



Department of Vermont Health Access

Therapeutic Class Review β-Adrenergic Blocking Agent - Diuretic Combination Products

Overview/Summary

The β-adrenergic blocking agent (β-blocker)/diuretic combination products contain two classes of medications that are well established in the management of hypertension; β-blockers and thiazide and related diuretics. Specifically, the β-blockers are a class of medications that can be further categorized by their pharmacologic and pharmacokinetic properties. The β-blockers differ in their adrenergic-receptor blocking, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.¹⁻⁶ Thiazide-type diuretics primarily inhibit sodium transport in the distal tubule but also may have a potential effect in the cortical collecting tubule, and are effective in the management of uncomplicated hypertension.⁷

Of the β-blockers contained within the combination products, all are available generically as single-entity agents, while chlorthalidone and hydrochlorothiazide are the only thiazide and related diuretics available generically as single-entity agents. Bendroflumethiazide is no longer available within the United States as a single-entity agent. All of the combination products are Food and Drug Administration approved for the treatment of hypertension. With the exception of Ziac[®] (bisoprolol/ hydrochlorothiazide), all of the combination products have specific wording within the respective package labeling stating that the product is not approved for initial therapy.¹⁻⁵ All of the β-blocker/diuretic combination products are available generically.

For the management of hypertension, a large number of drugs are currently available and most patients will require more than one drug to be adequately controlled. Of the various diuretic medication classes available for the management of hypertension, the thiazide and related diuretics have the most supporting evidence and are recommended as initial therapy. There has been extensive experience with β-blockers in clinical practice, and clinical trials do not consistently demonstrate a clinical advantage of one agent over another for the management of hypertension. In general, treatment guidelines also do not recommend the use of one β-blocker over the other, as recommendations regarding the use of these agents are made for the class as a whole.⁸⁻¹² Little guidance on the use of fixed dose combination products are available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to favor compliance. With regards to the β-blocker/diuretic combination products, these agents should be avoided unless required for other reasons.^{10,11}

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Atenolol/chlorthalidone (Tenoretic ^{®*})	β-adrenergic blocking agent – diuretic combination products	✓
Bisoprolol/hydrochlorothiazide (Ziac ^{®*})	β-adrenergic blocking agent – diuretic combination products	✓
Metoprolol/hydrochlorothiazide (Lopressor HCT ^{®*})	β-adrenergic blocking agent – diuretic combination products	✓
Nadolol/bendroflumethiazide (Corzide ^{®*})	β-adrenergic blocking agent – diuretic combination products	✓
Propranolol/hydrochlorothiazide	β-adrenergic blocking agent – diuretic combination products	✓

*Generic available in at least one dosage form and/or strength.

There are at least three distinct types of β receptors distributed throughout the body: β_1 , β_2 and β_3 . The β_1 receptors are located predominantly in the heart and kidney; therefore, β -adrenergic blocking agents (β -blockers) that have a greater affinity to β_1 receptors are considered to be cardioselective. The cardioselectivity of the β -blockers is highlighted in Table 2. Cardioselective agents within the class may be safer for use in patients with certain concomitant diagnoses. Because the β_2 receptors mediate vasoconstriction and bronchospasm, cardioselective β -blockers may be preferred in patients with asthma, chronic obstructive pulmonary disease and peripheral vascular disease because less inhibition of β_2 receptors is produced. Of note, cardioselectivity of β -blockers is dose dependent; therefore, β_2 blockade can occur at higher doses with certain agents.¹⁻⁶

Table 2. Selected Pharmacologic Properties of β -Adrenergic Blocking Agent – Diuretic Combination Products¹⁻⁵

Generic Name	Adrenergic-Receptor Blocking Activity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity
Atenolol	β_1^*	✓ †	✓ (weak)
Bisoprolol	β_1^*	✓ (weak)	✓ (weak)
Metoprolol	β_1^*	- †	-
Nadolol	β_1, β_2	-	-
Propranolol	β_1, β_2	✓ †	-

*Inhibits β_2 receptors (bronchial and vascular) at higher doses.

†Detectable only at doses much greater than required for β blockade.

Indications

Table 3. Food and Drug Administration Approved Indications¹⁻⁵

Generic Name	Hypertension
Atenolol/chlorthalidone	✓ *†
Bisoprolol/HCTZ	✓
Metoprolol/HCTZ	✓ *
Nadolol/bendroflumethiazide	✓ *†
Propranolol/HCTZ	✓ *†

HCTZ=hydrochlorothiazide

*This fixed dose combination drug is not indicated for initial therapy of hypertension.

†If the fixed dose combination represents the dose appropriate to the individual patient's needs, it may be more convenient than the separate components.

Pharmacokinetics

The pharmacokinetic parameters of the individual drug components of the β -adrenergic blocking agent (β -blocker)/diuretic combination products are summarized in Table 4.

