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Drug Class Literature Scan: Diuretics

Date of Review: June 2020

Date of Last Review: November 2014
Literature Search: 09/01/14 – 11/22/19

Current Status of PDL Class: See **Appendix 1**.

Conclusions:

- Seven clinical practice guidelines[1-7], 17 systematic reviews[8-24], and 2 randomized controlled trials (RCTs)[25,26] identified for this update.
- Thiazide-type diuretics are recommended as a first-line treatment option for hypertension. High-dose diuretic regimens have been shown to reduce mortality and stroke (moderate quality evidence), while low-dose regimens have been found to reduce mortality, stroke, coronary heart disease, and total cardiovascular events (high quality evidence). Evidence for use of "low" dose thiazide-type diuretics is stronger than "high" dose thiazide-type diuretics.[1-4,10,12] Low doses are less than chlorthalidone (CTDN) 50 mg per day, indapamide (INDAP) 5 mg per day or hydrochlorothiazide (HCTZ) 50 mg per day.[10] High doses are CTDN 50 mg or more each day, INDAP 5 mg more each day, or HCTZ 50 mg or more each day.[10]
- Thiazide-like diuretics [e.g. CTDN and INDAP] are preferred over thiazide diuretics [e.g HCTZ] by certain high quality guidelines,[1-3] while another guideline has no preference between the two agent types.[4] These recommendations were all based on the same body of literature. High quality RCTs of CTDN and INDAP show cardiovascular benefits as well as pharmacokinetic superiority in the form prolonged half-life compared to HCTZ, but there is insufficient evidence to *directly* compare these agents for efficacy and safety.[1-4,18,27]
- Loop diuretics are recommended for edema in heart failure (HF) but they have not been shown to reduce mortality, and there is insufficient evidence to differentiate between agents.[5-7,19,28] (low quality evidence)
- Mineralocorticoid receptor antagonists (MRA) are recommended to reduce mortality in most patients with HF with reduced ejection (HF*r*EF) who already take an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) and a beta blocker (BB).[5-7] (High quality evidence)
- MRAs (e.g. spironolactone and eplerenone) have limited evidence that they improve protein/creatinine ratio in diabetic nephropathy (DN) when used in combination with an ACEI or ARB. Hyperkalemia incidence increases with this combination.[24]
- MRA use in HF with preserved ejection fraction (HF*p*EF) and HF with moderately reduced ejection fraction (HF*mr*EF) may reduce hospitalizations. There is possible mortality benefit for those patients who are also status post ST-elevation myocardial infarction (STEMI).[6,7,20-22] (low quality evidence)
- Spironolactone has evidence to support its use in resistant hypertension, with appropriate monitoring due to higher incidence of hyperkalemia.[1,2,14,15,17] (moderate quality evidence)
- The effect of thiazide-type diuretics on glucose metabolism, particularly HCTZ, is unclear.[23] (insufficient quality evidence)
- There is insufficient data to differentiate between different MRA medications.[5-7] (insufficient quality evidence)
- There is insufficient evidence for the use of loop diuretics for blood pressure reduction.[9] (insufficient quality evidence)
- There is insufficient evidence to make recommendations regarding diuretic use in children.[8] (insufficient quality evidence)

Recommendations:

- CTDN added to the OHP FFS preferred drug list (PDL).
- Costs evaluated in executive session.
- Generic triamterene/HCTZ products added to OHP FFS PDL.

Summary of Prior Reviews and Current Policy

- High quality evidence suggests thiazide-type diuretics should continue to be recommended as a first-line option for hypertension due to benefit at reducing mortality and stroke.
- Thiazide-type diuretics with high quality data include HCTZ, CTDN and INDAP.
- 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 (BP).
- There is high quality evidence loop diuretics provide short-term relief of fluid retention in symptomatic heart failure patients with preserved or reduced left ventricular ejection fraction (LVEF). However, there is insufficient evidence to confirm long term benefits of diuretics in patients with heart failure.
- 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. 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.

Background:

The diuretics class encompasses multiple sub-classes of agents which differ mechanistically.[29] The most familiar agents are loop diuretics, thiazide-type diuretics, and potassium-sparing diuretics.[29] Potassium sparing diuretics are divided into agents which directly block sodium channels without antagonism of mineralocorticoid receptor (e.g., amiloride) and agents which function with direct inhibition of the mineralocorticoid receptor (e.g., spironolactone).[29] Additionally, there are a number of miscellaneous medications such as carbonic anhydrase inhibitors, osmotic diuretics, or vasopressin antagonists which function with diuretic properties; however, their clinical use varies significantly from disease states commonly treated with loop, thiazide-type, and potassium sparing agents.[29] These miscellaneous agents were excluded for the purpose of this review.

