ D. Add enalapril 2.5 mg 2 times/day and digoxin 0.25 mg/day.

Page Number 2-239

Patient Case Question 2

- M.J. reports feeling much better. His BP is now 110/70 mm Hg; HR 80 beats/minute, and SCr 1.1 mg/dL. He newly complains of a dry, hacking cough. The medical resident seeks your recommendation about handling M.J.'s symptoms.

Page Number 2-240

What is HF?

- *HF is a clinical syndrome (symptoms and signs) related to inability of the heart to provide adequate flow to vital organs at rest and with exercise without excessive increase in filling pressures and can be preceded by dysfunction or risk factors that are likely to lead to HF*

Page Number 2-234

Pathophysiology of HF

Historical perspective

- "Hemodynamic disorder"
 - Abnormal pumping capacity
- Cardio-renal model
 - Excessive salt and water retention

Current perspective

- Neurohormonal activation
- Left ventricular (LV) remodeling



Primary determinants of HF disease progression

Page Number 2-234

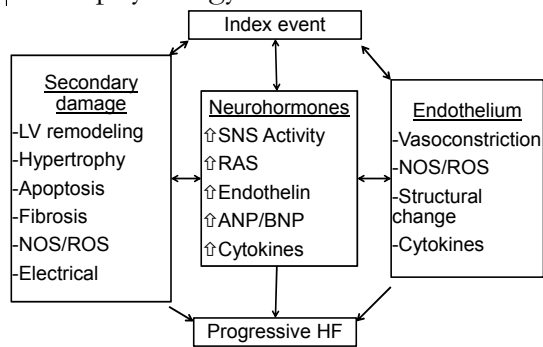
Patient Case Question 2

Which one of the following is the best recommendation for this patient?

- ☐ A. Discontinue ACE inhibitor and initiate losartan because of superior mortality benefits.
- ☐ B. Confirm assessment of ACE inhibitor cough; maintain on ACE inhibitor if possible; if not, start on ARB.
- ☐ C. Continue ACE inhibitor and add an ARB because the ARB will block the effects of ACE inhibitors on bradykinin.
- ☐ D. Discontinue ACE inhibitor; add hydralazine/nitrates.

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Pathophysiology of HF



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Patient Case Question 3

- An African American patient presents to your clinic with NYHA class III stage C HF on an optimal dosing regimen of ACE inhibitor and β -blocker; BP is 138/70 mm Hg, HR is 62 beats/minute, SCr is 3.0 mg/dL, and K is 4.9 mEq/L. *Which one of the following is the best recommendation for this patient?*

- ☐ A. Add candesartan 16 mg/day.
- ☐ B. Add spironolactone 25 mg/day.
- ☐ C. Add hydralazine 37.5 mg orally 3 times/day and isosorbide dinitrate 20 mg orally 3 times/day.
- ☐ D. Add digoxin 0.250 mg/day.

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Patient Case Question 4

- J.T. is a 72-year-old man with a history of stage C HF (LVEF 35%), post-MI, and hyperlipidemia. Current medications include ASA 325 mg/day, lisinopril 20 mg 2 times/day, simvastatin 40 mg/day, carvedilol 25 mg 2 times/day, digoxin 0.125 mg/day, furosemide 40 mg/day, and KCl 20 mEq/day. Other pertinent diagnostic and laboratory findings include BP 110/60 mm Hg, HR 58 beats/minute, SCr 1.3 mg/dL, BUN 30 mg/dL, and K 4.3 mEq/L. The patient is currently NYHA class II with stable symptoms.

Page Number 2-243

Pathophysiology of HF

Systolic HF

- "dilated cardiomyopathy"
- Increased filling pressures due to *inadequate emptying*
- Inability to further increase cardiac output (CO) during exercise or increased activity

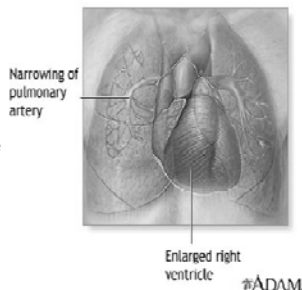
Diastolic HF

- "ventricular hypertrophy"
- Increased filling pressures due to a *ventricle that is non-distensible or unable to relax adequately*

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Right HF

- Most common cause is due to LEFT HF
- Isolated Right HF is usually secondary to chronic respiratory disease
 - Interstitial lung disease
 - Pulmonary HTN
 - *Cor pulmonale*
- Limited Rx options
- Edema often prominent issue and requires diuretic titration.



National Library of Medicine (NLM)

Patient Case Question 4

Which one of the following is the best recommendation for this patient?

- ☐ A. Discontinue lisinopril and initiate losartan.
- ☐ B. Add losartan to existing regimen.
- ☐ C. Increase dose of digoxin.
- ☐ D. Maintain current regimen without any change.

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Patient Case Question 5

- B.C. is 50-year-old man with history of stage C HF with reduced LVEF and dyspnea on exertion. The patient also has a history of ischemic heart disease with stable angina symptoms at present. Daily weights have been stable, and there is no evidence of fluid retention on physical examination. Current medications include lisinopril 5 mg 2 times/day, ASA 325 mg/day, furosemide 40 mg/day, KCl 10 mEq/day, and isosorbide dinitrate 20 mg 3 times/day. His BP is 115/70 mm Hg and HR 85 beats/minute. Laboratory values are within normal limits.

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Symptoms of HF

'Classic'

- Fatigue
- Orthopnea
- Diminished exercise capacity
- Dyspnea and/or paroxysmal nocturnal dyspnea (PND)
- Edema (ankles, lungs)

Less common

- GI symptoms
- Wheezing/cough
- Unexplained fatigue
- Confusion/delerium
- Depression/weakness

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Physical Examination Findings

- Displaced apical pulse
- Cardiac dysfunction (S3)
- Rales / wheezes
- Edema → anasarca
- Elevated jugular-venous pressure (JVP) or hepatjugular reflux
- Rapid weight gain
- Elevated BNP
- Cool extremities

When 'BAAD' is Good...

β-blocker

ER metoprolol 200 mg
Bisoprolol 10 mg
Carvedilol 50 mg

ACE-Inhibitor or ARB

Lisinopril 20-40 mg
Losartan 100 mg

Aldosterone antagonist

Spironolactone 25 mg
Eplerenone 50 mg

Diuretic and Digoxin

Furosemide 20 mg
Digoxin 0.125 mg

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β-Blockers

- Provide cardioprotection (inhibition of NE)
- Reduce myocardial oxygen demand (MVO_2)
- Along with ACE-inhibitors, are the cornerstone of HF therapy

Precautions	Contraindications
Bradycardia Decompensated HF	Reactive Airway Disease Severe PAD > 1 st degree AVB

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Generic Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Bisoprolol	1.25 mg qd	10 mg qd	8.6 mg/day
Carvedilol	3.125 mg bid	25 mg bid	37 mg/day
Carvedilol	10 mg qd	80 mg qd	N/A
Metoprolol succinate	12.5–25 mg qd	200 mg qd	159 mg/day

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Patient Case Question 5

Which one of the following is the best recommendation for this patient?