Table 4. Pharmacokinetics⁶

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
β-blockers				
Atenolol	46 to 60	40 to 50	None	6 to 7
Bisoprolol	82 to 94	50 to 60	None	10.0 to 12.4
Metoprolol	50	95	None	3 to 7
Nadolol	20 to 40	24.6	None	20 to 24
Propranolol	30 to 70	<1	4-hydroxypropranolol	3 to 4
Diuretics				
Bendroflumethiazide	Not reported	Not reported	Not reported	Not reported
Chlorthalidone	65	50 to 74	None	40 to 89
Hydrochlorothiazide	60 to 80	50 to 70	Unknown	10 to 12

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the β -adrenergic blocking agent (β -blocker)/diuretic combination products for the treatment of hypertension are outlined in Table 5. In general, the trials compare the combination product to placebo, other antihypertensive medications or one or two of the individual drug components of the combination product. Results demonstrate that all combination products are “superior” to placebo and that additional blood pressure lowering is achieved when compared to one of the individual drug components administered as monotherapy. There are no trials to demonstrate differences in clinical outcomes when the two individual drug components are administered concurrently compared to the combination product.¹³⁻²⁵

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Lewin et al (abstract)¹³</p> <p>Bisoprolol/HCTZ 5/6.25 mg/day</p> <p>vs</p> <p>placebo</p> <p>All patients entered a run in placebo phase.</p>	<p>MC, PC</p> <p>Adult patients with stable mild to moderate essential HTN (sitting DBP 95 to 114 mm Hg)</p>	<p>N=36</p> <p>4 weeks</p>	<p>Primary: Changes in 24-hour ambulatory daytime and nighttime BP</p> <p>Secondary: Not reported</p>	<p>Primary: There were significant reductions in BP and pulse ($P<0.01$) at weeks two and four of treatment.</p> <p>There were significant reductions ($P<0.01$) in 24 hour SBP and DBP, daytime and nighttime BP, compared to the end of the placebo phase. There was a reduction in systolic and diastolic load also ($P<0.01$).</p> <p>Combination therapy was well tolerated, and the scores from the overall QOL questionnaire indicated an improvement with combination therapy ($P=0.02$).</p> <p>Secondary: Not reported</p>
<p>de Leeuw et al¹⁴</p> <p>Verapamil SR/trandolapril 180/2 mg/day, atenolol/chlorthalidone 100/25 mg/day or lisinopril/HCTZ 20/12.5 mg/day</p> <p>vs</p> <p>placebo</p> <p>All patients entered a SB, placebo 4 week run in period.</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 70 years of age with essential HTN (WHO I or II) newly or unsuccessfully treated, with supine DBP 101 to 114 mm Hg in week 4 of the run in period</p>	<p>N=205</p> <p>12 weeks</p>	<p>Primary: Changes in supine BP, standing BP response rates, normalization rates</p> <p>Secondary: Not reported</p>	<p>Primary: Each of the three treatments was significantly more effective than placebo in reducing seated DBP. Changes in DBP were as follows: verapamil SR/trandolapril, -13 (95% CI, -16 to -9); atenolol/chlorthalidone, -13 (95% CI, -16 to -9); lisinopril/HCTZ, -12 (95% CI, -15 to -9) and placebo, -3 (95% CI, -7 to 0) ($P=0.0001$ for all vs placebo), but there was not a significance among the treatments (P values were not reported).</p> <p>Each of the three treatments was significantly more effective than placebo in reducing seated SBP. Changes in SBP were as follows: verapamil SR/trandolapril, -27 (95% CI, -33 to -21); atenolol/chlorthalidone, -28 (95% CI, -34 to -22); lisinopril/HCTZ, -23 (95% CI, -29 to -17) and placebo, -3 (95% CI, -9 to 3) ($P=0.0001$ for all vs placebo), but there was not a significance among the treatments (P values were not reported).</p> <p>Effects on standing BP demonstrated similar results as the effects on sitting BP (P values not reported).</p> <p>Normalization of DBP (<90 mm Hg), corrected for placebo, were significantly higher with all treatments compared to placebo (verapamil SR/trandolapril, 33% [95% CI, 16 to 50; $P<0.0005$]; atenolol/chlorthalidone, 31% [95% CI, 14 to 48; $P<0.002$] and lisinopril/HCTZ, 25% [95% CI, 9 to 42; $P<0.005$]).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Response rates (normalization of DBP or a reduction in DBP >10 mm Hg), corrected for placebo, were significantly higher with all treatments compared to placebo (verapamil SR/trandolapril, 40% [95% CI, 22 to 58; $P<0.0001$], atenolol/chlorthalidone, 44% [95% CI, 27 to 61; $P<0.0001$] and lisinopril/HCTZ, 37% [95% CI, 19 to 55; $P<0.0002$]).</p> <p>Secondary: Not reported</p>