Loop, thiazide-type, and potassium-sparing diuretics are most commonly used for hypertension and heart failure.[1,6] Elevated blood pressure increases risk of complications such as myocardial infarction, stroke, heart failure, and kidney disease.[1] It was the leading cause of death and disability-adjusted life years worldwide in 2010.[1] Hypertension has been the cause of more cardiovascular deaths than any other modifiable risk factor.[1] Risk for developing hypertension increases with age and is more common in African-Americans than other races.[1] Diuretics, with thiazide-type agents being used most commonly for hypertension, work by causing a net excretion of water, resulting in decreased blood pressure.[29] Depending upon comorbidities and electrolyte levels, different diuretic sub-types can be combined[1], though combinations require close monitoring to avoid adverse effects such as electrolyte abnormalities, dehydration, and acute kidney injury.[29]

Heart failure is a clinical syndrome involving structural or functional impairment of ventricular filling or ejection of blood.[28] It primarily manifests with symptoms of dyspnea, fatigue, and fluid retention.[28] There is a 20% lifetime risk for development of heart failure in Americans 40 years of age and older, and risk increases with increasing age.[28] Diuretics, primarily loop agents, find utility in reducing symptoms of fluid overload in heart failure.[28] Potassium-sparing agents with mineralocorticoid inhibition have also been shown to improve outcomes,[28] likely due to a reduction of the adverse effects of excess aldosterone on the heart.[29]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 26 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[27,30-54]

New Systematic Reviews on Hypertension:

Cochrane Review-Pharmacological Interventions for Hypertension in Children
A 2014 *Cochrane Review* assessed antihypertensive agents in children with hypertension.[8] Randomized controlled trials using mono- or combination therapy and an active or placebo control of at least two weeks duration were included.[8] None of the included trials assessed effectiveness of medications on target end organ damage, and only one study evaluated use of a diuretic (bisoprolol plus HCTZ versus placebo; n=94).[8] This study did not show a significant systolic BP (SBP) reduction versus placebo [mean difference -4 mmHg, 95% confidence Interval [CI] -8.99 to 0.19 mmHg].[8] It did report a significant reduction of diastolic BP (DBP) [-4.5 mmHg, 95% CI -8.26 to -0.74 mmHg].[8] Outcomes were graded as very low quality.[8]

Cochrane Review-Blood Pressure-Lowering Efficacy of Loop Diuretics for Primary Hypertension
A 2015 *Cochrane Review* assessed the dose-dependent BP-lowering effects of loop diuretics versus placebo in patients with primary hypertension.[9] Additionally, adverse events such as participant withdrawal and adverse biochemical effects (serum potassium, uric acid, creatinine, glucose, and lipids profile) were assessed.[9] Double-blind, placebo-controlled RCTs with a minimum of 3-weeks duration that studied loop diuretics for primary hypertension in patients with baseline BP of more than 140/90 mmHg were included.[9] Nine studies evaluating furosemide, ciclentanine, piretanide, indacrinone enantiomer, or etozolin met inclusion criteria (n=460).[9] Furosemide is the only included product available in the US. Patients in the included studies had an average baseline BP of 162/103 mmHg and were treated with loop diuretics for a mean duration of 8.8 weeks. The estimated SBP-lowering effect for loop diuretics was -7.9 mmHg (95% CI -10.4 to -5.4 mmHg) and DBP-lowering was -4.4 mmHg (95% CI -5.9 to -2.8 mmHg). Evidence was of low quality based on high risk of bias in included studies and high likelihood of

publication bias.[9] There was minimal reporting of adverse drug effects and the studies were of short duration, making the review unable to estimate incidence of harm associated with loop diuretic use for primary hypertension.[9]

Cochrane Review-Pharmacotherapy for Hypertension in Adults Aged 18 to 59 Years

A 2017 *Cochrane Review* assessed antihypertensive drug therapy in adults to quantify all-cause mortality and morbidity and mortality secondary to cardiovascular, cerebrovascular, and coronary heart disease (CHD).[11] Reviewers included placebo-controlled RCTs in adult patients aged 18-59 years with mild-to-moderate hypertension (defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) for a least one year duration.[11] The overall quality of evidence for all outcomes was rated as low to very low, and risk of bias was high or unclear in multiple domains.[11] Seven studies (N=17,327) met inclusion criteria, and of these one study included 84% (N=14,541) of the total participants.[11] Patients in this study had a mean age of 50 years, mean baseline BP of 160/98 mmHg, and mean follow-up of 5 years.[11] The medication intervention in the primary study was bendrofluazide (not available in US) or propranolol with the addition of methyldopa if needed.[11] There was no difference observed in all-cause mortality [relative risk (RR) 0.94, 95% CI 0.77 to 1.13] or CHD (RR 0.99, 95% CI 0.82 to 1.19).[11] Cardiovascular mortality and morbidity (fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, sudden death, hospitalization or death from congestive heart failure or other significant vascular death such as ruptured aneurysms) was reduced over a period of 5 years (3.2% treatment vs. 4.1% active control; RR 0.78, 95% CI 0.67 to 0.91), in part driven by a reduction in cerebrovascular mortality and morbidity (0.6% treatment vs. 1.3% control; RR 0.46, 95% CI 0.34 to 0.64).[11] There was a higher rate of withdrawals from adverse events for those taking drug therapy when compared to placebo or untreated controls (3% treatment vs. 0.7% control; RR 4.82, 95% CI 1.67 to 13.92).[11]

