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Diuretic Agents: Abbreviated Class Review

Month/Year of Review: August 2012
Classes Included: Loop, thiazide/thiazide-like, aldosterone antagonists, and potassium-sparing diuretics.
End date of literature search: May 2012

Issues:

- What is the evidence regarding the role of diuretics in the management of hypertension and chronic heart failure?
- What is the comparative evidence for effectiveness and harms for different diuretics?
- What is the comparative evidence for diuretics for benefits and harms within subgroups of patients?

Conclusions:

- Thiazide diuretics improve mortality and stroke in hypertensive patients. Thiazides are recommended as first line blood pressure lowering agents by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of high Blood Pressure (JNC 7) treatment guidelines in adults[5] and by other national treatment guidelines in children[6], adolescents[6] and the elderly[7].
- There is insufficient evidence demonstrating efficacy and safety differences among different thiazide diuretics.
- Loop diuretics lower blood pressure modestly but play a role in heart failure patients with reduced left ventricular ejection fraction (LVEF) who are symptomatic with fluid retention. They are recommended over thiazide diuretics in severe heart failure. In this patient population, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) gives them a class I recommendation for treatment. (Level of evidence: C)
- There is insufficient evidence comparing efficacy and safety of different loop diuretics. One small study provided low strength evidence to suggest a lower mortality with torsemide compared to furosemide/other diuretics.
- Potassium sparing diuretics, specifically aldosterone antagonists, reduce heart failure hospitalization and decrease mortality in patients with LVEF < 35%. ACCF/AHA heart failure treatment guidelines include a class I recommendation for aldosterone antagonists in this subset of heart failure patients (Level of evidence: B). There is insufficient evidence comparing efficacy and safety of spironolactone and eplerenone. Spironolactone is recommended over eplerenone in the Institute for Clinical Systems Improvement ICSI guideline due to fewer outcome studies in heart failure, although both agents have high grade evidence on reduction of mortality.
- Both spironolactone and eplerenone should only be used in patients whose serum creatinine is 2.5 mg per dL or less in men or 2.0 mg per dL or less in women and potassium should be less than 5.0 mEq per liter. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. (Level of evidence: B)

Recommendations:

- Add loop, thiazide/thiazide like and potassium sparing diuretics to PDL.
- Evaluate price comparisons of individual agents for each class due to lack of clinical distinction in efficacy or harms and include agents from each class on preferred PDL.
- Include aldosterone antagonists due to mortality benefit in select patients with heart failure and include agents based upon cost.

Reason for Review:

Diuretics commonly used for hypertension, heart failure and edema and are not currently on the Preferred Drug List (PDL). This review will examine their place in therapy for PDL placement, and identify any relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Background:

High blood pressure is the most common chronic medical problem prompting visits to primary health care providers in the USA. Hypertension increases the risk for heart disease and stroke, the first and third leading causes of death. Nearly 68 million people in the U.S. have hypertension. Another 28% of American adults have pre-hypertension (Internal analysis from National Health and Nutrition Examination Survey).[1] Reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease.[2] A recent meta-analysis by the Center for Reviews and Dissemination reviewed 25 randomized control trials (RTCs) in 64,162 patients with pre-existing cardiovascular disease or cardiovascular disease equivalents (such as diabetes) to compare antihypertensive treatment versus control for the prevention of cardiovascular events (fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, congestive heart failure and mortality) with blood pressure less than 140 mmHg systolic or less than 90 mmHg diastolic.[3] The results showed antihypertensive treatment reduced the risk of stroke (RR 0.77, 95% CI 0.61 to 0.98; seven RCTs, I^2=61.9%), myocardial infarction (RR 0.80, 95% CI 0.69 to 0.93; six RCTs, I^2=26.5%), congestive heart failure (RR 0.71, 95% CI 0.65 to 0.77; eight RCTs, I2=0.0%), cardiovascular disease events (RR 0.85, 95% CI 0.80 to 0.90; 13 RCTs, I^2=35.4%), cardiovascular disease mortality (RR 0.83, 95% CI 0.69 to 0.99; six RCTs, I^2=43.6%) and all-cause mortality (RR 0.87, 95% CI 0.80 to 0.95; 15 RCTs, I^2=46.1%).