<p>Fogari et al¹⁵</p> <p>Weeks 1 to 4: Atenolol 50 mg Daily</p> <p>vs</p> <p>chlorthalidone 12.5 mg Daily</p> <p>Weeks 5 to trial end: atenolol/chlorthalidone 50/2.5 mg Daily</p> <p>All patients entered a 4 week run in period during which the patients took their previous antihypertensive treatment.</p>	<p>RCT, SB</p> <p>Patients 61 to 80 years of age inadequately controlled (SBP >170 mm Hg and/or DBP >100 mm Hg) on anti-hypertensive medications</p>	<p>N=38</p> <p>6 months</p>	<p>Primary: Changes in BP</p> <p>Secondary: Not reported</p>	<p>Primary: After the first four weeks, atenolol significantly reduced BP (177.5 to 161.1 mm Hg) compared to baseline, but chlorthalidone did not (176.6 to 179.1 mm Hg) (P values not reported).</p> <p>Atenolol/chlorthalidone significantly reduced mean standing SBP and DBP, supine SBP and DBP and supine and standing heart rate compared to previous therapies ($P<0.001$ for all).</p> <p>Atenolol/chlorthalidone significantly reduced mean standing SBP and DBP, supine SBP and DBP and supine and standing heart rate compared to either monotherapy ($P<0.001$ or $P<0.01$ for all).</p> <p>Mean BP reduction achieved with atenolol/chlorthalidone was 30/15 mm Hg in the standing position ($P<0.001$).</p> <p>Serum potassium rose significantly with atenolol/chlorthalidone (4.45 mEq/L) compared to chlorthalidone (4.01 mEq/L) (difference of 0.44 ± 0.10; $P<0.001$).</p> <p>Secondary: Not reported</p>
<p>Leonetti et al¹⁶</p> <p>Atenolol 50 mg Daily</p> <p>vs</p> <p>atenolol 100 mg Daily</p>	<p>DB, RCT</p> <p>Patients 24 to 68 years of age with mild to moderate HTN (WHO I or II), with supine</p>	<p>N=28</p> <p>16 weeks</p>	<p>Primary: Changes in BP</p> <p>Secondary: Not reported</p>	<p>Primary: Mean supine BP was $165\pm12/102\pm8$ mm Hg with placebo. Mean supine BP was significantly reduced with all treatments compared to placebo (atenolol 50 mg, $153\pm18/93\pm9$ mm Hg; atenolol 100 mg, $155\pm22/91\pm8$ mm Hg, chlorthalidone, $148\pm17/93\pm11$ mm Hg and atenolol/chlorthalidone, $144\pm16/89\pm6$ mm Hg). All of the changes in BP were significant compared to placebo ($P<0.01$).</p> <p>Supine SBP was lower with atenolol/chlorthalidone compared to atenolol 100 mg</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>chlorthalidone 12.5 mg Daily</p> <p>vs</p> <p>atenolol/chlorthalidone 50/12.5 mg Daily</p> <p>All patients entered a 4 week placebo washout period.</p>	<p>DBP \geq95 mm Hg at the end of the 4 week washout period</p>			<p>($P < 0.05$).</p> <p>Upright SBP was lower with atenolol/chlorthalidone compared to atenolol 50 mg ($P < 0.05$) and 100 mg ($P < 0.05$).</p> <p>Mean supine heart rate was 77 ± 7 bpm after placebo, which decreased to 69 ± 10 bpm ($P < 0.01$) with atenolol 50 mg, to 67 ± 6 bpm ($P < 0.01$) with atenolol 100 mg, and to 77 ± 10 bpm (P value not significant) with chlorthalidone.</p> <p>Chlorthalidone demonstrated a significant reduction in serum potassium levels compared to placebo (3.88 vs 4.09 mEq/L; $P < 0.05$), and no change was observed when atenolol/chlorthalidone was compared to placebo (3.98 vs 4.09; P value not significant).</p> <p>Chlorthalidone and atenolol/chlorthalidone demonstrated significant increases in serum uric acid levels compared to placebo (4.90 ± 1.52 and 5.07 ± 1.33 vs 4.24 ± 1.12 mg/dL; $P < 0.05$ for both).</p> <p>All treatments were well tolerated. Some adverse events reported included dyspnea, precordial discomfort and cold extremities.</p> <p>Secondary: Not reported</p>
<p>Nissinen et al¹⁷</p> <p>Atenolol 100 mg Daily plus chlorthalidone 25 mg Daily in the morning</p> <p>vs</p> <p>atenolol/chlorthalidone 100/25 mg Daily in the morning</p> <p>vs</p>	<p>DB, RCT</p> <p>Patients with newly diagnosed mild to moderate HTN (supine DBP 100 mm Hg on ≥ 3 occasions)</p>	<p>N=23</p> <p>16 weeks</p>	<p>Primary: Changes in BP and heart rate</p> <p>Secondary: Not reported</p>	<p>Primary: Each of the combination therapies significantly reduced standing, supine and post-exercise BP compared to placebo at two and four weeks ($P < 0.001$, $P < 0.01$ and $P < 0.05$). There was not a significant difference between the two combination therapies (P value not significant).</p> <p>Each of the combination therapies significantly reduced standing, supine and post-exercise heart rate compared to placebo at two and four weeks ($P < 0.001$, $P < 0.01$ and $P < 0.05$). There was not a significant difference between the two combination therapies (P value not significant).</p> <p>Side effects did not differ between the two combination therapies compared to placebo in terms of frequency or severity. Reported side effects included dizziness, headache and tiredness (P values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>All patients entered a 4 week placebo run in period.</p>				<p>Secondary: Not reported</p>