Cochrane Review-Eplerenone for Hypertension

A 2017 *Cochrane Review* assessed evidence from placebo-controlled RCTs of eplerenone monotherapy for primary hypertension in adults.[13] Trials evaluating secondary hypertension or which used multiple antihypertensives were excluded.[13] This review identified 5 RCTs (n = 1,437 patients) with treatment durations of 8 to 16 weeks and eplerenone doses ranging from 25 mg to 400 mg daily.[13] There was moderate quality evidence of a significant change in SBP (-9.21 mmHg, 95% CI -11.08 to -7.34 mmHg) and DBP (-4.18 mmHg, 95% CI -5.03 to -3.33 mmHg) for eplerenone doses of 50 mg to 200 mg each day.[13] The studies had an unclear risk of bias in multiple domains, including: sequence generation; blinding of participants, personnel, and assessors; incomplete outcome data; and selective outcome reporting.[13] All were unclear or had other known sources of bias.[13] Adverse events were recorded in only 3 of 5 studies and evidence was of low quality.[13] There was insufficient evidence on clinically meaningful outcomes of morbidity and mortality.[13]

Cochrane Review-First-line Drugs for Hypertension

A 2018 *Cochrane Review* assessed the use of different first-line antihypertensive classes and their effect on morbidity and mortality.[10] The authors included thiazide diuretics, BB, calcium channel blockers (CCB), ACEI, ARB, and alpha blockers compared to placebo or no treatment.[10] This update from a 2009 review included RCTs of at least 1 year duration, comparing these drugs to placebo or no treatment with clearly defined morbidity and mortality endpoints and analysis using intention-to-treat (ITT).[10] No additional citations met inclusion criteria since the initial search in 2009.[10] Results for individual thiazide agents were not separately evaluated, and were presented as “low-dose” and “high-dose” subgroups.[10] Low doses are less than CTDN 50 mg per day, INDAP 5 mg per day or HCTZ 50 mg per day.[10] High doses are CTDN 50 mg or more each day, INDAP 5 mg or more each day, or HCTZ 50 mg or more each day.[10] Low-dose thiazides had high quality evidence, while high-dose thiazides were of low-moderate quality evidence.[10] Low-dose thiazides significantly reduced mortality (9.8% treatment vs. 11% control; RR 0.89, 95% CI 0.82 to 0.97; N=19,874), stroke (4.2% treatment vs. 6.2% control; RR 0.68, 95% CI 0.6 to 0.77; N=19,874), CHD (2.8% treatment vs. 3.9% control; RR 0.72, 95% CI 0.61 to 0.84; N=19,022) and total cardiovascular events (9% treatment vs. 12.9% control; RR 0.7, 95% CI 0.64 to 0.76; N=19,022).[10] High-dose thiazides did not significantly reduce mortality or CHD, but did reduce stroke (0.9% treatment vs. 1.9% control; RR 0.47, 95% CI 0.37 to 0.61; N=19,839) and total cardiovascular events (3.7% treatment vs. 5.1% control; RR 0.72, 95% CI 0.63 to 0.82; N=19,839).[10]

Cochrane Review-Pharmacotherapy for Hypertension in Adults 60 Years or Older

A 2019 Cochrane review updated previous publications from 1998 and 2009 to assess the mortality and morbidity associated with antihypertensive treatment versus placebo or no treatment for patients 60 years and older with BP over 140/90 mmHg.[12] This update included one additional trial for a total of 16 trials (N=26,795).[12] The mean age was 73.4 years, baseline BP was 182/95 mmHg, and thiazide diuretics were the most common first-line therapy.[12] Patients were followed for a mean duration of 3.8 years and were primarily from western, industrialized countries.[12] Treatment reduced all-cause mortality (10% treatment vs. 11% control; RR 0.91, 95% CI 0.85 to 0.97) with high quality evidence.[12] Cardiovascular morbidity and mortality (9.8% treatment vs. 13.6% control; RR 0.72, 95% CI 0.68 to 0.77), cerebrovascular morbidity and mortality (3.4% treatment vs. 5.2% control; RR 0.66, 95% CI 0.59 to 0.74), and CHD morbidity and mortality (3.7% treatment vs. 4.8% control; RR 0.78; 95% CI 0.69 to 0.88) were all reduced based on moderate quality evidence.[12] Additionally, an analysis of patients aged 60-79 years provide high quality evidence that much of the overall benefit for those over 60 years of age is derived from the all-cause mortality reduction in this subgroup (2.9% treatment vs. 3.8 % control; RR 0.86, 95% CI 0.79 to 0.95).[12] Adverse effects resulting in withdrawal from studies were higher in treatment groups (15.7% treatment vs. 5.4% control; RR 2.91, 95% CI 2.56 to 3.3) based on low quality evidence.[12]

Treatment-Resistant Hypertension

Four systematic reviews of moderate quality evaluated spironolactone for resistant hypertension, defined as uncontrolled BP while on optimal doses of 3 or more antihypertensive agents from different pharmacological classes.[14-17] Significant overlap of source trials existed in the included analyses, as well as marked variation of the results of the risk of bias assessment for identical included trials.[14-17] Authors of all these systematic reviews noted significant heterogeneity among included studies. Average reduction in SBP was estimated at 8 to 10 mmHg with average reductions in DBP of 4 to 5 mmHg. In one review, rates of withdrawals and serious adverse events, usually hyperkalemia, were non-significantly higher in spironolactone-treated patients (OR 2.11, 95% CI 0.98 to 4.53, p=0.05). In another review, mean serum potassium increases of 0.181 mEq/L (95% CI 0.042 to 0.319 mEq/L, p=0.011) were observed.