- ☐ A. Increase lisinopril to target dose 10 mg 2 times/day.
- ☐ B. Add carvedilol 3.125 mg 2 times/day.
- ☐ C. Add digoxin 0.25 mg/day.
- ☐ D. Increase lisinopril to target dose 10 mg 2 times/day, and add carvedilol 3.125 mg 2 times/day.

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Patient Case Question 6

- B.C. returns to the clinic after 3 weeks. He is clinically stable, with no evidence of worsening HF. His BP is 110/65 mm Hg, HR is 78 beats/minute, and laboratory values are within normal limits. Which one of the following is the best recommendation for this patient?

- ☐ A. Add digoxin 0.25 mg/day.
- ☐ B. Increase lisinopril to target dose 10 mg 2 times/day.
- ☐ C. Increase carvedilol to 6.25 mg 2 times/day.
- ☐ D. Make no changes at this time; the patient is stable.

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ACE-Inhibitors

- First agent to show improved survival and cardiac function
- Delay or reverse cardiac remodeling
- Reduce vasoconstriction

Precautions	Contraindications
K ⁺ > 5.0 mEq/L eGFR < 30 mL/min <i>Nuisance cough</i>	Bilateral renal artery stenosis Angioedema Pregnancy Unstable hypotension Severe aortic stenosis

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Generic Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Captopril	6.25 mg tid	50 mg tid	122.7 mg/day
Enalapril	2.5 mg bid	10 mg bid	16.6 mg/day
Fosinopril	5–10 mg qd	80 mg qd	N/A
Lisinopril	2.5–5 mg qd	20 mg qd	33.2 mg/day (high dose ATLAS)
Quinapril	5 mg bid	80 mg qd	N/A
Ramipril	1.25–2.5 mg qd	10 mg qd	N/A
Trandolapril	1 mg qd	4 mg qd	N/A

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Angiotensin Receptor Blockers (ARBs)

- Alternative to ACE-inhibitors (due to nuisance cough)
- Improves survival, but < ACE-Inhibitors
- In patients with post-MI LV systolic dysfunction and/or heart failure symptoms

Precautions	Contraindications
K ⁺ > 5.0 mEq/L eGFR < 30 mL/min <i>ACE-Inhibitor-associated angioedema</i>	Bilateral renal artery stenosis Pregnancy Unstable hypotension

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Generic Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Candesartan	4–8 mg qd	32 mg qd	24 mg/day
Losartan	12.5–25 mg qd	150 mg qd	129 mg/day
Valsartan	40 mg bid	160 mg bid	254 mg/day

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Aldosterone Antagonists

- Improved survival when added to β -blocker + ACE-Inhibitor for patients with systolic HF and NYHA Class III–IV symptoms (RALES)
- Guideline recommendations are currently being reconsidered in light of recent evidence from EMPHASIS-HF which was conducted in NYHA class II patients, and demonstrated an improvement in survival with eplerenone

Precautions	Contraindications
K ⁺ > 5.0 mEq/L eGFR < 30 mL/min Use of salt substitutes	<i>Painful gynecomastia (alternative = eplerenone)</i>

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Generic Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Spironolactone	12.5–25 mg qd	25 mg qd	26 mg/day
Eplerenone	25 mg qd	50 mg qd	42.6 mg/day

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Patient Case Question 7

- A patient with HF caused by systolic dysfunction presents with a 5-day history of progressive SOB and worsening peripheral edema. The patient was recently (about 1½ weeks ago) titrated to carvedilol 12.5 mg 2 times/day (from 6.25 mg 2 times/day). Other medications include furosemide 40 mg 2 times/day, enalapril 20 mg 2 times/day, digoxin 0.125 mg/day, and spironolactone 25 mg/day. Laboratory values have been stable (SCr 1.2 mg/dL, K 4.4 mEq/L), and the patient reports stable daily weights.

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Patient Case Question 7

Which one of the following is the best recommendation for this patient?

- ☐ A. Discontinue carvedilol because of worsening HF symptoms.
- ☐ B. Continue current dose of carvedilol and increase furosemide to 80 mg 2 times/day until weight returns to baseline.
- ☐ C. Decrease carvedilol to 6.25 mg 2 times/day.
- ☐ D. Switch carvedilol to metoprolol XL 25 mg once daily.

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Hydralazine and Nitrates

- Example: Hydralazine 10 mg BID with ISDN* 10 mg BID
- Improved survival – especially for African-Americans
- Useful alternative to ACE-I or ARB in patients at risk for ARF

Precautions	Contraindications
Hypotension Reflex tachycardia	Hypersensitivity Dissecting aortic aneurysm

Page Number 2-247

Generic Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Fixed-dose hydralazine / isosorbide dinitrate	37.5 mg hydralazine/20 mg isosorbide dinitrate tid	75 mg hydralazine/40 mg isosorbide dinitrate tid	142.5 mg hydralazine/76 mg isosorbide dinitrate/day
Hydralazine	37.5 mg qid depending on the BP of the patient you can start 10 mg QID	75 mg qid	270 mg/day
Isosorbide dinitrate	20 mg qid depending on the BP of the patient you can start 10 mg QID	40 mg qid	136 mg/day

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Page Number 2-247

Diuretics

- Manage hypervolemia
- Improve symptoms related to edema
- Furosemide most commonly used loop diuretic

Precautions	Contraindications
Hypotension / hypovolemia K ⁺ < 4 mEq/L Diuretic combination	Anuria Hypersensitivity (including rash)

Page Number 2-247

Diuretics, continued

Bumetanide (\$)

80-100% absorption
Useful alternative to furosemide

Torsemide (\$\$)

Absorption near 100%
Possible anti-fibrotic effects

Ethacrynic Acid (\$\$\$)

Useful as alternative for sulfa-allergic patients

Metolazone (\$\$\$)

Typically used in combo with loop diuretic for short periods (2-3 days)

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Generic Name	Initial Daily Dose	Target Dose
Furosemide	20–40 mg qd or bid	Max total daily dose: 600 mg
Bumetanide	0.5–1.0 mg qd or bid	Max total daily dose: 10 mg
Torsemide	10–20 mg qd	Max total daily dose: 200 mg

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Patient Case Question 8

■ C.O. is a 62-year-old man who is admitted with worsening HF symptoms. He has been diagnosed with systolic HF. He has gained 8 lb during the past 4 days and has worsening SOB, new-onset two-pillow orthopnea, and PND. Before admission, he was doing well with stable HF (stage C). His medical regimen (stable for 3 months) includes lisinopril 20 mg 2 times/day, digoxin 0.125 mg/day, carvedilol 25 mg 2 times/day, ASA 325 mg/day, furosemide 80 mg/day, and KCl 20 mEq/day. Other pertinent findings include BP 112/68 mm Hg, HR 70 beats/minute, BUN 30 mg/dL, SCr 2.6 mg/dL, and K 5.6 mEq/L. The admitting resident makes a recommendation on rounds to discontinue the β -blocker in this patient because of worsening HF.