<p>Frishman et al¹⁸</p> <p>Bisoprolol 2, 5, 10 or 40 mg Daily</p> <p>vs</p> <p>HCTZ 6.25 or 25 mg Daily</p> <p>vs</p> <p>bisoprolol plus HCTZ, all possible combinations</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥21 years of age with mild to moderate essential HTN, whose weight was 35% of the ideal for height and frame and mean sitting DBP was stable and between 95 to 115 mm Hg</p>	<p>N=512</p> <p>12 weeks</p>	<p>Primary: Changes in DBP and SBP</p> <p>Secondary: Not reported</p>	<p>Primary: All doses of bisoprolol, HCTZ and combination therapy significantly reduced sitting DBP from baseline ($P<0.01$).</p> <p>The reduction in BP was significantly greater as the doses of bisoprolol, HCTZ and combination therapy were increased ($P<0.05$).</p> <p>Combination therapy significantly reduced sitting DBP compared to either monotherapy ($P<0.01$).</p> <p>With higher doses of HCTZ, there was a significantly higher incidence of hypokalemia (potassium <3.5 mmol/L) ($P<0.01$). Incidence of hyperuricemia also significantly increased with the increase in HCTZ dose ($P<0.01$). Adverse events associated with hypokalemia and hyperuricemia were not reported.</p> <p>As the dose of bisoprolol was increased, the frequency and severity of adverse events reported significantly increased ($P<0.05$). Adverse events reported included asthenia, diarrhea, dyspepsia and somnolence, but severity of effects was not reported.</p> <p>Secondary: Not reported</p>
<p>Frishman et al¹⁹</p> <p>Bisoprolol 5 mg Daily</p> <p>vs</p> <p>HCTZ 25 mg Daily</p> <p>vs</p> <p>bisoprolol/HCTZ 5/6.25 mg</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥21 years of age with mild to moderate (stage II or II) systemic HTN, whose body weight was not</p>	<p>N=547</p> <p>10 weeks</p>	<p>Primary: Changes in BP, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: All treatments significantly reduced sitting DBP and SBP from baseline compared to placebo ($P<0.01$).</p> <p>Addition of HCTZ 6.25 mg contributed significantly to the BP lowering effects of bisoprolol 5 mg (P values not reported).</p> <p>Bisoprolol/HCTZ 5/6.25 mg produced a significantly greater reduction in mean sitting DBP from baseline (-12.6 ± 0.5 mm Hg) compared to bisoprolol 5 mg (-10.5 ± 0.5 mm Hg; $P=0.02$) and HCTZ 25 mg (-8.5 ± 0.5 mm Hg; $P<0.01$). Bisoprolol 5 mg was significantly better at reducing DBP compared to HCTZ 25 mg</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Daily vs placebo (received during run in period)</p> <p>All patients entered a 4 to 6 week placebo run in period.</p>	<p>>10% below or 35% above the ideal weight for height and frame, off all anti-hypertensive medications before trial entry and sitting DBP 95 to 115 mm Hg on 3 consecutive weekly visits</p>			<p>($P=0.03$).</p> <p>Bisoprolol/HCTZ 5/6.25 mg produced a significantly greater reduction in mean sitting SBP from baseline (-15.8 mm Hg) compared to bisoprolol 5 mg (-10 mm Hg; $P<0.01$) and HCTZ 25 mg (-15.8 mm Hg; $P<0.01$). There was not a significant difference in mean reduction between bisoprolol 5 mg and HCTZ 25 mg (P value not reported).</p> <p>Bisoprolol/HCTZ 5/6.25 mg had a 73% response rate compared to 61% for bisoprolol and 47% for HCTZ (P values not reported).</p> <p>Bisoprolol/HCTZ 5/6.25 mg was found to be significantly more effective than bisoprolol 5 mg or HCTZ 25 mg in all subgroups of patients regardless of age, race, gender or smoking history ($P>0.05$ for all comparisons).</p> <p>Bisoprolol/HCTZ 5/6.25 mg did not have an increase in frequency or severity of adverse events. The adverse events were comparable to that with placebo, and frequency among the treatments was not significant (P values not reported). The most common adverse events reported were headache, dizziness, fatigue and cough. Severity of events was not reported.</p> <p>Significantly greater number patients receiving HCTZ 25 mg experienced hypokalemia (potassium <3.4 mEq/L) compared to patients receiving bisoprolol 5 mg (6.5 vs 0.7%; $P<0.01$), patients receiving bisoprolol/HCTZ (0.7%; $P<0.01$) and patients receiving placebo (0%; $P<0.01$).</p> <p>Hyperglycemia occurred in 7.4% of patients receiving HCTZ 25 mg, which was significantly higher than patients receiving placebo (5.2%; $P=0.03$). Also, the incidence of hyperuricemia (uric acid >7.5 mg/dL) was significantly higher with patients receiving HCTZ 25 mg (24.4%) compared to patients receiving placebo (2.7%; $P<0.01$).</p> <p>Secondary: Not reported</p>
