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PDL Classes: Diuretics, Cardiovascular

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Table 1. Current Status of PDL Class.

Current Preferred Agents[1]	**Current Non-Preferred Agents**
Thiazide/Thiazide-like Diuretics	
Bendroflumethiazide tablet (*unavailable*)[2] Hydrochlorothiazide tablet, capsule or solution (*generic*, Microzide®) Indapamide tablet (*generic*)	Chlorothiazide (*generic*, Diuril®) Chlorthalidone (*generic*) Metolazone (*generic*, Zaroxolyn®)
Loop Diuretics	
Bumetanide tablet (*generic*) Furosemide tablet or solution (*generic*, Lasix®) Torsemide tablet (*generic*, Demadex®)	Ethacrynic Acid (Edecrin®)
Potassium-sparing Diuretics	
Amiloride/HCTZ tablet (*generic*) Spironolactone tablet (*generic*, Aldactone®) Spironolactone/HCTZ tablet (*generic*, Aldactizide®) Triamterene capsule (Dyrenium®) Triamterene/HCTZ capsule (*generic*, Maxzide®, Dyazide®)	Amiloride (*generic*) Eplerenone (*generic*, Inspra®)

Previous Recommendations and Conclusions:[3]

- Thiazide diuretics are recommended as first-line blood pressure lowering agents because they have shown to improve mortality and stroke.
- 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.
- There is insufficient evidence comparing efficacy and safety of different loop diuretics.
- Potassium sparing diuretics, specifically aldosterone antagonists, reduce heart failure hospitalization and decrease mortality in patients with LVEF less than 35%.
- There is insufficient evidence comparing efficacy and safety of spironolactone and eplerenone.
- Add loop, thiazide/thiazide-like and potassium sparing diuretics to PDL.
- Include aldosterone antagonists in PDL due to mortality benefit in select patients with heart failure.

Conclusions and Recommendations:

- High quality evidence suggests thiazide diuretics should continue to be recommended as a first-line option for hypertension due to benefit at reducing mortality and stroke.[6,7]
- Thiazide diuretics with high quality data include hydrochlorothiazide, chlorthalidone and indapamide.[4]

- There is insufficient evidence demonstrating efficacy and safety differences among different thiazide diuretics. Hydrochlorothiazide is the only thiazide diuretic with evidence of dose-dependent lowering of blood pressure.[4]
- There is high quality evidence loop diuretics provide short-term relief of fluid retention in symptomatic patients heart failure patients with preserved or reduced LVEF.[8,9] However, there is insufficient evidence to confirm long-term benefits of diuretics in patients with heart failure.[5]
- There is insufficient evidence comparing efficacy and safety differences among different loop diuretics.
- There is high quality evidence that aldosterone receptor antagonists (spironolactone or eplerenone), unless contraindicated, reduce morbidity and mortality when added to evidence-based heart failure therapy in patients with systolic heart failure and reduced LVEF.[8,9] There is insufficient evidence comparing spironolactone with eplerenone.
- There is moderate quality evidence that adding spironolactone to patients with systolic heart failure and preserved LVEF reduces hospitalizations; however, spironolactone does not yield any additional morbidity or mortality benefit.[9,10]
- Remove bendroflumethiazide from the PDL due to market unavailability[2] and limited data versus other thiazide diuretics.[4]
- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) from 2012 through September 2014 comparing diuretics or diuretic combination therapy to placebo or active controls was performed. The search was limited to evaluation of patients with hypertension or heart failure and was conducted with limits to randomized controlled trials and for English. Search terms included: hypertension; heart failure; bendroflumethiazide; hydrochlorothiazide; indapamide; chlorothiazide; chlorthalidone; metolazone; bumetanide; furosemide; torsemide; ethacrynic acid; amiloride; spironolactone; triamterene; and eplerenone. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews for Hypertension:

No systematic reviews have been recently published assessing cardiovascular morbidity and mortality outcomes with diuretics.