Page Number 2-243

Digoxin

- No change in survival
- Target serum digoxin trough < 1.0 ng/mL
- Trend toward reduced hospitalizations

Precautions	Contraindications
K ⁺ > 5.0 mEq/L; < 4 mEq/L eGFR < 50 mL/min Bradycardia	eGFR < 30mL/min > 1 st degree AVB

Page Number 2-248

Patient Case Question 8

Which one of the following is the best recommendation for this patient?

- ☐ A. Discontinue carvedilol because of worsening HF.
- ☐ B. Continue carvedilol and add intravenous dobutamine.
- ☐ C. Increase the furosemide dose to achieve euvolemia.
- ☐ D. Continue carvedilol at the current dose and add spironolactone.

Page Number 2-243

Patient Case Question 9

■ N.S. is a 75-year-old woman with systolic HF, HTN, and diabetes. Current medications are ramipril 10 mg/day; metoprolol XL 150 mg/day; digoxin 0.125 mg on Monday, Wednesday, and Friday; furosemide 80 mg/day; and KCl 10 mEq/day. This regimen has been stable for the past 6 months. The patient presents with worsening SOB and a progressive decline in exercise tolerance during the past several months. She has NYHA class III/IV HF symptoms, stage C HF. The patient does not appear hypervolemic on physical examination. Other pertinent findings include BP 108/60 mm Hg, HR 62 beats/minute, BUN 30 mg/dL, SCr 1.6 mg/dL, and K 4.0 mEq/L.

Page Number 2-245

Therapies Not Recommended

- Outpatient intermittent nesiritide infusions
 - Based on FUSION II results
- Outpatient intermittent inotrope infusions
 - No benefit in terms of outcomes, increased mortality risk
 - Continuous infusions may be used as a bridge to transplant or palliative care

Page Number 2-249

Drugs To Avoid in HF

- Non-steroidal anti-inflammatories (NSAIDs)
- Thiazolidinediones (TZDs)
- ? Metformin ?
- Certain calcium channel blockers
- Most anti-arrhythmics
- Sympathomimetics (e.g. OTC pseudoephedrine, ephedra)
- Glucocorticoids
- Certain herbal products

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Patient Case Question 9

Which one of the following is the best recommendation for this patient?

- ☐ A. Add spironolactone 12.5 mg/day.
- ☐ B. Add valsartan 80 mg/day.
- ☐ C. Add intermittent inotropic therapy.
- ☐ D. Add metolazone 2.5 mg on Monday, Wednesday, and Friday.

Page Number 2-245

Patient Case Question 10

- A 72-year-old white man with systolic HF, HTN (10 years), and type 2 diabetes mellitus (6 years) is currently receiving lisinopril 20 mg/day, carvedilol 12.5 mg 2 times/day, digoxin 0.125 mg/day, and furosemide 40 mg/day. Patient denies SOB or peripheral edema; however, he reports excessive fatigue with greater than moderate levels of physical activity. Other pertinent findings include BP 102/62 mm Hg; HR 62 beats/minute, regular; BUN 22 mg/dL; SCr 1.5 mg/dL; and K 4.2 mEq/L.

Page Number 2-246

Non-pharmacologic Strategies

Device(s)

- Implantable cardioverter defibrillators (ICDs)
- LV Assist Devices (LVADs)
- Cardiac resynchronization with biventricular pacemaker (Bi-V CRT)

Procedure(s)

- Ultrafiltration
- Coronary revascularization
- Valvular surgery
- Heart transplant

Page Number 2-251

Acute Decompensated HF (LIV)

- Loop diuretics
 - Recent evidence suggests no difference in outcomes between bolus or continuous infusion dosing
 - High doses retrospectively appear to be associated with worse outcomes
- Intotropes
 - Reserved for low output HF and cardiogenic shock
- Vasodilators

Page Number 2-254

Patient Case Question 10

Which one of the following is the best recommendation for this patient?

- ☐ A. Add metolazone.
- ☐ B. Add isosorbide dinitrate/hydralazine.
- ☐ C. Add spironolactone.
- ☐ D. Titrate current β -blocker and ACE inhibitor to full dose, and observe/reevaluate in 2 months.

Page Number 2-246

Patient Case Question 11

- N.N. is a 60-year-old white man with ischemic cardiomyopathy and LVEF 20%–25%. He is currently treated with enalapril 20 mg orally 2 times/day, digoxin 0.125 mg/day, metoprolol XL 100 mg/day, furosemide 80 mg/day, KCl 20 mEq/day, ASA 325 mg/day, and simvastatin 40 mg/day. Medication regimen has been stable for several months. Other pertinent clinical findings include BP 114/70 mm Hg, HR 67 beats/minute, 1+ edema bilaterally, SCr 1.0 mg/dL, K 4.0 mEq/L, and digoxin level 0.6 ng/mL (therapeutic range indicated on laboratory report 0.5–2.0 ng/mL). Other laboratory values are within normal limits. He remains functionally NYHA class III despite the above medications.

Page Number 2-246

Clinically Significant Interactions

Drug-Disease

- ▼ Absorption
- ▼ Distribution
- ▼ Metabolism
- ▼ Excretion

Drug-Drug

- Pharmacokinetic
 - B-blockers and CYP2D6 inhibitors
 - Digoxin and p-glycoprotein inhibitors
- Pharmacodynamic
 - Additive BP effects
 - Additive HR effects
 - Additive eGFR effects
 - Additive K effects

Page Number 2-255

Patient Case Question 11

Which one of the following is the best recommendation for this patient?

- ☐ A. Increase digoxin to 0.25 mg/day.
- ☐ B. Add spironolactone 25 mg/day.
- ☐ C. Add felodipine.
- ☐ D. Add hydralazine and nitrates.

Page Number 2-246

Patient Case Question 12

- J.B. is a 62-year-old white man who was recently discharged from an HF-related hospitalization. Before hospitalization, his medication regimen included lisinopril 20 mg 2 times/day, valsartan 80 mg 2 times/day, metoprolol XL 100 mg/day, and furosemide 40 mg 2 times/day. The patient is now in stage C HF with stable NYHA class III/IV symptoms. Other pertinent diagnostic and laboratory findings include BUN 30 mg/dL, SCr 1.4 mg/dL, K 4 mEq/L, BP is 124/70 mm Hg, and HR 67 beats/minute.