<p>Dafgard et al²⁰</p> <p>Metoprolol/HCTZ 200/25 mg</p>	<p>DB, MC, RCT</p> <p>Patients with</p>	<p>N=31</p> <p>32 weeks</p>	<p>Primary: To compare the changes in BP,</p>	<p>Primary: After the eight week run in period with HCTZ 25 mg, the mean supine BP was significantly reduced from 183/110 to 172/103 mm Hg ($P<0.01/P<0.01$). The</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Daily in the morning</p> <p>or</p> <p>HCTZ 50 mg Daily in the morning</p> <p>vs</p> <p>HCTZ 25 mg Daily in the morning (received during run in period)</p> <p>There was a SB 8 week run in period where all patients received HCTZ 25 mg Daily in the morning.</p> <p>After the run in period, patients with BP $\geq 160/95$ mm Hg continued on to randomization.</p>	<p>essential HTN (WHO I or II) not adequately controlled ($\geq 160/95$ mm Hg) on HCTZ 25 mg/day</p>		<p>heart rate, adverse events, laboratory values</p> <p>Secondary: Not reported</p>	<p>increased dose of HCTZ 50 mg following the run in period did not further significantly reduce the mean BP (165/104 mm Hg; <i>P</i> values not reported).</p> <p>A small, but significant, reduction in supine heart rate was seen when the HCTZ dose was increased from 25 to 50 mg (82 down to 78 bpm; <i>P</i><0.05).</p> <p>After the 12 week DB treatment period, the mean supine BP was 153/98 mm Hg with HCTZ 50 mg. After the 12 week follow up period, there was not any additional decreases in BP (153/97 mm Hg; <i>P</i> value not reported).</p> <p>Metoprolol/HCTZ produced a significant reduction in supine BP after 12 weeks, from 172/105 mm Hg on HCTZ 25 mg to 154/97 mm Hg on combination therapy (<i>P</i><0.001/<i>P</i><0.01). Similar results were observed with reductions in standing BP, from 165/108 to 147/97 mm Hg (<i>P</i><0.001/<i>P</i><0.001).</p> <p>After the eight week run in period, the supine heart rate was 80 bpm which decreased to 64 bpm with metoprolol/HCTZ (<i>P</i><0.001). The values for standing heart rate demonstrated similar significant reductions (85 to 66 bpm; <i>P</i><0.001).</p> <p>After the additional 12 week follow up, metoprolol/HCTZ did not demonstrate a significant further reduction in heart rate or BP in any position (<i>P</i> values not reported).</p> <p>Both treatments were tolerated, and the most common adverse events reported included insomnia, headache, tiredness and shortness of breath. A majority of events were mild, few were moderate and none were severe (<i>P</i> values not reported).</p> <p>The only significant changes in laboratory values occurred with HCTZ 25 and 50 mg, where an increase in serum uric acid was observed from 0.30 to 0.34 and 0.35 mmol/L, respectively (<i>P</i><0.01 and <i>P</i><0.05).</p> <p>Secondary: Not reported</p>
<p>Liedholm et al²¹</p> <p>Group A:</p>	<p>RCT</p> <p>Patients 18 to</p>	<p>N=55</p> <p>12 weeks</p>	<p>Primary: Change in BP</p>	<p>Primary: In Group A, there was a significant decrease in supine BP from 189/112 to 172/105 mm Hg with metoprolol, and a further reduction to 148/92 mm Hg with</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Metoprolol/HCTZ 100/12.5 mg BID</p> <p>vs</p> <p>Group B: metoprolol/HCTZ 100/25 mg BID</p> <p>All patients entered a 6 week run in period with metoprolol 100 mg BID.</p> <p>Extended study: metoprolol/HCTZ 100/12.5 2 tablets Daily in the morning</p>	<p>72 years of age with mild to moderate essential HTN (WHO I or II)</p> <p>Extended study: OL</p> <p>Those patients who participated in the initial trial, had poor BP control on existing anti-hypertensive therapy and who were being treated with a β-blocker and additional diuretic therapy</p>	<p>Extended study: N=49</p> <p>6 months</p>	<p>Secondary: Not reported</p> <p>Extended study: Primary: Change in BP</p> <p>Secondary: Not reported</p>	<p>metoprolol/HCTZ ($P<0.001/P<0.001$).