Comparison of Diuretics for Hypertension

A moderate quality systematic review with meta-analysis evaluated head-to-head trials of HCTZ versus thiazide-like diuretics (INDAP or CTDN).[18] There were 12 included studies (n=1,580 patients) which ranged from 4 to 24 weeks in duration.[18] Compared to HCTZ, thiazide-like diuretics had a greater reduction in SBP (-5.59 mmHg, 95% CI -5.69 to -5.49 mmHg, p<0.00001) and DBP (-1.98 mmHg, 95% CI -3.29 to -0.66 mmHg, p<0.00001).[18] Heterogeneity was low in the SBP calculation (I^2=10%), but high in the DBP calculation (I^2=85%).[18] Analysis of serum markers showed no between-group differences in hypokalemia (OR 1.58, 95% CI 0.8 to 3.12, p=0.16), hyponatremia [standard mean difference (SMD) -0.14, 95% CI -0.57 to 0.3, p=0.71], total cholesterol (0.11, 95% CI -0.02 to 0.24, p=0.11), or glucose (0.13, 95% CI -0.16 to 0.41, p=0.39).[18] Significant heterogeneity was present for the glucose calculation only (I^2=69%).[18]

Metabolic and Renal Outcomes in Diabetic Patients

The adverse metabolic effects of HCTZ were assessed in patients with hypertension and type 2 diabetes mellitus (T2DM).[23] This review included studies of 4 to 144 weeks duration in patients taking an active control of a BB, CCB, ACEI, or ARB and found a statistically significant increase in fasting glucose (SMD 0.27, 95% CI 0.11 to 0.43, p<0.05) and HbA1C (SMD 1.09, 95% CI 0.47 to 1.71, p<0.05) for patients in the HCTZ-treated group versus active controls.[23] Results were consistent even in patients treated with a low dose HCTZ of 25 mg per day or less.[23]

The effect of MRA was evaluated in a systematic review of patients with diabetic nephropathy.[24] Eligible studies evaluated spironolactone (n=13), eplerenone (n=2), and finerenone (n=2; not available in US).[24] The protein/albumin excretion was significantly reduced with the addition of a MRA to ACEI/ARB therapy versus

ACEI/ARB monotherapy [mean difference (MD) -44.17 mg/24 hours, 95% CI -61.73 to -26.61 mg/24 hours, p<0.00001].[24] There was a significant increase in serum potassium with addition of an MRA (MD 0.27 mEq/L, 95% CI 0.18 to 0.35 mEq/L, p<0.00001) and increased risk of hyperkalemia (RR 4.02, 95% CI 2.48 to 6.52, p<0.00001).[24]

New Systematic Reviews on Heart Failure:

Moderate Quality Systematic Reviews on Diuretic use in Heart Failure (HF)

Three separate meta-analyses evaluated the use of MRAs in patients with HF*p*EF.[20-22] Dahal, et al. focused on patients post-STEMI without HF or with LVEF greater than 40%. The review included 10 studies, with oral MRA (spironolactone, potassium canrenoate, eplerenone) or intravenous (IV) potassium canrenoate followed by oral spironolactone or potassium canrenoate compared to placebo or no treatment .[20] One study included eplerenone.[20] The authors found an overall reduction in the risk of mortality with MRA use versus control (2.4% vs 3.9%; OR 0.62; 95% CI 0.42-0.91, p=0.01). No difference between the groups were found in the incidence of MI, congestive heart failure, or ventricular arrhythmia.[20]

A second meta-analysis of RCTs for patients with HF*p*EF (defined as EF ≥45%) identified two studies related to all-cause mortality and hospitalization taking spironolactone or placebo.[21] No reduction in all-cause mortality (OR 0.91; 95% CI 0.76-1.1; p=0.32) or hospitalization rates (OR 1.0; 95% CI 0.8-1.25; p=1.00) was found.[21] Similarly, a meta-analysis of RCTs enrolling HF*p*EF (EF > 50%) and HF*mr*EF (EF = 40-49%) found no difference in mortality between patients taking spironolactone versus placebo (RR 0.72; 95% CI 0.31-1.69; p=0.45; n=3 RCTs).[22] However, 2 pooled studies showed spironolactone decreased hospital readmissions (OR 0.84; 95% CI 0.73-0.95; p=0.006).[22]

The third meta-analysis evaluated ambulatory heart failure patients (primarily NYHA class II-III) on torsemide or furosemide for 5 to 12 months.[19] There was no difference in all-cause mortality (OR 1.01, 95% CI 0.64-1.59).[19] Patients taking furosemide showed higher risk of heart failure related readmission (OR 2.16, 95% CI 1.28-2.64). Those taking torsemide were more likely to have NYHA class improvement during the follow-up time range (OR 0.73, 95% CI 0.58-0.93).[19]