Page Number 2-247

Role of the Pharmacist

Case Management

- Provide active therapy management
- Identify drug-related problems
- Direct patients to assistance programs
- Provide counseling to patients
- Pharmacist involvement has been associated with reduced mortality and need for hospital admission

Page Number 2-256

Role of the Pharmacist, continued

Population Management

- Developing clinical pathways or guidelines
- Providing education to healthcare providers and patients
- Identifying quality improvement opportunities
- Developing registries

Page Number 2-256

Patient Case Question 12

Which one of the following is the best recommendation for this patient?

- ☐ A. Increase furosemide to 80 mg 2 times/day.
- ☐ B. Add spironolactone 25 mg/day.
- ☐ C. Add digoxin 0.125 mg/day.
- ☐ D. Discontinue valsartan and add spironolactone 25 mg/day.

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Patient Case Question 13

- A 68-year-old AA woman with HF presents to your clinic. Comorbidities include HTN and type 2 diabetes mellitus. During the past year, she has had two hospitalizations for decompensated HF and significant volume overload with each hospitalization. Current symptoms are SOB with minimal exertion, 2+ peripheral edema bilaterally, and NYHA class III. Other pertinent findings include BP 160/72 mm Hg, HR 68 beats/minute, SCr 2.1 mg/dL, BUN 25 mg/dL, K 4.3 mEq/L, Na 140 mEq/L, hemoglobin A1C 8%, digoxin 0.6 ng/mL, and LVEF 28%. Current medications include enalapril 20 mg 2 times/day, metoprolol XL 150 mg once daily, pioglitazone 30 mg once daily, digoxin 0.125 mg 3 times/week, furosemide 80 mg once daily, and KCl 20 mEq once daily.

Page Number 2-248

Patient Case Question 13

Which one of the following is the best recommendation for this patient?

- ☐ A. Increase digoxin to daily administration.
- ☐ B. Add spironolactone.
- ☐ C. Add an ARB.
- ☐ D. Discontinue pioglitazone and add hydralazine/nitrates.

Page Number 2-248

Patient Case Question 14

- T.S. is a 77-year-old man with ischemic cardiomyopathy. Recent LVEF was 24%. Current medications include lisinopril 20 mg/day, furosemide 120 mg 2 times/day, KCl 40 mEq 2 times/day, digoxin 0.125 mg orally every other day, glyburide 10 mg/day, atorvastatin 10 mg/day, isosorbide 20 mg 3 times/day, and ASA 325 mg/day. Two weeks ago, T.S. presented to the clinic with stable HF symptoms, and carvedilol 3.125 mg orally 2 times/day was initiated. Today, the patient denies worsening HF symptoms and reports stable weights; however, he has experienced light-headedness. Other pertinent diagnostic and laboratory findings include BP (seated) 110/70 mm Hg, HR is 65 beats/minute; and, BP (standing) is 98/60 mm Hg with HR 78 beats/minute.

Page Number 2-248

Patient Case Question 14

Which one of the following is the best recommendation for this patient?

- ☐ A. Decrease lisinopril.
- ☐ B. Decrease furosemide.
- ☐ C. Continue with carvedilol titration.
- ☐ D. Discontinue carvedilol.

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Take Home Points

Detect care delivery gaps to ensure optimal heart failure (HF) treatment according to published evidence-based guidelines

Develop patient-specific treatment, monitoring, and follow-up plans for patients with HF

Detail the role of the clinical pharmacist in HF management

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Updates in Therapeutics® 2012:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Thromboembolism
Nathan Clark, Pharm.D., BCPS
Kaiser Permanente Colorado

Conflict of Interest Disclosures

- No financial conflict of interest

Learning Objectives

1. Discuss pharmacologic prevention strategies for patients at risk of venous thromboembolism
2. Recognize appropriate diagnosis of deep vein thrombosis and pulmonary embolism
3. Formulate appropriate treatment strategies for patients who are at risk for or who develop venous or arterial thromboembolism
4. Select appropriate dosing and monitoring strategies for patients treated with antithrombotic medications

Learning Objectives

4. Develop a comprehensive education plan for patients receiving antithrombotic medications
5. Formulate an opinion regarding the role of dabigatran, rivaroxaban, and apixaban for stroke prevention in atrial fibrillation

Venous Thromboembolism

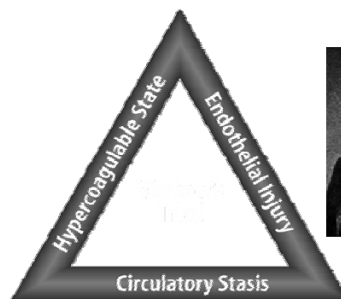
Epidemiology:

- Estimated that as many as 2 million cases of venous thromboembolism (VTE) occur in the U.S. annually
 - Including ~ 100,000 cases of fatal PE
- Incidence of VTE doubles each decade of life after age 50

Etiology

- Convergence of inherited and acquired prothrombotic states

Venous Thromboembolism



Risk Factor for VTE	Examples*
Age	After 50 yrs, risk doubles each decade
History of VTE	Strongest risk for DVT and PE
Venous stasis	Major medical illness Major surgery Paralysis Obesity
Vascular injury	Major orthopedic surgery Trauma (bone fracture) Indwelling catheter
Hypercoagulability	Malignancy Thrombophilia Pregnancy/postpartum
Drug therapy	Estrogen Chemotherapy

*Not a comprehensive list

VTE Prevention		
Risk Level Description	VTE Risk (%) ^a	Prevention Strategies
Low Minor surgery Fully mobile medical patients	<10	Early and aggressive ambulation
Moderate Major surgery, no other risks Acutely ill medical patients on bed rest (e.g. AMI, CVA, HF)	10-40	UFH 5,000 units q12h or q8h LMWH or fonda @ prophyl dose IPCs ^b Graduated compression stockings ^b
High Hip or knee replacement Hip fracture surgery Major trauma or spinal injury	40-80	LMWH or fonda @ prophyl dose Warfarin (INR 2-3) Rivaroxaban 10mg daily (TKA/THA)

a-Includes asymptomatic events; b-used where risk of bleeding is high

VTE Prevention

- 2012 ACCP Update
 - For major orthopedic surgery we recommend one of the following for a minimum of 10 to 14 days
 - LMWH
 - Fondaparinux
 - Adjusted dose VKA (**no target INR specified**)
 - **Low dose unfractionated heparin**
 - **Dabigatran, apixaban, rivaroxaban**
 - **Aspirin**
 - Suggest LMWH in preference over other agents

Patient Case 1

S.G., a 76-year-old, obese (92 kg, 6 ft tall) man, presents to the emergency department with swelling of his entire right lower extremity, erythema, and soreness of his right calf. He had knee replacement surgery 2 weeks ago. He denies shortness of breath, cough, or chest pain.