A 2014 *Cochrane Review* assessed the dose-related effect on blood pressure with thiazide diuretics compared to placebo in patients with primary hypertension.[4] This review did not assess different thiazides in reducing mortality or cardiovascular morbidity. Double-blind, randomized, controlled trials comparing a fixed-dosed, 3- to 12-week regimen of thiazide diuretic monotherapy with placebo were included. Sixty trials assessing six different thiazide diuretics in 11,282 patients with a mean duration of 8 weeks were included in the review. The mean age was 55 years and mean baseline blood pressure was 158/99 mmHg. Adequate data were available for hydrochlorothiazide, chlorthalidone and indapamide. There was no evidence of dose-dependent lowering of blood pressure of any of the thiazide diuretics other than hydrochlorothiazide, which demonstrated moderate to high quality evidence. Overall, maximum lower of blood pressure was similar between thiazide diuretics, with a mean lowering of 9 mmHg/4 mmHg (95% CI, 9-10 mmHg/3-4 mmHg) versus placebo. Thiazide diuretics have demonstrated a greater effect on lowering systolic blood pressure compared to diastolic blood pressure, and lowers pulse pressure by 4 to 6 mmHg.

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Table 2. Comparative Mean Blood Pressure Lowering of Thiazide Diuretics.[4]

Hydrochlorothiazide Daily Dose *(33 trials)*	Mean SBP Lowering vs. Placebo	Mean DBP Lowering vs. Placebo
	Baseline Mean 150-100 mmHg	
6.25 mg	4 mmHg (95% CI, 2-6 mmHg)	2 mmHg (95% CI, 1-4 mmHg)
12.5 mg	6 mmHg (95% CI, 5-7 mmHg)	3 mmHg (95% CI, 3-4 mmHg)
25 mg	8 mmHg (95% CI, 7-9 mmHg)*	3 mmHg (95% CI, 3-4 mmHg)*
50 mg	11 mmHg (95% CI, 6-15 mmHg)**	5 mmHg (95% CI, 3-7 mmHg)**

Chlorthalidone Daily Dose *(7 trials)*	Mean SBP Lowering vs. Placebo	Mean DBP Lowering vs. Placebo
	Baseline Mean 163/88 mmHg	
12.5 – 75 mg	12 mmHg (95% CI, 10-14 mmHg)**	4 mmHg (95% CI, 3-5 mmHg)**

Indapamide Daily Dose *(10 trials)*	Mean SBP Lowering vs. Placebo	Mean DBP Lowering vs. Placebo
1 – 5 mg	9 mmHg (95% CI, 7-10 mmHg)**	4 mmHg (95% CI, 3-5 mmHg)**

*Judged to be high-quality evidence; **Judged to be low-quality evidence
Key: SBP = systolic blood pressure; DBP = diastolic blood pressure

The authors concluded that hydrochlorothiazide has a dose-related blood pressure-lowing effect. However, trials were short term and important clinical cardiovascular outcomes were not evaluated.

New Systematic Reviews for Heart Failure:

A 2012 *Cochrane Review* assessed the risks and benefits of diuretics for chronic heart failure.[5] Double-blind, randomized, controlled trials comparing one diuretic with placebo, or one diuretic with another active agent in patients with chronic heart failure were included in the review. Fourteen small trials lasting from 4 to 24 weeks were identified for inclusion (525 participants); half were placebo-controlled and half the trials actively compared a diuretic to another agent, such as an angiotensin converting enzyme inhibitor (ACE-I) or digoxin. Analysis of mortality was limited to three trials (202 participants), which was lower if patients received a diuretic versus placebo, with an odds ratio (OR) of 0.24; 95% confidence interval (CI), 0.07 – 0.83; p=0.02. According to the review, about 80 deaths may be avoided for every 1000 people treated with diuretics. Analysis of hospital admission for worsening heart failure was limited to two trials (169 participants), which was lower if patients received a diuretic versus placebo, OR 0.07; 95% CI 0.01 – 0.52; p=0.01. Diuretics also improved exercise capacity by 28% - 33% compared to active controls, difference in means WMD 0.72; 95% CI, 0.40 – 1.04; p<0.0001.