</p> <p>In Group B, there was a significant decrease in supine BP from 184/111 to 170/104 mm Hg with metoprolol, and a further reduction to 152/96 mm Hg with metoprolol/HCTZ after 12 weeks ($P<0.01/P<0.05$).</p> <p>Supine heart rate fell in Group A from 78 to 68 bpm with metoprolol ($P<0.001$), with no further heart rate reduction with metoprolol/HCTZ. In Group B, supine heart rate fell from 76 to 69 bpm ($P<0.05$), with no further heart rate reduction with metoprolol/HCTZ (P value not reported).</p> <p>In Group A, serum sodium fell from 143 to 140 mmol/L ($P<0.01$).</p> <p>In Group B, serum potassium fell with from 4.4 to 4.0 mmol/L ($P<0.001$).</p> <p>Secondary: Not reported</p> <p>Extended study: Primary: After six months of extended therapy, there was no further significant reductions in supine or standing BP (P values not reported), but there was a reduction in standing DBP from 97 to 95 mm Hg ($P<0.05$).</p> <p>Secondary: Not reported</p>
<p>Smilde²²</p> <p>Metoprolol 400 mg Daily in the morning for 5 weeks, followed by metoprolol/HCTZ 200/25 mg Daily in the morning for 5 weeks (Group 1)</p> <p>vs</p>	<p>DB, PG, RCT, XO</p> <p>Patients <65 years of age with essential HTN (supine DBP ≥ 95 mm Hg) not controlled on metoprolol 200</p>	<p>N=37</p> <p>15 weeks</p>	<p>Primary: Changes in DBP, SBP and heart rate</p> <p>Secondary: Not reported</p>	<p>Primary: Groups 1 and 2 achieved significant reductions in DBP ($P<0.01$) from baseline and there was no significant difference between the two groups (P value not reported).</p> <p>Metoprolol/HCTZ significantly reduced SBP from baseline ($P<0.05$ or $P<0.01$ depending on comparison).</p> <p>Group 2 significantly reduced heart rate at the end of the trial compared to baseline ($P<0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>metoprolol/HCTZ 200/25 mg Daily in the morning for 5 weeks, followed by metoprolol 400 mg Daily in the morning for 5 weeks (Group 2)</p> <p>All patients entered a run in period in which they received metoprolol 200 mg Daily for 5 weeks, and those with DBP ≥ 95 mm Hg after the 5 weeks entered randomization.</p>	<p>mg</p>			<p>Clinically relevant changes in laboratory parameters or mean body weight were not observed between the two groups (<i>P</i> values not reported).</p> <p>Secondary: Not reported</p>
<p>No authors listed²³ Veterans Administration Cooperative Study Group on Antihypertensive Agents</p> <p>Nadolol 80 mg Daily in the morning, titrated to 240 mg/day</p> <p>vs</p> <p>bendroflumethiazide* 5 to 10 mg Daily in the morning</p> <p>vs</p> <p>nadolol/bendroflumethiazide</p> <p>All patients entered a 2 to 8 week placebo run in period.</p>	<p>DB, RCT</p> <p>Men 20 to 69 years of age with pretreatment DBP of 95 to 114 mm Hg</p>	<p>N=365</p> <p>12 weeks</p>	<p>Primary: Changes in BP, change in BP among races, heart rate, adverse events, laboratory values</p> <p>Secondary: Not reported</p>	<p>Primary: A DBP <90 mm Hg was achieved in 49, 46 and 85% of patients receiving nadolol, bendroflumethiazide and nadolol/bendroflumethiazide. There was a significantly higher percentage of patients who achieved the DBP goal with nadolol/bendroflumethiazide compared to nadolol and bendroflumethiazide (<i>P</i><0.01 for both).</p> <p>The reduction in SBP was significantly greater with nadolol/bendroflumethiazide compared to nadolol and bendroflumethiazide (-25.3\pm1.4, -10.5\pm1.6 and -17.4\pm1.7 mm Hg, respectively; <i>P</i><0.001 for both), and bendroflumethiazide produced a significantly greater reduction compared to nadolol (<i>P</i><0.01).</p> <p>The reduction of DBP in white patients was significantly greater than the decrease in African American patients (15.6 vs 9.6 mm Hg, respectively; <i>P</i><0.001). In addition, 77% of white patients achieved DBP <90 mm Hg compared to 31% of African American patients (<i>P</i><0.001).</p> <p>Adverse events were infrequent. The most common were impotence, lethargy, weakness and postural dizziness, which occurred more often with bendroflumethiazide compared to nadolol (<i>P</i> values not reported).</p> <p>Significant reductions in average heart rate from baseline were observed with nadolol (16.1 bpm; <i>P</i><0.001) and with nadolol/bendroflumethiazide (15.8 bpm; <i>P</i><0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Serum potassium levels significantly decreased from baseline with bendroflumethiazide by 0.57 ± 0.06 mEq/L ($P < 0.001$) and with nadolol/bendroflumethiazide by 0.44 ± 0.05 mEq/L ($P < 0.001$).