Medical history:

- Deep vein thrombosis (DVT) after leg fracture at age 24
- Coronary artery disease
- Hypercholesterolemia

Patient Case 1 Continued

Laboratory values:

- Hematocrit 36.5% (normal 42%–52%)
- Prothrombin time (PT) 10.8 seconds (INR 1.0)
- aPTT 23.6 seconds (normal 24–36)
- Platelet count 255,000/mm³ (normal 150,000–300,000)
- Creatinine clearance (CrCL) 74 mL/minute

Current medications:

- Diltiazem (Cardizem CD) 360 mg/day orally
- Isosorbide mononitrate (Imdur) 120 mg/day orally
- Atenolol (Tenormin) 50 mg/day orally
- Aspirin 325 mg/day orally
- Simvastatin (Zocor) 5 mg orally every night

Patient Case 1, Question #1

Which one of the following most accurately reflects the clinical probability of this patient having DVT?

- ☐ A. Low
- ☐ B. Moderate
- ☐ C. High
- ☐ D. Very High

Workbook Page 2-287; Answer: Page 2-327

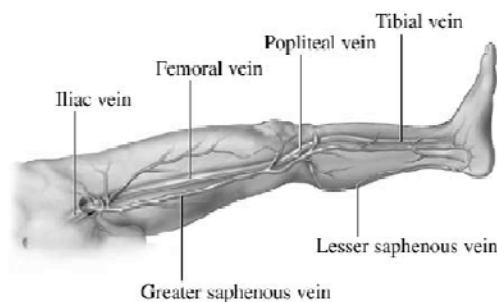
Deep Vein Thrombosis

Presentation:

- DVT most often occurs in the lower extremities
 - Embolus in up to 50% of cases
- Pain, swelling, and redness in the affected leg

Diagnosis:

- D-dimer
 - By-product of fibrin generation, nonspecific measure
 - Useful to rule out DVT when pretest probability is LOW
- Duplex ultrasonography
 - Most commonly used test
 - Cannot reliably detect small clots in distal veins (calf)
- Venography
 - Gold standard, but rarely used outside clinical trials



DVT Clinical Probability Model

Active cancer (treatment w/in 6 months or palliative)	1pt
Paralysis, paresis, or recent plaster LE immobilization	1pt
Recently bedridden ≥ 3 days or major surgery w/in 12 weeks	1pt
Localized tenderness along distribution of deep venous system	1pt
Entire leg swollen	1pt
Calf swelling at least 3cm > than asymptomatic leg	1pt
Pitting edema confined to symptomatic leg	1pt
Collateral superficial veins (non-varicose)	1pt
Previously documented DVT	1pt
Alternative diagnosis at least as likely as DVT	-2pts

Clinical probability of DVT: Low < 1; moderate 1-2; high > 2

Pulmonary Embolism

Presentation:

- Signs and symptoms are nonspecific
 - Common s/s include: chest pain, shortness of breath, and tachypnea

Diagnosis:

- D-dimer is almost always elevated with PE
 - Normal D-dimer and LOW pretest probability rules out PE
- Computerized tomography
 - Preferred method for confirmation of diagnosis unless contraindicated (contrast dye)
- Ventilation/perfusion scanning
 - Measures distribution of blood and airflow in the lungs
 - Evaluates mismatch in perfusion and ventilation
- Pulmonary angiography

PE Clinical Probability Model

Clinical Characteristic	Score
Cancer	+1
Hemoptysis	+1
Previous VTE	+1.5
Heart rate > 100 bpm	+ 1.5
Recent surgery or immobility	+1.5
Clinical signs of DVT	+3
Alternate diagnosis less likely than PE	+3

Clinical probability of PE: low 0-1; moderate 2-6; high > 6

Patient Case 1, Question #1

Which one of the following most accurately reflects the clinical probability of this patient having DVT?

- ☐ A. Low
- ☐ B. Moderate
- ☐ C. High
- ☐ D. Very High

Workbook Page 2-287; Answer: Page 2-327

Patient Case 1, Question #2

Which one of the following is the best diagnostic and treatment approach for this patient?

- ☐ A. Order a D-dimer test and start a rapid-onset injectable anticoagulant
- ☐ B. Order a duplex scan
- ☐ C. Order venography and start a rapid-onset injectable anticoagulant
- ☐ D. Start a rapid-onset injectable anticoagulant

Workbook Page 2-287; Answer: Page 2-327

Acute Management of VTE

Disease suspected:

- ☐ Obtain baseline PT/INR, CBC and SrCr
- ☐ Confirm objective diagnosis
- ☐ Check for contraindications to anticoagulation
- ☐ Estimate renal function (Cockcroft-Gault)
- ☐ Treat with heparin while awaiting diagnostic confirmation

Patient Case 1, Question #2

Which one of the following is the best diagnostic and treatment approach for this patient?

- ☐ A. Order a D-dimer test and start a rapid-onset injectable anticoagulant
- ☐ B. Order a duplex scan
- ☐ C. Order venography and start a rapid-onset injectable anticoagulant
- ☐ D. Start a rapid-onset injectable anticoagulant

Workbook Page 2-287; Answer: Page 2-327

Patient Case 1, Question #3

Which one of the following best represents how long this patient should be treated with anticoagulant therapy?

- ☐ A. At least 3 months
- ☐ B. 6 months
- ☐ C. 12 months
- ☐ D. Indefinitely

Workbook Page 2-287; Answer: Page 2-327

VTE Duration of Therapy

Characteristic	Duration
First VTE provoked by transient risk factor	3 months
First VTE and cancer	6 months (consider indefinite or until CA resolved) ^a
First VTE idiopathic +/- hypercoagulability	At least 3 months ^b
First VTE with APAS or 2+ thrombophilia traits	At least 12 months ^b
Recurrent VTE	Indefinite

a – LMWH is preferred over warfarin

b – Continue if low bleeding risk and adherent to therapy; reassess periodically

Patient Case 1, Question #3

Which one of the following best represents how long this patient should be treated with anticoagulant therapy?

- ☐ A. At least 3 months
- ☐ B. 6 months
- ☐ C. 12 months
- ☐ D. Indefinitely

Workbook Page 2-287; Answer: Page 2-327

Patient Case 1, Question # 4

The decision is made to initiate anticoagulation therapy in the ED and then discharge patient home. Which of the following is the best initial anticoagulant regimen?