New Guidelines:

Hypertension

National Institute for Health and Care Excellence (NICE)

In 2019, NICE published guidelines for the diagnosis and management of hypertension in non-pregnant adults, including those with T2DM.[2] Treatment is recommended in stepwise fashion, and is based on various age, race, and comorbidity factors. For step 1 therapy, initiation of an ACEI or ARB is recommended for patients with T2DM or for non-African/African-Caribbean patients who are under 55 years of age.[2] See **Table 1** before for full details of step therapy. For those initiating or changing diuretic treatment, thiazide-like agents, such as INDAP, are preferred over conventional thiazide diuretics of HCTZ and bendroflumethiazide.[2] CTDN was removed as an example due to limited availability in the European market and confusion over being listed prior to INDAP in a previous iteration of this guideline.[2] Patients who are well controlled on conventional thiazides should continue those agents.[2]

Table 1: NICE Guidelines Step Therapy for Hypertension[2]

Patient Characteristics	Step 1	Step 2	Step 3	Step 4
Type 2 diabetes mellitus • Regardless of age or family origin	ACEI or ARB	CCB or thiazide-like diuretic	Combination of: (ACEI or ARB) AND CCB AND thiazide-like diuretic	If potassium 4.5 mEq/L or less consider: Low-dose spironolactone Monitor potassium and use caution in patients with reduced renal function. If potassium 4.5 mEq/L or higher consider: Alpha-blockers or beta-blockers
Age 55 or older • **NOT** African or African-Caribbean origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic		
Age 55 and older • African or African-Caribbean Origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic **Consider ARB in preference to ACEI*		
Age under 55 years • **NOT** African or African-Caribbean origin	ACEI or ARB	ACEI or ARB or thiazide-like diuretic		
Age under 55 years • African or African-Caribbean Origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic **Consider ARB in preference to ACEI*		
Clinical suspicion of heart failure	Consider thiazide-like diuretic, then follow chronic heart failure guidelines			

<u>Department of Veterans Affairs/Department of Defense (VA/DoD)</u>

In 2014, the VA/DoD published an update of the 2004 guidelines on the diagnosis and management of hypertension in the primary care setting.[3] Recommendations for treatment initiation vary by age and comorbidities, but there is a strong recommendation to offer pharmacologic treatment for a SBP of ≥ 160 mmHg in patients 60 years and older, and a weak recommendation to begin pharmacologic treatment with a SBP of ≥ 160 mmHg in patients younger than 60 years old.[3] For patients who are 30 years and older, there is a strong recommendation to offer pharmacologic treatment for DBP of ≥ 90 mmHg, and a weak recommendation to suggest offering pharmacologic treatment for patients 18-29 years with a DBP of ≥ 90 mmHg.[3] The guidelines offer a weak recommendation to initiate combination therapy for patients with a baseline SBP of 20 mmHg or DBP of 10 mmHg above the goal BP based upon an individual patient's age and comorbidities.[3]

These guidelines have a strong recommendation (grade A) for the use of thiazide-type diuretics as first-line therapy, either as monotherapy or in combination with other agents, with preferred doses of 12.5-25 mg per day for CTDN, 25-50 mg per day for HCTZ, or 2.5 mg per day for immediate-release INDAP.[3] A weak recommendation supports the use of CTDN or INDAP preferentially over HCTZ for treatment initiation or in switching patients who are inadequately controlled on 50 mg per day of HCTZ.[3] Patients with refractory hypertension or who are unable to tolerate triple therapy of ACEI or ARB, CCB, and thiazide-type diuretics

have a number of other pharmacologic classes which can be considered.[3] These include aldosterone receptor antagonists such as spironolactone or eplerenone and other potassium-sparing diuretics, such as amiloride.[3] Preference for one of these classes over another is not specified.[3]

American College of Clinical Cardiology (ACC)/American Heart Association (AHA), et al.

The ACC, AHA, and numerous partners published 2017 guidelines for the prevention, detection, evaluation, and management of high BP in adults.[1] Recommendations were delineated by strength based on the anticipated risk and benefit ratio (Class I-III) and quality of evidence (Level A evidence from multiple RCTs or meta-analyses to Level C evidence derived from limited data or expert opinion).[1] Recommended first-line therapy includes thiazide-type diuretics, CCBs, and ACEI/ARBs (Class I, Level A from systematic reviews).[1] Of the thiazide-type diuretics, CTDN has a prolonged half-life and was found to be superior to both amlodipine and lisinopril in preventing HF in head-to-head comparison in the ALLHAT trial.[1] This guideline reported that results from meta-analyses suggest that thiazide-like diuretics, specifically CTDN, are the best choice for first step therapy in patients without contraindications or other important comorbidities (e.g. chronic kidney disease).[1] MRAs, including eplerenone and spironolactone, are preferred agents for primary aldosteronism and as add-on therapy for resistant hypertension. Spironolactone generally has greater incidence of particular adverse events, including gynecomastia and impotence, compared to eplerenone, which usually requires twice daily dosing for BP lowering.[1] Loop diuretics are recommended for symptomatic HF, and potassium sparing agents can be considered for those with hypokalemia on monotherapy with a thiazide-type agent.[1] These nuanced class specific recommendations were not graded.[1]