</p> <p>Serum uric acid levels significantly increased from baseline with bendroflumethiazide by 1.7 ± 0.2 mg/dL ($P < 0.001$) and by 0.4 ± 0.1 mg/dL ($P < 0.01$) with nadolol, and decreased with nadolol/bendroflumethiazide by -1.9 ± 0.1 mg/dL ($P < 0.001$).</p> <p>Fasting glucose levels significantly increased from baseline with bendroflumethiazide by 6.1 ± 2.1 mg/dL ($P < 0.001$) and with nadolol/bendroflumethiazide by 7.4 ± 1.1 mg/dL ($P < 0.001$).</p> <p>Cholesterol significantly increased from baseline with bendroflumethiazide by 11.5 ± 4.3 mg/dL ($P < 0.001$).</p> <p>TGs significantly increased from baseline with bendroflumethiazide by 34.6 ± 14.8 mg/dL ($P < 0.01$), with nadolol by 38.7 ± 13.2 mg/dL ($P < 0.01$) and with nadolol/bendroflumethiazide by 67.8 ± 11.9 mg/dL ($P < 0.001$).</p> <p>Secondary: Not reported</p>
<p>Stevens et al²⁴</p> <p>Dose-finding phase: Propranolol 80, 160, 240 or 320 mg/day in 2 divided doses</p> <p>vs</p> <p>propranolol/HCTZ 80/50, 160/50, 240/50 or 320/50 mg/day in 2 divided doses</p> <p>DB phase:</p>	<p>DB, PG, RCT</p> <p>Patients with mild to moderate essential HTN (DBP 100 to 125 mm Hg)</p>	<p>N=158</p> <p>25 weeks</p>	<p>Primary: Mean changes of SBP, DBP, heart rate, lab values</p> <p>Secondary: Not reported</p>	<p>Primary: After the 12 week dose finding-phase, 94% of patients had a decrease ≥ 10 mm Hg in DBP. The mean SBP/DBP reduced from $158.0(\pm 17.3)/105.6(\pm 6.0)$ to $131.5(\pm 14.4)/86.4(\pm 6.7)$ mm Hg ($P < 0.001$).</p> <p>After the 10 week portion of the study, there were significantly greater increases ($P < 0.05$) in mean SBP or DBP with propranolol and HCTZ compared to propranolol/HCTZ from the end of the dose-finding phase to the last four biweekly visits to the mean of those visits, and to the last visit. The mean increases of SBP and DBP at the endpoint where: propranolol, $10.2/6.3$ mm Hg; HCTZ, $13.1/9.3$ mm Hg and propranolol/HCTZ, $3.0/1.5$ mm Hg (P values not reported).</p> <p>There was a significant decrease in heart rate as the dose of propranolol was increased thought the trial ($P > 0.30$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
propranolol/HCTZ vs propranolol vs HCTZ All patients entered a 3 week placebo run in period.				The only lab value that showed a significant change was serum chloride. The percent of patients that fell outside of the normal range were as follows: propranolol, 6/36 (17%); HCTZ, 14/37 (38%) and propranolol/HCTZ, 4/28 (14%) ($P<0.05$). Secondary: Not reported
No authors listed ²⁵ VA Cooperative Study Group on Antihypertensive Agents Propaserp group: propranolol 40 to 160 mg TID (P) or propranolol 40 to 160 mg TID plus HCTZ 35 mg (P+T) or propranolol 40 to 160 mg TID plus hydralazine 35 mg (P+H) or propranolol 40 to 160 mg TID plus HCTZ 35 mg plus hydralazine 35 mg (P+T+H) vs	DB, RCT Males 18 to 59 years of age with DBP 90 to 114 mm Hg	N=450 18 months	Primary: Percent of patients who achieved a DBP <90 mm Hg at six months, heart rate, withdrawal rate Secondary: Not reported	Primary: At six months, significantly more patients receiving R+T (88%) attained a DBP <90 mm Hg and ≥ 5 mm Hg less than the initial BP compared to patients receiving P (52%; $P<0.01$) and P+H (72%; $P<0.05$). The other treatments (P+T [81%] and P+T+H [92%]) were not significantly different compared to R+T (P values not reported). The 12 and 18 month results do not have the statistical validity of the six month results due to the reduced sample size. The following percentage of patients attained DBP <90 and ≥ 5 mm Hg less than the initial pressure: R+T, 89.1 and 82.6%; P, 59.5 and 58.1%; P+T, 86.0 and 86.4%; P+H, 67.4 and 76.1% and P+T+H, 89.4 and 91.8% (P values not reported). There was not a significance difference in heart rate reductions at six and 18 months between the treatments (mean change in heart rate: R+T, 5.0 ± 1.3 and 5.0 ± 1.3 ; P, 9.1 ± 1.3 and 9.2 ± 1.8 ; P+T, 8.8 ± 1.2 and 6.3 ± 1.5 ; P+H, 8.9 ± 1.3 and 7.8 ± 1.5 and P+T+H, 5.9 ± 1.1 and 7.7 ± 1.5 [P values not reported]). Withdrawals for any reason were similar between the treatments and were not significant (R+T, 14 patients; P, 11; P+T, 12; P+H, 14 and P+T+H, 16 [P values not reported]). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hydrazide group: reserpine 35 mg plus HCTZ 35 mg (R+T)				