Heart failure is generally defined as the inability of the heart to supply sufficient blood flow to meet the needs of the body. Fluid overload is a common problem for people with heart failure. Heart failure is caused by any condition which reduces the efficiency of the myocardium, or heart muscle, through damage or overloading. Around 5.8 million people in the United States have heart failure. About 670,000 people are diagnosed with it each year.

Diuretics help excrete sodium and water, which, in turn decrease the amount of fluid in the blood vessels to reduce blood pressure. There are three types of diuretics: loop, thiazide/thiazide like and potassium sparing. Each type of diuretic works at a different part of the kidneys. A diuretic provides a means of forced diuresis which elevates the rate of urination. Loop diuretics inhibit the body's ability to reabsorb sodium at loop of Henle, proximal and distal convoluted tubule, which leads to an excretion of water in the urine whereas water normally follows sodium back into the extracellular fluid. Thiazide type

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diuretics act on the distal convoluted tubule and inhibit the sodium-chloride resorption. The short-term anti-hypertensive action is based on the fact that thiazide diuretics decrease preload, and result in decreased blood pressure. Potassium sparing diuretics inhibit distal convoluted tubule aldosterone-induced sodium resorption.[4]

Methods:

A MEDLINE Ovid search was conducted using all diuretics including: cardiovascular disease, hypertension, heart failure, diuretics. The search was limited to meta-analysis, English language, and to studies conducted in humans in the last 10 years. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Drugs Included in This Review

Drug	Generic Availability
Loop diuretics	
Bumetanide (Bumex®)	Yes
Ethacrynic acid (Edecrin®)	Yes
Furosemide (Lasix®)	Yes
Torsemide (Demadex®)	Yes
Thiazide/thiazide-like diuretics	
Chlorothiazide (Diuril®)	Yes
Chlorthalidone	Yes
Hydrochlorothiazide(HCTZ) (Micronize®, Esidrix®)	Yes
Indapamide (Lozol®)	Yes
Metolazone (Zaroxolyn®)	Yes
Potassium sparing diuretics	
Amiloride (Midamor®); Amiloride/HCTZ	Yes
Eplerenone (Inspra®)	Yes
Spironolactone (Aldactone®), spironolactone/HCTZ (Aldactizide®)	Yes
Triamterene (Dyrenium); triamterene/HCTZ(Maxzide®, Dyazide®)	Yes

Hypertension Treatment Guidelines:

The Seventh Report of the Joint National Committee (JNC 7) Report (August, 2004)[5]

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The JNC7 report on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure is a landmark report developed by the U.S Department of Health and Services and supported by the National Heart, Lung, and Blood Institute. In patients without compelling indications, thiazide diuretics are recommended as first line therapy with no specific distinction between agents; in patients with compelling indications, thiazide diuretics are recommended as one of the initial options for patients with heart failure, high cardiovascular disease (CVD) risk , diabetes and patients who need recurrent stroke prevention. The potassium sparing diuretics are recommended as one of the initial options for patients with heart failure and post MI. The key pharmacologic treatment recommendations are summarized in Appendix A.

The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents by National High Blood Pressure Education Program (NHBPEP) working group (August, 2004) recommendations on drug therapy[6]:

- According to the NHBPEP guidelines, indications for antihypertensive drug therapy in children include secondary hypertension and insufficient response to lifestyle modifications and recent clinical trials have expanded the number of drugs that have pediatric dosing information. Pharmacologic therapy, when indicated, should be initiated with a single drug. Acceptable drug classes for use in children include ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics. The goal for antihypertensive treatment in children should be reduction of BP to <95th percentile, unless concurrent conditions are present. In that case, BP should be lowered to <90th percentile.

Expert Consensus Document on Hypertension in the Elderly (April, 2011) by American College of Cardiology Foundation (ACCF) and American Heart Association (AHA)[7]:

This consensus report recommended general principles on initiation of antihypertensives in the elderly. With similar approach to JNC 7 report, the recommendations also targeted initial treatment options in patients with compelling indication. Thiazide diuretics are recommended in patients with heart failure, CAD or high CAD risk, airtopathy/aortic aneurysm, diabetes or for recurrent stroke prevention. See Appendix A for the summary of the key recommendations.