Evidence for diuretics in heart failure is limited to a few small trials of short duration for a chronic health condition. The methodological quality of the fourteen trials was found to be inconsistent as diuretic use was not standardized across the studies. According to the investigators, more research is needed to confirm long-term benefits of diuretics in patients with heart failure.[5]

New Hypertension Treatment Guidelines:

The Eighth Report of the Joint National Committee (JNC 8) (2014)[6]

Earlier this year, guidelines for the management of high blood pressure in adults were reported from the JNC8 panel. Quality of evidence was rated as High, Moderate or Low, depending on the limitations of the evidence. For example, a well designed randomized controlled trial or meta-analysis would be high quality evidence, but randomized controlled trials with major limitations or observational studies would be low quality evidence. Strength of the recommendation

was graded A (strong), B (moderate), C (weak), D (against recommending), E (opinion) or N (insufficient evidence for recommendation).

The JNC 8 retains thiazide-type diuretics as a first-line treatment option in all hypertensive adult patients *without* chronic kidney disease. Specifically for nonblack patients, first-line options include a thiazide-type diuretic, an ACE-I, an angiotensin receptor-blocker (ARB) or calcium channel blocker (CCB), alone or in combination (*Moderate Recommendation, Grade B*); for black patients, ACE-Is and ARBs are not first-line options (*Weak Recommendation, Grade C*). In all hypertensive adult patients *with* chronic kidney disease, regardless of race, an ACE-I or ARB, alone or in combination with other drug classes, is recommended as the first-line option (*Moderate Recommendation, Grade B*).

The guidelines reminds readers that drug selection, dose and titration schedule of the first-line therapy options are flexible in order to quickly achieve a goal blood pressure in any individual patient.

American Heart Association/American Stroke Association Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2014)[7]

Recommendations follow the American Heart Association (AHA) and the American College of Cardiology (ACC) methods of classifying the level of certainty of the treatment effect and the class of evidence. Class of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effects. Level A evidence is from data derived from multiple randomized, controlled trials or meta-analyses; Level B evidence is from data derived from a single randomized trial or nonrandomized studies; Level C evidence consists of consensus opinion, case studies or standard of care.

Diuretics, or diuretics in combination with an ACE-I, are the only specific regimens recommended in this guideline for secondary prevention of stroke or transient ischemic attack based on clinical evidence for efficacy in this population (*Class I Recommendation, Level of Evidence A*). However, the choice of specific drugs utilized should be individualized based on drug pharmacology and specific patient characteristics and indications (e.g., renal impairment, cardiac disease, diabetes mellitus, etc.).

New Heart Failure Treatment Guidelines:

2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation and the American Heart Association Task Force on Practice Guidelines (2013)[8]

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. Grading of evidence is the same as AHA/ASA guideline detailed previously.

Oral diuretics are recommended for patients with heart failure with either preserved or reduced ejection fraction and evidence of fluid retention to improve symptoms (*Class I Recommendation, Level of Evidence C*). Oral diuretics recommended for use in the treatment of symptomatic chronic heart failure are illustrated in the table extracted from the guidelines below.

Table 3. Recommended Doses of Oral Diuretics for Symptomatic Heart Failure.[8]

Drug	Initial Daily Dose	Maximum Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5 to 1 mg once or twice	10 mg	4 to 6 hours
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 hours
Torsemide	10 to 20 mg once	200 mg	12 to 16 hours
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 hours
Chlorthalidone	12.5 to 25 mg once	100 mg	24 to 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 hours
Indapamide	2.5 mg once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 to 24 hours
Potassium-sparing diuretics*			
Amiloride	5 mg once	20 mg	24 hours
Spironolactone	12.5 to 25 mg once	50 mg	1 to 3 hours
Triamterene	50 to 75 mg twice	200 mg	7 to 9 hours
Sequential nephron blockade			
Metolazone	2.5 to 10 mg once with loop diuretic	N/A	N/A
Hydrochlorothiazide	25 to 100 mg once or twice with loop diuretic	N/A	N/A

*Eplerenone is a potassium-sparing diuretic but is primarily used for its aldosterone receptor antagonist properties in chronic heart failure without symptoms.