- ☐ A. Fondaparinux 7.5mg SC daily and warfarin 5mg/day
- ☐ B. Dalteparin 18,000 units SC twice daily and warfarin 5mg/day
- ☐ C. Enoxaparin 160mg SC daily and warfarin 5mg/day
- ☐ D. Tinzaparin 20,000 Units SC daily

Workbook Page 2-287; Answer: Page 2-327

Initial Therapy

- Initiate LMWH, UFH or fondaparinux with warfarin on Day 1
- Stop heparin/heparinoid after 5 days and INR > 2.0 for 24 hours and/or stable
- Ambulate adequately anticoagulated patients as tolerated
- Most patients with uncomplicated DVT can be treated as an outpatient
 - LMWH or fondaparinux preferred in this setting
- UFH is preferred in the setting of severe renal impairment (i.e. CrCL<30mL/min)
- Graduated compression stockings providing 30 to 40mm Hg pressure at the ankle
 - Reduce postthrombotic syndrome

Pharmacologic Options

Unfractionated heparin:

- IV bolus (wt based or 5,000 units) followed by IV infusion to achieve therapeutic aPTT or anti-Xa
- SC administration
 - 5,000 units IV infusion then 17,500 Units SC every 12 hours according to aPTT/anti-Xa
 - 333 units/kg SC x 1, then 250 units/kg SC every 12 hours, no coagulation monitoring

Low-molecular-weight heparin:

- Dalteparin 100U/kg BID, 200U/kg QD
- Enoxaparin 1mg/kg BID, 1.5mg/kg QD,
 - CrCL<30mL/min; 1mg/kg QD
- Tinzaparin 175U/kg once daily

Pharmacologic Options

Factor Xa inhibitor:

- Fondaparinux: dose according to actual body weight
 - Less than 50kg: 5mg SC once daily
 - 50 to 100kg: 7.5mg SC once daily
 - Greater than 100kg: 10mg SC once daily
- Contraindicated in CrCL less than 30mL/min

Patient Case 1, Question # 4

The decision is made to initiate anticoagulation therapy in the ED and then discharge patient home. Which of the following is the best initial anticoagulant regimen?

- ☐ A. Fondaparinux 7.5mg SC daily and warfarin 5mg/day
- ☐ B. Dalteparin 18,000 units SC twice daily and warfarin 5mg/day
- ☐ C. Enoxaparin 160mg SC daily and warfarin 5mg/day
- ☐ D. Tinzaparin 20,000 Units SC daily

Workbook Page 2-287; Answer: Page 2-327

Patient Case 1, Question # 5

Which one of the following reflects the appropriate time frame for anticoagulation clinic follow up after ED discharge for this patient?

- ☐ A. 1-3 days
- ☐ B. 3-5 days
- ☐ C. 5-7 days
- ☐ D. 7-10 days

Workbook Page 2-287; Answer: Page 2-327

Warfarin Considerations

- Typical initiation doses are between 5 and 10 mg
- Repeat INR on Day 3 and daily until greater than 2
- Address transitional care issues
 - Follow-up INR scheduled
 - Provider is aware of discharge
- Make sure the patient receives warfarin education and VTE education (Joint Commission mandate)
- Desired goal INR range is 2–3
 - Higher INR targets linked to more bleeding events
 - Lower INR targets (1.5–2) are less effective and not clearly safer (have not reduced bleeding)

Patient Case 1, Question # 5

Which one of the following reflects the appropriate time frame for anticoagulation clinic follow up after ED discharge for this patient?

- ☐ A. 1-3 days
- ☐ B. 3-5 days
- ☐ C. 5-7 days
- ☐ D. 7-10 days

Workbook Page 2-287; Answer: Page 2-327

Patient Case 2

C.D., a 78-year-old woman, presents to the cardiology clinic after experiencing several days of fatigue and a “racing heart.”

On physical examination, her pulse is irregularly irregular, and her heart rate is 120 beats/minute.

Using electrocardiography (ECG), a diagnosis of AF is made, and cardioversion is planned.

Patient Case 2, Question # 6

Which one of the following is the most appropriate anticoagulant treatment plan for this patient?

- ☐ A. ASA 325mg for 3 weeks before and 4 weeks after CVN
- ☐ B. IV UFH starting 48 hours before- and warfarin (INR 2-3) for 4 weeks after CVN
- ☐ C. Warfarin (INR 2-3) for 3 weeks before and 4 weeks after CVN
- ☐ D. Rivaroxaban 15mg/day for 3 weeks before and 4 weeks after CVN

Workbook Page 2-295; Answer: Page 2-327

Atrial Fibrillation

- Major risk factor for stroke and SE
 - 90% of embolic events are stroke related
 - 10% systemic embolism
- 15% of all strokes occur in patients with AF
 - Annual risk is 3 to 8%
- Classification of AF
 - Acute AF– onset within 48 hours
 - Paroxysmal AF – terminates spontaneously within 7 days
 - Recurrent AF– more than one episode
 - Persistent AF – duration of more than 7 days
 - Permanent AF – persistence of AF despite CVN

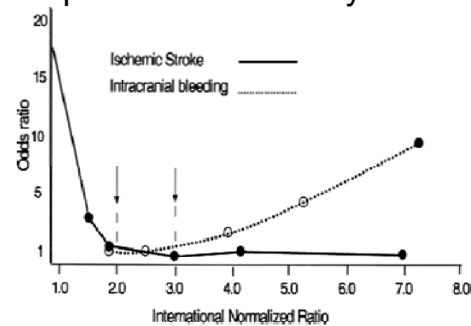
AF Antithrombotic Therapy

- Aspirin provides a modest reduction in nonfatal stroke versus placebo
 - RRR = 21% (95% CI, 0 – 38%)
- Clopidogrel plus aspirin superior to aspirin alone but increases bleeding including ICH
 - 2012 CHEST guidelines state preference for aspirin plus clopidogrel over aspirin alone
 - ACTIVE-W primary outcome (stroke, SE, MI or vascular death):
 - RR = 1.44 (95% CI, 1.18-1.76) vs. warfarin (INR 2-3)
- Warfarin decreases risk of stroke versus placebo, aspirin, and aspirin plus clopidogrel

AF Optimal INR Intensity

- Anything new?
 - No.