European Society of Cardiology (ESC)/European Society of Hypertension (ESH)

In 2018, ESC/ESH published guidelines for the management of arterial hypertension using identical grading systems for class of recommendation and level of evidence as ACC/AHA type guidelines.[4] Most patients should begin with duel combination treatment as initial therapy with either ACEI or ARB plus a CCB or thiazide-type diuretic (Class I, Level A).[4] INDAP and CTDN have a number of RCTs showing improvement in cardiovascular events.[4] Additionally, they have higher potency than HCTZ without an increased rate in side effects.[4] However, a recent meta-analysis of placebo-controlled RCTs evaluating HCTZ, INDAP, and CTDN found similar rates of CV events.[4] Therefore, in the absence of direct head-to-head comparison between thiazide diuretic HCTZ and thiazide-like diuretics of INDAP and CTDN, the authors do not give preference to one agent over another.[4] Patients with HF and edema should begin loop diuretics over thiazide-type diuretics.[4] Thiazides-type diuretics should be avoided due to lack of efficacy for those with renal impairment.[4] If duel antihypertensive therapy is ineffective, patients should advance to step 2, triple therapy, with an ACEI or ARB PLUS CCB PLUS thiazide-type diuretic. Those patients who remain uncontrolled at step 2, with no additional comorbidities dictating antihypertensive therapy should move to step 3 with the addition of spironolactone, another diuretic (such as a potassium sparing agent), an alpha-blocker, or a beta-blocker.[4] It is noted that a thiazide-type diuretic plus a potassium-sparing diuretic may be equivalent to CCB-based treatment and result in fewer metabolic effects such as hypokalemia and glucose intolerance than the combination of thiazide-type diuretics and BBs.[4] However, the dual diuretic combination was not recommended in preference to a thiazide-type diuretic plus BB combination.[4]

Heart Failure

National Institute for Health and Care Excellence (NICE)

In 2018, NICE published guidelines for the diagnosis and management of chronic HF in adults.[5] In treating HF*r*EF, an ACEI should be considered first-line therapy in the absence of significant valvular disease and should be titrated upward at short intervals to a maximal tolerated dose. An ARB should be used in patients unable to take an ACEI. Additionally, those without contraindications are recommended to begin a BB indicated for heart failure (e.g. metoprolol succinate or carvedilol), and slowly titrated as tolerated. A MRA can be considered for those already taking an ACEI and BB. Recommendations between different MRA drugs are not made. Other medications, including ivabradine, sacubitril-valsartan, hydralazine plus isosorbide, and digoxin can be considered in specific patients under

specialist consultation. Loop diuretics are recommended for the relief of congestion and fluid retention. Specific preference for one loop agent over another are not included. Non-dihydropyridines and short-acting dihydropyridine medications should be avoided in patients who have HF*r*EF. A low to medium dose of a loop diuretic should be offered to HF*p*EF.[5]

2017 ACC/AHA/HFSA Focused Update of the 2013 Guideline for the Management of Heart Failure

The ACC issued a 2017 update of the 2013 guidelines for the management of HF.[6] The recommendation to use diuretics for relief of symptoms related to volume overload from HF*p*EF (Class I, Level C) remains unchanged from the previous guideline.[6,28] The choice of diuretic for volume overload may include loop, thiazide-type, or potassium-sparing (including spironolactone, but excluding eplerenone).[6,28] A new recommendation is to consider a MRA to decrease hospitalizations for select HF*p*EF patients meeting all the following criteria (Class IIB, Level B based on RCTs):

- EF ≥ 45%,
- Elevated B-type natriuretic peptide (BNP) or HF admission within 1 year,
- Glomerular filtration rate (GFR) over 30 mL/min,
- Serum creatinine less than 2.5 mg/dL, and
- Potassium less than 5 mEq/L.[6]

Recommendations related to diuretic use in HF*r*EF Stage C and D remain unchanged from the previous full guideline.[28] Step 1 therapy is to initiate an ACEI or ARB plus a BB, with loop diuretic use as needed (Class 1, Level C). Step 2 for HF*r*EF involves assessment of individual patient parameters. For those with New York Heart Association class II-IV disease and an EF of less than 35%, a MRA is recommended (Class I, Level A).[28] Patients with an EF of 40% or less following an acute myocardial infarction with T2DM or symptoms of HF should also begin MRA therapy (Class I, Level B).[28] Both groups should have a GFR of over 30 mL/min and a serum potassium of less than 5 mEq/L to avoid harm in starting MRA (Class III-harm, Level B).[28]

European Society of Cardiology (ESC)/European Society of Hypertension (ESH)

The 2016 ESC/ESH guidelines address the diagnosis and treatment of acute and chronic HF. MRAs are recommended to reduce mortality and risk of HF hospitalization in patients with HF*r*EF without contraindications (Class I, Level A).[7] Diuretics (loop, thiazide, MRA, or potassium-sparing) can be used to relieve symptoms of congestion (Class I, Level B) and to reduce the risk of HF hospitalization in patients with congestion (Class IIa, Level B).[7] For patients with HF*p*EF and HF*mr*EF there has been no reduction in mortality seen with the use of ACEI, ARB, BB, and MRA medications.[7] There is limited evidence that spironolactone may reduce HF hospitalizations in these patients when they are in sinus rhythm.[7] Diuretics continue to be recommended for HF*p*EF and HF*mr*EF patients to treat congestion (Class I, Level B).[7]

After review, 5 guidelines were excluded due to poor quality.[55-59] Guidelines for pregnancy were reviewed and excluded as diuretics are generally not recommended for those patients.