Though not technically diuretics, spironolactone and eplerenone block receptors that bind aldosterone, and are more appropriately described as mineralocorticoid receptor antagonists (MRAs). Both of these agents are recommended to decrease morbidity and mortality in patients with NYHA class II-IV heart failure who have a LVEF of 35% or less. Patients with NYHA class II heart failure should have a history of prior cardiovascular hospitalization or elevated brain natriuretic peptide (BNP) levels to be considered for this therapy. These agents should not be initiated in patients with an estimated glomerular filtration rate of 30 mL/min or less, nor should they be initiated in patients with serum potassium higher than 5.0 mEq/L due to risk of hyperkalemia (*Class I Recommendation, Level of Evidence A*).

The 2012 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Acute on Chronic Heart Failure (2013)[9]

The Canadian Cardiovascular Society recommendations follow the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The GRADE system classifies the quality of evidence as High (further research very unlikely to change confidence in the estimate of effect), Moderate (further research likely to have an important impact on confidence in the estimate of effect and may change the estimate), Low (further research very likely to have an important impact on confidence in the estimate of effect and likely to change the estimate), and Very Low (estimate of effect very uncertain). The GRADE system offers 2 grades of recommendation: “Strong” (desirable effects clearly outweigh undesirable effect or clearly do not) and “Weak”.

Diuretics are recommended to control symptoms from pulmonary congestion and peripheral edema (*Strong Recommendation, High-Quality Evidence*). A loop diuretic is particularly recommended for patients with symptomatic heart failure and the guideline recommends reducing the dose of the diuretic to the lowest dose effective at stabilizing signs and symptoms of the disease (*Strong Recommendation, Low-Quality Evidence*). A second diuretic, such as a thiazide or metolazone, is recommended for patients with persistent volume overload despite optimal medical therapy and increasing doses of the loop diuretic, as long as it is possible to monitor morning weight, renal function and serum potassium (*Weak Recommendation, Moderate-Quality Evidence*).

Eplerenone is recommended in addition to standard heart failure therapy for patients older than 55 years with mild to moderate heart failure and reduced LVEF of 30% or less and recent cardiovascular hospitalization (within 6 months) or elevated BNP (*Strong Recommendation, High-Quality Evidence*).

Spironolactone is recommended in addition to standard heart failure therapy in patients with severe heart failure (NYHA class IIIb-IV) and reduced LVEF below 30% (*Strong Recommendation, High-Quality Evidence*).

European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2012)[10]

The level of evidence and the strength of recommendation set by the European Society of Cardiology is weighed and graded according to pre-defined scales. The COR is an estimate of the size of the treatment effect, with consideration given to risks versus benefits. The LOE is an estimate of the certainty or precision of the treatment effects. Level A evidence is from data derived from multiple randomized, controlled trials or meta-analyses; Level B evidence is from data derived from a single randomized trial or nonrandomized studies; Level C evidence consists of consensus opinion, case studies or standard of care.

The guideline does not differentiate between spironolactone and eplerenone in its recommendations, as any subtle differences between the populations studied or pharmacology with each agent are not considered clinically significant. The guideline therefore recommends an MRA for all patients with persistent heart failure symptoms (NYHA class II-IV) and an LVEF of 35% or less, despite treatment with an ACE-I or ARB and a beta-blocker to reduce the risk of heart failure hospitalization and the risk of premature death in these patients (*Class I Recommendation, Level of Evidence A*).

Data from the Randomized Aldactone Evaluation Study (RALES)[11] published in 1999 and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[12] trial published in 2011 largely drove this recommendation. In RALES (n=1663), spironolactone decreased both mortality and heart failure hospitalizations in patients with NYHA class III heart failure and reduced LVEF. In EMPHASIS-HF (n=2737), eplerenone had similar results in patients with NYHA class II heart failure and reduced LVEF.

New drugs:
None.

New Formulations/Indications:
None.

New FDA safety alerts:
None.