Heart Failure (HF) Treatment Guidelines:

In March 2009, the ACCF/AHA released a focused guideline update on the diagnosis and management of heart failure in adults.[8] The guidelines give a class I recommendation for the initiation of diuretics in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention; the class I recommendation also includes the addition of an aldosterone antagonist in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be 2.5 mg per dL or less in men or 2.0 mg per dL or less in women and potassium should be less than 5.0 mEq per liter prior to initiation. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. (See Appendix A for summary of key drug therapy recommendations.)

ICSI guideline on heart failure in adults recommends loop diuretics over thiazide diuretics in severe heart failure and in refractory cases of volume overload[9]. They could not recommend a single, ideal diuretic for heart failure patients other than to use the lowest possible dose. One small study provided low strength evidence to suggest a lower mortality with torsemide compared to furosemide/other diuretics.[16] Aldosterone antagonists have been shown to

reduce mortality in HF are recommended in selected patients with moderately severe to severe symptoms and reduced LVEF. Spironolactone is recommended over eplerenone in the ICSI guideline due to fewer outcome studies in heart failure, although both have been shown to reduce mortality in studies. (See Appendix A for key clinical highlights.)

The Veterans Affairs (VA) Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure in Primary Care Practice (September, 2007)[10] also has similar recommendations regarding the position of diuretics and aldosterone antagonists in management of heart failure in adults. (See Appendix A for summary of key drug therapy recommendations.)

Systematic Reviews

Sciarretta et al. [11]
This published systematic review compared different antihypertensive strategies (as first-line treatment) in the prevention of heart failure in patients with hypertension or populations with high cardiovascular risk (> 65% with hypertension). The analysis included 26 randomized controlled trials (RCTs) including 223,313 patients. The authors reported that angiotensin-converting enzyme inhibitors (OR 0.78, 95% CI 0.69 to 0.98; one RCT), angiotensin II receptor blockers (OR 0.85, 95% CI 0.55 to 1.31; two RCTs), calcium-channel blockers (OR 0.67, 95% CI 0.48 to 0.94; three RCTs) and diuretics (OR 0.37, 95% CI 0.23 to 0.61; one RCT) were more effective than placebo in preventing heart failure. Diuretics were statistically significantly more effective than α-blockers (OR 0.49, 95% CI 0.43 to 0.55; one RCT), angiotensin-converting enzyme inhibitors (OR 0.86, 95% CI 0.78 to 0.95; two RCTs) and calcium-channel blockers (OR 0.71, 95% CI 0.64 to 0.79; five RCTs) in preventing heart failure. The authors reported that conventional treatment, which differed slightly between trials, (OR 0.84, CI 0.72 to 0.98; three RCTs), angiotensin-converting enzyme inhibitors (OR 0.84, 95% CI 0.76 to 0.93; three RCTs) and angiotensin II receptor blockers (OR 0.88, 95% CI 0.76 to 1.01; one RCT) were significantly more effective than calcium-channel blockers in preventing heart failure. There was no evidence of statistical heterogeneity or publication bias based on authors' assessment. The authors concluded diuretics and angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers) should be used as first-line treatment for the prevention of heart failure in hypertensive patients. These treatments should be used in preference to calcium-channel blockers and beta blockers. Given the potential for bias in the review, possible limitations with the included studies and uncertainties around the use of multiple treatment comparisons, caution should be applied when interpreting the authors' conclusions.

Cochrane Collaboration Reviews
In 2009, Wright et al. performed a systematic review that compared the evidence of first-line drugs for hypertension versus placebo and no treatment.[12] Of 57 trials identified, 24 trials with 28 arms, including 58,040 patients met the inclusion criteria. In comparison to untreated control group, thiazides (19 RCTs) demonstrated a significantly reduced mortality (RR 0.89, 95% CI 0.83, 0.96), stroke (RR 0.63, 95% CI 0.57, 0.71), coronary heart disease (CHD) (RR 0.84, 95% CI 0.75, 0.95) and total cardiovascular events (RR 0.70, 95% CI 0.66, 0.76). Low-dose thiazides (8 RCTs) significantly reduced all outcomes, including CHD (RR 0.72, 95% CI 0.61, 0.84), but high-dose thiazides (11 RCTs) did not reduce CHD(RR 1.01, 95% CI 0.85, 1.20) or mortality. Five RCTs allowed for a comparison of beta-blockers to thiazides and suggests less benefit for beta-blockers in reducing total stroke and total cardiovascular events than all thiazide trials (RR 0.70 [0.64-0.76] versus RR 0.89 [0.81-0.98] for beta blockers). Based on these results, authors concluded first-line low-dose thiazides reduce all morbidity and

mortality outcomes; first-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust; first-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.