New Formulations:

Spironolactone (Carospir®) 25 mg/5mL oral suspension was approved August 2017.

New FDA Safety Alerts:

No FDA safety alerts involving diuretics from 2014 to 2019.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	CAPSULE	Y
hydrochlorothiazide	MICROZIDE	CAPSULE	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	SOLUTION	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	TABLET	Y
indapamide	INDAPAMIDE	TABLET	Y
spironolactone	ALDACTONE	TABLET	Y
spironolactone	SPIRONOLACTONE	TABLET	Y
triamterene	TRIAMTERENE	CAPSULE	Y
amiloride HCl	AMILORIDE HCL	TABLET	Y
spironolact/hydrochlorothiazid	ALDACTAZIDE	TABLET	Y
spironolact/hydrochlorothiazid	SPIRONOLACTONE-HCTZ	TABLET	Y
triamterene/hydrochlorothiazid	DYAZIDE	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	CAPSULE	Y
amiloride/hydrochlorothiazide	AMILORIDE HCL W/HCTZ	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE-HYDROCHLOROTHIAZIDE	TABLET	Y
furosemide	FUROSEMIDE	SOLUTION	Y
furosemide	FUROSEMIDE	TABLET	Y
furosemide	LASIX	TABLET	Y
bumetanide	BUMETANIDE	TABLET	Y
torsemide	TORSEMIDE	TABLET	Y
chlorothiazide	DIURIL	ORAL SUSP	N
chlorothiazide	CHLOROTHIAZIDE	TABLET	N
methyclothiazide	METHYCLOTHIAZIDE	TABLET	N
chlorthalidone	CHLORTHALIDONE	TABLET	N
metolazone	METOLAZONE	TABLET	N
spironolactone	CAROSPIR	ORAL SUSP	N
eplerenone	EPLERENONE	TABLET	N
eplerenone	INSPRA	TABLET	N
triamterene/hydrochlorothiazid	MAXZIDE	TABLET	N
triamterene/hydrochlorothiazid	MAXZIDE-25 MG	TABLET	N
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	TABLET	N
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	TABLET	N
ethacrynic acid	EDECRIN	TABLET	N
ethacrynic acid	ETHACRYNIC ACID	TABLET	N
furosemide	FUROSEMIDE	SOLUTION	N

Appendix 2: New Comparative Clinical Trials

A total of 293 citations were manually reviewed from the initial literature search. After further review, 291[30,60-233,234-347] citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials[25,26] are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Cushman et al[26] MC, DB, RCT, phase 4	AZL-M/CTDN 20/12.5 mg vs. AZL-M/CTDN 40/12.5 mg vs. OLM/HCTZ 20/12.5 mg *All doses to be doubled at week 4 if not at target BP* 3 to 4 week washout period of previous antihypertensives before randomization Stratified by race (i.e. black or nonblack) 8 weeks of treatment	Stage 2 systolic HTN N=1085	Change SBP from baseline at week 8	AZL-M/CTDN 20/12.5 mg vs. OLM/HCTZ 20/12.5 mg -6.1 mmHg (95% CI -8.4 to -3.8 mmHg; p<0.001) Favors AZL-M/CTDN AZL-M/CTDN 40/12.5 mg vs. OLM/HCTZ 20/12.5 mg -6.7 mmHg (95% CI -9.1 to -4.4 mmHg; p<0.001) Favors AZL-M/CTDN Use of different ARB agents in comparison groups makes results difficult to interpret.
Korol et al[25] MC, DB, RCT, phase 4	Spironolactone 25 mg/day vs. Eplerenone 50 mg/day 16 weeks of treatment	Adults with HF; LVEF ≤ 40%; NYHA class II-IV; T2DM or glucose intolerance; and appropriate background HF pharmacotherapy (BB and ACEI/ARB) N=62 randomized, 55 analyzed for primary endpoint	Change in HbA_{1c} from baseline to 16 weeks Per protocol analysis	Spironolactone change -0.2% ± 0.83% SD Eplerenone change 0.1% ± 0.38% Between group difference 0.3%; p = 0.2152

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AZL-M = azilsartan medoxomil; BB = beta blocker; BP = blood pressure; CI = 95% confidence interval; CTDN = chlorthalidone; DB = double-blind; HbA_{1c} = glycated hemoglobin; HCTZ = hydrochlorothiazide; HF = heart failure; HR = hazard ratio; HTN = hypertension; LVEF = left ventricular ejection fraction; MC = multi-center; NYHA = New York Heart Association; OL = open-label; OLM = olmesartan; RCT = randomized clinical trial; SD=standard deviation; T2DM = type 2 diabetes mellitus.