New Trials:

A total of 178 citations resulted from the initial Medline search. The majority of articles were excluded due to the inappropriate study design (observational, retrospective) or if clinically meaningful outcomes such as cardiovascular morbidity or mortality were not assessed. The remaining 2 RCTs evaluating morbidity or mortality outcomes are briefly described below.

Pitt, et al.[13] conducted a randomized, multi-centered, double-blind, placebo-controlled trial that evaluated spironolactone using a composite endpoint of death from cardiovascular causes, aborted cardiac arrest or hospitalization for the management of heart failure in 3445 participants with heart failure with preserved ejection fraction. The study was supported by a grant from the National Heart, Lung, and Blood Institute, National Institutes of

Health. Eligible patients were at least 50 years of age with at least one symptom of heart failure, preserved LVEF, with controlled systolic blood pressure and normal serum potassium levels. In addition, eligible patients had to have been hospitalized in the last 12 months secondary to heart failure or had to have an elevated BNP level at least 100 pg/mL or greater or an N-terminal pro-BNP level at least 360 pg/mL or greater in the 60 days before randomization. Randomization occurred with the use of permuted blocks and was stratified according to whether the patient met the criterion for previous hospitalization or elevated BNP. Spironolactone was initiated at 15 mg daily and increased to a maximum of 45 mg daily. Participants continued to receive treatment for heart failure and other coexisting illnesses throughout the trial. Baseline characteristics were similar between the spironolactone and placebo group but information regarding concurrent treatment for cardiovascular conditions, including heart failure, was missing. Mean follow-up was 3.3 years in each group and attrition rates were similar. The primary outcome occurred in 320 patients (18.6%) in the spironolactone group and 351 patients (20.4%) in the placebo group, with a hazard ratio (HR) of 0.89 (95% CI, 0.77 to 1.04; p=0.14). Of the components making up the composite outcome, only hospitalization for heart failure was statistically improved for spironolactone (12.0% vs. 14.2%, HR 0.83; 95% CI, 0.69 to 0.99; p=0.04). In addition, treatment with spironolactone was associated with increased serum creatinine levels and double the rate of hyperkalemia compared to the placebo group (18.7% vs. 9.1%). The investigators concluded that adding spironolactone to existing therapy in patients with heart failure and preserved ejection fraction does not significantly reduce the incidence of the primary outcome studied.

Vizzardi, et al.[14] conducted a small randomized, single-blind, placebo-controlled, single-centered trial evaluating the effect of spironolactone in patients with heart failure and mild to no symptoms (NYHA functional classes I-II) on cardiovascular mortality and hospitalizations. Eligible patients had heart failure with a LVEF less than 40% and no history of acute decompensation (NYHA class III or IV) in the previous year and were treated with an ACE-I or ARB, and a beta-blocker, unless contraindicated. Notable exclusion criteria included a estimated glomerular filtration rate (eGFR) less than 30 mL/min per $1.73m^2$; serum potassium greater than 5 mEq/L; and recent unstable angina, acute myocardial infarction or coronary revascularization procedure. After a 4-week run-in phase, participants were randomized to spironolactone 25 mg once daily or placebo. Spironolactone was titrated to 50 mg once daily at 4 weeks if serum potassium was not greater than 5 mEq/L and eGFR was at least 50 mL/min per 1.73^2. Mean duration of follow-up was 44 months in a total of 130 participants (65 in the spironolactone group and 65 in the placebo group). The primary composite outcome of cardiovascular death or cardiovascular hospitalization occurred in 13.5% of patients receiving spironolactone and 43% of patients receiving placebo, with a HR of 0.37 (95% CI, 0.1856 to 0.7184; p=0.0035). However, there was not a significant difference in cardiovascular death as the composite outcome results were influenced by cardiovascular hospitalizations, which occurred in 9.2% of patients receiving spironolactone and 36.9% of patients receiving placebo, with a HR of 0.29 (95% CI, 0.1385 to 0.6147; p=0.0012). In addition, all-cause mortality was equal between the groups (12.3% in each arm). Six patients had a serum potassium greater than 5.5 mEq/L in the spironolactone group (9.2%) and 1 patient (1.5%) in the placebo group.

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