There were two Cochrane reviews[13, 14] that investigated the loop diuretics and potassium sparing diuretics with regards to blood pressure lowering ability. Based on the limited number of published RCTs, the SBP/DBP lowering effect of loop diuretics is modest at -8/-4 mmHg and is likely an overestimate due to the high risk of bias in the included studies. There is no clinically meaningful BP lowering differences between different drugs within the loop diuretic class. The dose ranging effects of loop diuretics could not be evaluated. The review did not provide a good estimate of the incidence of harms associated with use because of the short duration of the trials and the lack of reporting of adverse effects in many of the trials. Similar conclusions were also reported that potassium sparing diuretics do not have a statistically or clinically significant BP lowering effect at low doses but trials at higher doses are not available. The review did not provide a good estimate of the incidence of harms associated with potassium sparing diuretics.

In February 2012, Faris et al. published a Cochrane review to assess the harms and benefits of diuretics for chronic heart failure.[15] The review includes 14 trials (525 participants), seven were placebo-controlled, and seven compared diuretics against other agents such as ACE inhibitors or digoxin. The authors analyzed the data for mortality and for worsening heart failure. Mortality data were available in three of the placebo-controlled trials (202 participants). Mortality was lower for participants treated with diuretics than for placebo (odds ratio (OR) 0.24, 95% CI 0.07 to 0.83; P = 0.02). Admission for worsening heart failure was reduced in those taking diuretics compared to placebo in two trials including 169 participants (OR 0.07, 95% CI 0.01 to 0.52; P = 0.01). In four trials (91 participants) comparing diuretics to a other active agent (three with captopril, one with digoxin), diuretics improved exercise capacity in participants with CHF (difference in means 0.72, 95% CI 0.40 to 1.04; P < 0.0001). The authors concluded that the available data from several small trials show that in patients with chronic heart failure, conventional diuretics appear to reduce the risk of death and worsening heart failure compared to placebo. Compared to active control, diuretics appear to improve exercise capacity. However, the authors also noted most of the trials had small numbers and lasted from 4 to 24 weeks, a short time for a chronic disease. The age of the participants was 59 years, which is relatively young, and the use of diuretic drug was not standardized across the studies. More research would be needed to further confirm the long term benefits of diuretic treatment for CHF patients because these studies were small. The authors assessed the risk of bias for individual studies included in the analysis. Although there is considerably heterogeneity among these studies, no statistical heterogeneity test was conducted by authors. Due to study limitations, the conclusions of this analysis should be interpreted with caution.

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References:

1. "CDC Features - May Is High Blood Pressure Education Month", n.d. http://www.cdc.gov/Features/HighBloodPressure/. Accessed April 23, 2012.

2. Law M, Wald N, Morris J. Lowering blood pressure to prevent myocardial infarction and stroke: A new preventive strategy. *Health Technol Assess* 2003;**7**(31). *Health Technology Assessment* is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

3. Thompson AM, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA 2011; 305(9): 913-922

4. Micromedex Healthcare Series Version 2.0. Thomson Reuters (Healthcare) Inc. http://www.thomsonhc.com. Accessed May 7th, 2012.

5. Chobanian, A. V, G. L Bakris, H. R Black, W. C Cushman, L. A Green, J. L Izzo, D. W Jones, et al. "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure." *Hypertension* 42, no. 6 (2003): 1206–1252.

6. "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents", n.d. http://pediatrics.aappublications.org/content/114/Supplement_2/555.full.pdf+html.