AF Optimal INR Intensity



Fuster V et al. Circulation 2006;114:e257-e354

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Learn and Live

AF Optimal INR Intensity

- Risk of ICH increases at INR > 4.0
- Risk of stroke and stroke severity increases at INR < 2.0
- Lower targets suggested (INR 1.6-2.5) by ACC/AHA/ESC in patients unable to tolerate standard intensity
- Narrow ranges (e.g. INR 2.0-2.5) have been suggested in patients on warfarin, ASA, and clopidogrel after PCI
 - Neither of these alternate ranges are supported by good evidence

Rate vs. Rhythm Control in AF

- Rhythm control not necessary for asymptomatic patients
 - Ischemic events occur at similar frequency
 - More likely to occur in both populations if anticoagulation is discontinued
 - Anticoagulation is recommended for patients with rate or rhythm control with thromboembolic risk factors

Cardioversion Considerations

- Stable patients should receive 3 – 4 weeks of anticoagulation prior to CVN
 - Alternatively, perform TEE to rule out thrombus with immediate CVN followed by rapid acting anticoagulants and transition to warfarin
- Systemic embolism is a risk when NSR is reestablished regardless of method
 - At least 4 weeks of warfarin is recommended after successful CVN
- Unstable patients requiring emergent CVN should receive rapid acting anticoagulants (UFH or LMWH) postprocedure followed by warfarin
 - Unclear if there is a distinct benefit to either regimen

Cardioversion and Novel Anticoagulants

- 1983 cardioversions performed in the RELY trial
 - The frequency of stroke/SE in the two dabigatran doses was low and similar to warfarin
 - Pre-cardioversion TEE did not alter this finding, but more dabigatran patients had pre-cardioversion TEE
- Planned cardioversion was an exclusion in the rivaroxaban AF trial (ROCKET-AF)

Patient Case 2, Question # 6

Which one of the following is the most appropriate anticoagulant treatment plan for this patient?

- ☐ A. ASA 325mg for 3 weeks before and 4 weeks after CVN
- ☐ B. IV UFH starting 48 hours before- and warfarin (INR 2-3) for 4 weeks after CVN
- ☐ C. Warfarin (INR 2-3) for 3 weeks before and 4 weeks after CVN
- ☐ D. Rivaroxaban 15mg/day for 3 weeks before and 4 weeks after CVN

Workbook Page 2-295; Answer: Page 2-327

Patient Case 2, Question # 7

Four weeks after successful CVN, C.D. is readmitted in AF. Her CHADS₂ score is 1 (age > 75). Which of the following recommendations for long-term therapy is best?

- ☐ A. ASA 81mg/day
- ☐ B. Warfarin at a goal INR of 2.5 (range 2-3)
- ☐ C. Dabigatran 150mg twice daily
- ☐ D. The above option most acceptable to the patient

Workbook Page 2-295; Answer: Page 2-327

CHADS₂ Score

Score	Annual Stroke Rate % (range)	Recommended Treatment
0	1.9 (1.2-3.0)	ASA - 2012 ACCP suggest no Rx, but ASA for those electing Rx
1	2.8 (2-3.8)	Warfarin, dabigatran, rivaroxaban, ASA - 2012 ACCP suggest anticoagulation over antiplatelet Rx and ASA + clopidogrel over ASA alone
2 - 6	4 - 18	Warfarin, dabigatran, or rivaroxaban

C-congestive HF (1pt); H-hypertension (1pt); A-age>75 (1pt); D-diabetes (1pt); S-stroke, transient ischemic attack or systemic embolism (2pts)

CHA₂DS₂-VASc Score

Risk Factor	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Previous stroke, TIA, or SE	2
Vascular disease (MI, PAD, aortic plaque)	1
Age 65-74	1
Sex (female)	1
Score = 0: No anticoagulation (preferred) or ASA 75 – 325mg daily	
Score = 1: Either anticoagulation (preferred) or ASA 75 – 325mg daily	
Score > 1: Anticoagulation with warfarin, dabigatran, or rivaroxaban	

Patient Case 2, Question # 7

Four weeks after successful CVN, C.D. is readmitted in AF. Her CHADS₂ score is 1 (age > 75). Which of the following recommendations for long-term therapy is best?

- ☐ A. ASA 81mg/day
- ☐ B. Warfarin at a goal INR of 2.5 (range 2-3)
- ☐ C. Dabigatran 150mg twice daily
- ☐ D. The above option most acceptable to the patient

Workbook Page 2-295; Answer: Page 2-327

Study Name Population	Design	Treatment	Primary Efficacy	Primary Safety
ARISTOTLE Atrial fibrillation CHADS ₂ (mean) = 2.1	Randomized, double-blinded, double-dummy	Warfarin (INR 2-3, 62.2% TIR) Apixaban 5mg twice daily ¹	Stroke or SE: A - 1.27% W - 1.6% HR-0.79 (CI 0.66 - 0.95)	ISTH major hemorrhage: A - 2.13% W - 3.09% HR-0.69 (CI 0.60 to 0.80)
RELY Atrial fibrillation CHADS ₂ (mean) D - 2.2 W - 2.1	Randomized, open-label	Warfarin (INR 2-3, 64% TIR) Dabigatran 150mg twice daily ²	Stroke or SE: D - 1.11% W - 1.69% RR-0.66 (CI 0.53 - 0.82)	Major hemorrhage: D - 3.11% W - 3.36% RR-0.93 (CI 0.81-1.07) ns
ROCKET-AF Atrial fibrillation CHADS ₂ (mean) R - 3.48 W - 3.46	Randomized, double-blind, double-dummy	Warfarin (INR 2-3, 55% TIR) Rivaroxaban 20mg daily ³	Stroke or SE: R - 2.1% W - 2.4% HR-0.88 (CI 0.75-1.03) ns	Major ⁴ plus clinically-relevant bleeding: R - 14.9% W - 14.5% HR-1.03 (CI 0.96-1.11) ns

A-apixaban, W-warfarin, D-dabigatran, R-rivaroxaban, INR international normalized ratio, TIR-time-in-range, SE-systemic embolism, HR-hazard ratio, CI-95% confidence interval, RR-relative risk, ns-not statistically significant

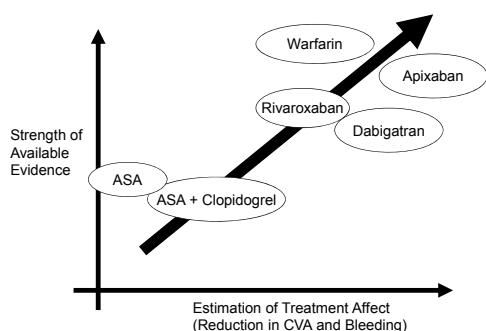
¹ Apixaban 2.5mg twice daily for two or more of the following: age > 79, weight < 60kg, or S-Cr > 1.4

² Dabigatran 110mg twice daily was studied but not reported here since not approved by FDA

³ Rivaroxaban 15mg daily used for CrCL 30 to 49mL/min

⁴ Major bleeding between rivaroxaban and warfarin was not significant

Continuum of AF Antithrombotic Data



Barriers to Novel AC Use

- Irreversibility
 - Rivaroxaban data with PCC?
 - Too early to be reassured
 - Correction of INR does not always reflect hemostasis
- Cost
- Renal function
 - Not studied where CrCL < 30 mL/min
- Lack of monitoring
 - No readily available test
 - No therapeutic interval