Author: Fletcher June 2020

Appendix 3: Abstracts of Comparative Clinical Trials

Cushman WC, Bakris GL, White WB, et al. A randomized titrate-to-target study comparing fixed-dose combinations of azilsartan medoxomil and chlorthalidone with olmesartan and hydrochlorothiazide in stage-2 systolic hypertension. *J Hypertens.* 2018;36(4):947-956

BACKGROUND: Azilsartan medoxomil (AZL-M), an angiotensin II receptor blocker, has been developed in fixed-dose combinations (FDCs) with chlorthalidone (CTD).
OBJECTIVE/METHODS: We compared FDCs of AZL-M/CTD 20/12.5 mg once daily titrated to 40/25 mg if needed or AZL-M/CTD 40/12.5 mg once daily titrated to 80/25 mg if needed with an olmesartan medoxomil (OLM)-hydrochlorothiazide (HCTZ) 20/12.5 mg FDC once daily titrated to 40/25 mg if needed in a randomized, double-blind, 8-week study of 1085 participants with clinic SBP 160-190 mmHg and DBP 119 mmHg or less. Titration to higher doses occurred at week 4 if BP was at least 140/90 mmHg (≥130/80 mmHg if diabetes or chronic kidney disease). The primary endpoint was change from baseline in clinic SBP; 24-h ambulatory BP monitoring was also measured.
RESULTS: Greater reductions in clinic SBP from a baseline of 165 mmHg were observed ($P < 0.001$) in both AZL-M/CTD arms (-37.6 and -38.2 mmHg) versus OLM/HCTZ (-31.5 mmHg), despite greater dose titration in the OLM/HCTZ group. At 8 weeks, both AZL-M/CTD FDCs reduced 24-h SBP more than OLM/HCTZ (-26.4 and -27.9 versus -20.7 mmHg; both $P < 0.001$), and higher proportions in both AZL-M/CTD groups achieved target BP compared with the OLM/HCTZ group (69.4 and 68.9 versus 54.7%, both $P < 0.001$). Adverse events leading to drug discontinuation occurred in 6.2, 9.5, and 3.1% with the AZL-M/CTD lower and higher doses, and OLM/HCTZ, respectively.
CONCLUSION: This large, titration-to-target BP study demonstrated AZL-M/CTD FDCs to have superior antihypertensive efficacy compared with the maximum approved dose of OLM/HCTZ.

Korol S, White M, O'Meara E, et al. A comparison of the effects of selective and non-selective mineralocorticoid antagonism on glucose homeostasis of heart failure patients with glucose intolerance or type II diabetes: A randomized controlled double-blind trial. *Am Heart J.* 2018;204:190-195.

Mineralocorticoid receptor antagonists (MRAs) decrease morbidity and mortality in patients with heart failure (HF). However, spironolactone, a non-selective MRA, has been shown to exert a harmful effect on glucose homeostasis. The objective of this multicenter, randomized, controlled, double-blind trial was to compare the effects of spironolactone to those of the selective MRA eplerenone on glucose homeostasis among 62 HF patients with glucose intolerance or type II diabetes. Trial registration number:NCT01586442

Appendix 4: Medline Search Strategy

Pubmed with MESH terms

#	**Searches** Limits: Clinical Trial; Clinical Trial, Phase III; Clinical Trial, Phase IV; Comparative Study; Controlled Clinical Trial; Guideline; Meta-Analysis; Multicenter Study; Practice Guideline; Pragmatic Clinical Trial; Randomized Controlled Trial; Systematic Reviews; Publication date from 2014/09/01 to 2019/11/22; Humans; English	**Results**
1	Heart Failure/drug therapy OR Hypertension/drug effects OR Hypertension/drug therapy	2740
2	Indapamide/therapeutic use OR Indapamide/toxicity OR Hydrochlorothiazide/therapeutic use OR Hydrochlorothiazide/toxicity OR Spironolactone/therapeutic use OR Spironolactone/toxicity OR Triamterene/therapeutic use OR Triamterene/toxicity OR Amiloride/therapeutic use OR Amiloride/toxicity OR Furosemide/therapeutic use OR Furosemide/toxicity OR Bumetanide/therapeutic use OR Bumetanide/toxicity OR Torsemide/therapeutic use OR Chlorothiazide/therapeutic use OR Chlorothiazide/toxicity OR Methyclothiazide/therapeutic use OR Methyclothiazide/toxicity OR Chlorthalidone/therapeutic use OR Chlorthalidone/toxicity OR Metolazone/therapeutic use OR Eplerenone/therapeutic use) OR Ethacrynic Acid/therapeutic use OR Ethacrynic Acid/toxicity OR Hydroflumethiazide/therapeutic use OR Hydroflumethiazide/toxicity	545
3	#1 AND #2	321

Appendix 5: Key Inclusion Criteria

Population	**Adults and pediatrics**
Intervention	Diuretic therapy
Comparator	Active control or placebo
Outcomes	Mortality, composite cardiovascular mortality, hospitalizations, blood pressure, safety outcomes (e.g. hyperkalemia, glucose intolerance)
Timing	N/A
Setting	Outpatient