7. Aronow, W. S., J. L. Fleg, C. J. Pepine, N. T. Artinian, G. Bakris, A. S. Brown, K. C. Ferdinand, et al. "ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly: A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents." *Circulation* 123, no. 21 (April 25, 2011): 2434–2506.

8. 2009 WRITING GROUP TO REVIEW NEW EVIDENCE AND UPDATE THE 2005 GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC HEART FAILURE WRITING ON BEHALF OF THE 2005 HEART FAILURE WRITING COMMITTEE, M. Jessup, W. T. Abraham, D. E. Casey, A. M. Feldman, G. S. Francis, T. G. Ganiats, et al. "2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in Collaboration With the International Society for Heart and Lung Transplantation." *Circulation* 119, no. 14 (March 26, 2009): 1977–2016.

9. Institute for Clinical systems Improvement health Care Guideline: Heart Failure in Adults. Twelfth Edition, August 2011. http://www.icsi.org/heart_failure_2/heart_failure_in_adults_.html

10. *The Pharmacologic Management of Chronic Heart Failure*. Washington, DC: Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs. September 2007 Update. PBM-MAP Publication No. 00-0015.

11. Sciarretta S, Palano F, Tocci G, Baldini R, Volpe M. Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. Archives of Internal Medicine 2010: doi:10.1001/archinternmed.2010.427

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12. Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD001841.pub2]

13. Musini VM, Wright JM, Bassett K, Jauca CD. Blood pressure lowering efficacy of loop diuretics for primary hypertension. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD003825. DOI: 10.1002/14651858.CD003825.pub2

14. Heran BS, Chen JMH, Wang JJ, Wright JM. Blood pressure lowering efficacy of potassium-sparing diuretics (that block the epithelial sodium channel) for primary hypertension. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD008167. DOI: 10.1002/14651858.CD008167.pub2

15. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJS. Diuretics for heart failure. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003838. DOI: 10.1002/14651858.CD003838.pub3

16. Cosín J, Díez J, on behalf of the TORIC Investigators. Torsemide in chronic heart failure: results of the TORIC study. *Eur J of Heart Fail* 2002;4: 507-13.

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Appendix A

1. **The Seventh Report of the Joint National Committee (JNC 7) Report (August, 2004) key recommendations:**

Patients without Compelling Indications:

- Stage I hypertension (Systolic Blood pressure 140-159 (SBP) or diastolic blood pressure (DBP) 90-99 mmHg): Thiazide-type (THIAZ) diuretics for most. May consider angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), beta blocker (BB), calcium channel blocker (CCB), or combination.
- Stage II hypertension (SBP ≥ 160 or DBP ≥ 100): two drug combination for most (usually THIAZ and ACEI or ARB, or BB, or CCB.

Patients with Compelling Indications:

- Heart failure: THIAZ, BB, ACEI, ARB, aldosterone antagonist (ALDO ANT) as initial therapy options.
- Post myocardial infarction (MI): BB, ACEI, ALDO ANT as initial therapy options.
- High cardiovascular disease (CVD) risk: THIAZ, BB, ACEI, CCB as initial therapy options.
- Diabetes: THIAZ, BB, ACEI, ARB, CCB as initial therapy options.
- Chronic kidney disease (CKD): ACEI, ARB as initial therapy options.
- Recurrent stroke prevention: THIAZ, ACEI as initial therapy options.

In addition to these general recommendations, JNC 7 also made treatment recommendations on subpopulations:

- Pregnant women: methyldopa is preferred first line therapy. Other agents include BBs, which is generally safe. There were reports of intrauterine growth retardation for atenolol. Labetolol is increasingly preferred to methyldopa due to reduced side effects. There were limited data on use of clonidine and CCB during pregnancy.
- Older people: Weight loss and reduced sodium intake are particularly beneficial in older people. Use of specific drug class in older people is largely similar to that recommended in the general algorithm and for individual compelling indication. Combination therapy with two or more drugs is generally needed to achieve optimal BP control.