Prosthetic Heart Valves

- Patients with mechanical heart valves are at high risk of TE and require lifelong antithrombotic prophylaxis
- Annual TE risk 4 to 23%
 - Decrease to < 2% with effective antithrombotic tx
- Greatest TE risk is within 3 months of surgery
 - Exposed suturing ring and valve surfaces
- Newer designs and materials decrease thrombogenicity
- Bioprosthetic are least thrombogenic, but are less durable and more prone to failure

Mechanical Heart Valves

Target INR Range			
	Caged	Tilting Disk ^a	Bileaflet ^b
AVR^c			
Low risk	2.5-3.5	2.5-3.5	2-3
High risk ^d	2.5-3.5 + ASA	2.5-3.5 + ASA	2.5-3.5 + ASA
MVR^c			
Low risk	2.5-3.5	2.5-3.5	2.5-3.5
High risk ^d	2.5-3.5 + ASA	2.5-3.5 + ASA	2.5-3.5 + ASA

^a-does not include Medtronic-Hall

^b-includes Medtronic-Hall

^c-ACC/AHA recommends ASA for all patients with mechanical heart valves

^d-high risk = multiple prosthetic valves, heart failure, AF, stroke/SE, or left atrial enlargement

Bioprosthetic Heart Valves

- AVR
 - Low risk – ASA
 - High risk^a – INR 2-3
- MVR
 - Low risk – INR 2-3 for 3 months, then ASA
 - High risk^a – INR 2-3 +/- ASA (ACC/AHA recommends INR 2.5-3.5 for first 3 months)
- Left atrial thrombus present during surgery
 - INR 2-3 until documented resolution

^a-high risk = multiple prosthetic valves, heart failure, AF, stroke/SE, or left atrial enlargement

Patient Case 3

J.Y. is a 76-year-old man with a history of hypertension, hypercholesterolemia, adult-onset diabetes, and AF. He receives warfarin 2.5 mg on Monday, Wednesday, and Friday and 5 mg on all other days for stroke prevention.

J.Y. is scheduled to have five teeth removed, and his dentist has recommended that warfarin be withheld for 5 days before the procedure; the dentist refers the patient back to you to design an appropriate plan.

Patient Case 3, Question # 8

Which of the following is the best assessment of the patient's risk of stroke if warfarin is interrupted for 5 days prior to the procedure?

- ☐ A. Low
- ☐ B. Moderate
- ☐ C. High
- ☐ D. Very high

Workbook Page 2-321; Answer: Page 2-327

Perioperative Risk Assessment

Mechanical Heart Valves	
High risk	<ul style="list-style-type: none"> ■ Mitral valve (any type) ■ Tilting disc or caged-ball valve in any position ■ Recent CVA or TIA (w/in 6 months)
Moderate risk	<ul style="list-style-type: none"> ■ Bileaflet aortic valve with one of the following: AF, HTN, DM, HF, CVA, TIA, or age > 75
Low risk	<ul style="list-style-type: none"> ■ Bileaflet aortic valve with no stroke risk factors listed above

Perioperative Risk Assessment

Atrial Fibrillation	
High risk	<ul style="list-style-type: none"> ■ CHADS₂ score > 4 ■ Recent CVA or TIA (within 3 months) ■ Rheumatic heart disease or mitral stenosis
Moderate risk	<ul style="list-style-type: none"> ■ CHADS₂ score 3 to 4
Low risk	<ul style="list-style-type: none"> ■ CHADS₂ score < 3 ■ No prior CVA or TIA

Perioperative Risk Assessment

Venous Thromboembolism	
High risk	<ul style="list-style-type: none"> ■ Recent VTE within 3 months ■ VTE history and severe thrombophilia (e.g. Protein C, S, or antithrombin deficiency, antiphospholipid antibody syndrome, multiple abnormalities)
Moderate risk	<ul style="list-style-type: none"> ■ VTE within the past 3 to 12 months ■ Nonsevere thrombophilia (e.g. heterozygous factor V Leiden or heterozygous PT G20210A mutation) ■ Active cancer ■ Recurrent VTE
Low risk	<ul style="list-style-type: none"> ■ Single VTE no other risk factor

Patient Case 3, Question # 8

Which of the following is the best assessment of the patient's risk of stroke if warfarin is interrupted for 5 days prior to the procedure?

- ☐ A. Low
- ☐ B. Moderate
- ☐ C. High
- ☐ D. Very high

Workbook Page 2-321; Answer: Page 2-327

Patient Case 3, Question # 9

Which of the following is the best therapeutic plan for J.Y.?

- ☐ A. Continue warfarin, control bleeding with local measures
- ☐ B. Stop warfarin x 5 days, resume at usual dose the evening after the procedure
- ☐ C. Stop warfarin x 5 days, start LMWH 2 days after warfarin stopped
- ☐ D. Stop warfarin x 5 days, start LMWH 1 to 2 days after procedure

Workbook Page 2-321; Answer: Page 2-328

Bleeding Risk During Procedures

Low Risk Procedure		High Risk Surgery
<ul style="list-style-type: none"> ■ Minor dermatologic ■ Minor dental ■ Minor ophthalmic ■ Diagnostic endoscopy 	Everything else	<ul style="list-style-type: none"> ■ Urologic ■ Pacemaker or ICD implantation ■ Polyp resection ■ Vascular organs (kidney, spleen, liver) ■ Intracranial, intraspinal ■ Cardiothoracic

Perioperative AC Management

Low Risk Procedure	Everything Else ^a	High Risk Surgery ^a
<ul style="list-style-type: none"> ■ Continue VKA throughout ■ Monitor INR closely to prevent excessive anticoagulation ■ Prohemostatic agents ■ Continue aspirin if for secondary prevention 	<ul style="list-style-type: none"> ■ Hold VKA 5 days ■ Hold LMWH 24 hours (if app) ■ Restart VKA 12 to 24h postop ■ Restart LMWH 24 to 48h postop (if app) 	<ul style="list-style-type: none"> ■ Hold VKA 5 to 7 days ■ Target normal INR prior to surgery ■ Hold LMWH at least 24h prior (if app) ■ Restart VKA 12 to 24h postop ■ Restart LMWH 48 to 72h postop (if app)

a-Restart LMWH only if hemostasis is secure

Patient Case 3, Question # 9

Which of the following is the best therapeutic plan for J.Y.?

- ☐ A. Continue warfarin, control bleeding with local measures
- ☐ B. Stop warfarin x 5 days, resume at usual dose the evening after the procedure
- ☐ C. Stop warfarin x 5 days, start LMWH 2 days after warfarin stopped
- ☐ D. Stop warfarin x 5 days, start LMWH 1 to 2 days after procedure

Workbook Page 2-321; Answer: Page 2-328

Thank you !!

Corrections to Thromboembolism Chapter

For Patient Case question 8, (2-321) the answer is reported as "A" (2-327) which is incorrect, as the correct answer to the question is that the patient is "moderate risk", therefore the correct answer should be listed as "B".