2. **Expert Consensus Document on Hypertension in the Elderly (April, 2011) by American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) key recommendations:**

General principle on initiation of therapy: The initial antihypertensive drug should be started at the lowest dose and gradually increased depending on the BP response to the maximum tolerated dose. If the antihypertensive response to the initial drug is inadequate after reaching full dose (not necessarily maximum recommended dose), a second drug from another class should be added, provided the initial drug is tolerated. If the person is having no therapeutic response or significant adverse effects, a drug from another class should be substituted. If a diuretic is not the initial drug, it is usually indicated as the second drug. If the antihypertensive response is inadequate after reaching the full dose of 2 classes of drugs, a third drug from another class should

be added. When the BP is > 20/10 mm Hg above goal, drug therapy should generally be initiated with 2 antihypertensive drugs, 1 of which should be a thiazide diuretic; however, in the elderly, treatment must be individualized.

Patients with Compelling Indications:

- Heart failure: THIAZ, BB, ACEI, ARB, CCB, ALDO ANT
- Post MI: BB, ACEI, ALDO ANT, ARB
- CAD or high CVD risk: THIAZ, BB, ACEI, CCB
- Angina Pectoris: BB, CCB
- Aortopathy/Aortic Aneurysm: BB, ARB, ACEI, THIAZ, CCB
- Diabetes: ACEI, ARB, CCB, THIAZ, BB
- CKD: ACEI, ARB
- Recurrent stroke prevention: THIAZ, ACEI, ARB, CCB

3. **ACCF/AHA Focused update: Guidelines for the diagnosis and management of HF in adults key recommendations on drug therapy:**

Class I Recommendations:

- Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention. *(Level of Evidence: C)*
- Angiotensin-converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated. *(Level of Evidence: A)*
- Beta blockers (using 1 of the 3 proven to reduce mortality, i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated. *(Level of Evidence: A)*
- Angiotensin II receptor blockers are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACE inhibitor-intolerant. *(Level of Evidence: A)*
- Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs. *(Level of Evidence: B)*
- Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be 2.5 mg per dL or less in men or 2.0 mg per dL or less in women and potassium should be less than 5.0 mEq per liter. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. *(Level of Evidence: B)*
- The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African-Americans, with moderate-severe symptoms on optimal therapy with ACE inhibitors, beta blockers, and diuretics. *(Level of Evidence: B)*

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Class IIa Recommendations:

- Angiotensin II receptor blockers are reasonable to use as alternatives to ACE inhibitors as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. *(Level of Evidence: A)*
- Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. *(Level of Evidence: B)*
- The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACE inhibitor and beta blocker for symptomatic HF and who have persistent symptoms. *(Level of Evidence: B)*

Class IIb Recommendations:

- A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency. *(Level of Evidence: C)*
- The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. *(Level of Evidence: B)*

4. **Institute for Clinical systems Improvement health Care Guideline: Heart Failure in Adults clinical highlights:**

- Evaluate patients presenting with heart failure for exacerbating and underlying causes, including coronary artery disease, hypertension, valvular disease and other cardiac and non-cardiac causes.
- Studies show that the distinction between systolic dysfunction and preserved systolic function is important, because the choice of therapy may be quite different and some therapies for systolic dysfunction may be detrimental if used to treat preserved systolic function.
- Daily weights are critical for managing heart failure and early detection of increases in fluid retention. Patients should call their provider about a two-pound or greater weight gain overnight or a five-pound or greater weight gain in a week. Patients can expect the provider to assess symptoms, adjust diuretics if appropriate, discuss dietary sodium compliance/restriction, review treatment plan, and recommend appropriate level of care (office visit, ER, etc.)
- Unless specific contraindications exist, treat all patients, including Class IV patients, with beta-blockers, starting with a low dose and titrating upward.
- Treat all patients with left ventricular systolic dysfunction with ACE inhibitors (or ARBs if intolerant) unless specific contraindications exist.
- Consider early specialty referral for patients with ischemia or those who are refractory despite optimal medical therapy.
- Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NTproBNP) are useful in the diagnosis and prognosis of heart failure in patients with dyspnea of unknown etiology.
- For patients self-described as African Americans who have moderate-to-severe symptoms on optimal therapy with ACE inhibitors, beta-blockers and diuretics, the combination of hydralazine and nitrates is recommended because the combination has resulted in significant benefit to the group in randomized controlled trials.

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5. **VA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure in Primary Care Practice key drug recommendations:**
    - In addition to risk factor modification, patients in Stage B should receive post-myocardial infarction (MI) treatment with an angiotensin-converting enzyme inhibitor (ACEI) and beta-adrenergic blocker, regardless of the presence of left ventricular systolic dysfunction, to prevent future development of HF and improve overall survival (Grade A Recommendation, Good Overall Quality of Evidence). It is also recommended that patients with evidence of left ventricular systolic dysfunction who are without symptoms should be treated with an ACEI (Grade A Recommendation, Good Overall Quality of Evidence) and beta-adrenergic blocker (Grade B Recommendation, Fair Overall Quality of Evidence). An angiotensin II receptor antagonist may be prescribed in patients with a history of MI who have a reduced left ventricular ejection fraction without symptoms of HF if they are ACEI intolerant (Grade A Recommendation, Good Overall Quality of Evidence).

    - Patients with HF in Stage C should also be educated on risk factor modification. Pharmacotherapy recommendations for these patients include:

        - A diuretic should be used in the treatment of patients with signs of fluid overload (Grade B Recommendation, Fair Overall Quality of Evidence).
        - All patients should be treated with an ACEI unless contraindicated or not tolerated (Grade A Recommendation, Good Overall Quality of Evidence). These agents improve HF symptoms, functional status, and quality of life, while decreasing frequency of hospitalization and mortality. An angiotensin II receptor antagonist may be considered as an alternative to an ACEI (in patients who are on standard therapy for HF) and are unable to tolerate an ACEI (Grade A Recommendation, Good Overall Quality of Evidence).
        - A beta-adrenergic blocker that has proven to reduce mortality (i.e., bisoprolol, carvedilol, sustained release metoprolol succinate) should be used in conjunction with an ACEI in all patients who are considered stable (i.e., minimal or no signs of fluid overload or volume depletion and not in an intensive care unit), unless contraindicated or not tolerated. These agents have been shown to reduce mortality and decrease the symptoms of HF (Grade A Recommendation, Good Overall Quality of Evidence).
        - Low dose of an aldosterone antagonist should be considered in patients with recent New York Heart Association (NYHA) Class IV HF and current Class III or IV symptoms and left ventricular ejection fraction (LVEF) < 35%, provided the patient has preserved renal function and normal potassium levels. This therapy improves symptoms (as assessed by change in NYHA functional class), decreases hospitalizations for worsening HF, and decreases mortality (Grade A Recommendation, Good Overall Quality of Evidence). An aldosterone antagonist may also be considered in patients with LVEF < 40% in patients early post-MI on standard therapy for HF.
        - The combination of hydralazine and a nitrate should be considered, especially in African American patients with NYHA Class III or IV HF, who continue to have symptoms despite therapy with an ACEI and beta-adrenergic blocker (Grade B Recommendation, Good Overall Quality of Evidence). The combination of hydralazine and a nitrate may be considered as an alternative to an ACEI in patients who are unable to tolerate an ACEI (or angiotensin II receptor antagonist) due to hypotension, renal insufficiency, hyperkalemia, or possibly, angioedema (Grade C Recommendation, Fair Overall Quality of Evidence).

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- Addition of an angiotensin II receptor antagonist to standard therapy (i.e., an ACEI and beta-adrenergic blocker) in patients with systolic HF may be considered to decrease cardiovascular death or HF hospitalizations (Grade B Recommendation, Fair Overall Quality of Evidence); although routine use of an angiotensin II receptor antagonist, ACEI, and aldosterone antagonist is not recommended.
- Digoxin can be used in patients whose symptoms persist despite treatment with an ACEI (or an angiotensin II receptor antagonist if an ACEI is not tolerated), a beta-blocker, and a diuretic. Digoxin reduces symptoms associated with HF and decreases the risk for hospitalizations due to HF but does not improve mortality (Grade B Recommendation, Fair Overall Quality of Evidence).
- Patients should receive regular follow-up in order to provide the most effective care. At each encounter, an inquiry should be made as to the patient's adherence to the medication regimen, nonpharmacologic measures, and adverse effects to therapy. Patients should be scheduled for routine laboratory monitoring. The patient should also be assessed for any change in functional status or frequency of hospitalizations, and medication therapy should be optimized.

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