*Agent not available in the United States.

Drug regimen abbreviations: BID=twice a day, SR=sustained-release, TID=three times a day

Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial, SB=single-blind, XO=cross over

Miscellaneous abbreviations: BP=blood pressure, bpm=beats per minute, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, HTN=hypertension, QOL=quality of life, SBP=systolic blood pressure, TG=triglycerides, WHO=World Health Organization

Special Populations**Table 6. Special Populations**¹⁻⁵

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Atenolol/ chlorthalidone	No dosage adjustment is required in the elderly. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances 15 to 35 mL/minute, a daily dose of 50 mg and for creatinine clearances <15 mL/minute, a daily dose of 50 mg administered every other day are recommended.	No dosage adjustment required.	D	Yes (% not reported); use with caution.
Bisoprolol/ HCTZ	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Use with caution; use is contraindicated in patients with anuria.	Use with caution.	C	Yes (<2% of HCTZ); use with caution.
Metoprolol/ HCTZ	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes (% not reported); use with caution.
Nadolol/ bendro- flumethiazide	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances >50 mL/minute, administer every 24 hours; for creatinine	No dosage adjustment required.	C	Yes (% not reported); use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		clearances 31 to 50 mL/minute, administer every 24 to 36 hours; for creatinine clearances 10 to 30 mL/minute; administer every 24 to 48 hours and for creatinine clearances <10 mL/minute, administer every 40 to 60 hours.			
Propranolol/ HCTZ	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes (% not reported); use with caution.

HCTZ=hydrochlorothiazide

Adverse Drug Events

Table 7. Adverse Drug Events¹⁻⁵

Adverse Event	β-blockers					Diuretics		
	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Bendroflumethiazide	Chlorthalidone	HCTZ
Cardiovascular								
Angina	-	-	-	-	✓	-	-	-
Arrhythmia	-	<1	-	1	-	-	-	-
Arterial/vascular insufficiency/Raynaud's phenomenon	1 to 10	-	1	2	✓	-	-	-
Atrioventricular nodal disturbances	-	-	-	-	✓	-	-	-
Bradycardia	1 to 10	1	2 to 16	1 to 10*	6 [†]	-	-	-
Cardiac failure/arrest	-	-	-	1	-	-	-	-
Cardiogenic shock	-	-	✓	-	✓	-	-	-
Chest pain	1 to 10	1 to 2	-	<1	2 to 4	-	-	-
Cold extremities	1 to 10	<1	1	1 to 10	✓	-	-	-
Congestive heart failure	1 to 10	<1	1	1 to 10	✓	-	-	-
Edema	1 to 10	4	-	1 to 10	2	-	-	-
Flushing	-	<1	-	-	-	-	-	-
Heart block	1 to 10	-	5	-	-	-	-	-
Hypertension	-	-	-	-	-	-	-	-
Hypotension	1 to 10	<1	1 to 27	1	✓	-	-	1 to 10
Myocardial contractility impaired	-	-	-	-	✓	-	-	<1
Orthostatic hypotension	-	<1	-	<1	-	✓	✓	1 to 10
Palpitations	-	<1	1	1 to 10	-	-	-	-
Peripheral circulation reduced	-	-	-	1 to 10	-	-	-	-
Peripheral edema	-	3	1	-	-	-	-	-
Postural hypotension	2	-	-	-	-	-	-	-
Rhythm disturbance	-	<1	-	-	-	-	-	-
Shortness of breath	-	-	3	-	-	-	-	-
Syncope	-	<1	1	-	-	-	-	-
Thrombosis, mesenteric arterial	-	-	-	-	✓	-	-	-
Central Nervous System								
Abnormal dreams	-	-	-	-	3	-	-	-
Amnesia	-	-	-	-	✓	-	-	-
Anxiety	-	<1	✓	-	-	-	-	-
Catatonia	-	-	-	-	✓	-	-	-
Cerebral ischemia	-	-	-	-	-	-	-	-
Cerebral vascular accident	-	-	-	-	-	-	-	-

Adverse Event	β-blockers					Diuretics		
	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Bendroflumethiazide	Chlorthalidone	HCTZ
Change in behavior	-	-	-	1	-	-	-	-
Cognitive dysfunction	-	-	-	-	✓	-	-	-
Confusion	1 to 10	<1	≥1	<1	✓	-	-	-
Convulsions	-	-	-	-	-	-	-	-
Depression	1 to 10	<1	5	1 to 10	1 to 3	-	-	-
Disorientation	-	-	-	-	-	-	-	-
Dizziness	1 to 10	4	2 to 10	2	2 to 11	✓	✓	✓
Drowsiness	1	-	-	>10	2	-	-	-
Emotional lability	-	-	-	-	✓	-	-	-
Fatigue	1 to 10	6 to 8	1 to 10	2	3 to 17	-	-	-
Fever	-	-	-	-	-	✓	-	✓
Hallucinations	<1	<1	≥1	<1	✓	-	-	-
Headache	1 to 10	11	≥1	-	1 to 9	✓	✓	✓
Hyper/hypoesthesia	-	1 to 2	-	-	-	-	-	-
Insomnia	1 to 10	2 to 3	≥1	>10	3 to 8	-	-	-
Lethargy	1 to 10	-	-	-	4	-	-	-
Lightheadedness	1	-	-	-	✓	-	-	-
Malaise	-	<1	-	-	-	-	-	-
Memory loss	-	<1	≥1	-	-	-	-	-
Mental impairment	1 to 10	-	-	-	-	-	-	-
Nervousness	-	<1	✓	-	2	-	-	-
Nightmares/vivid dreams	1 to 10	-	≥1	-	✓	-	-	-
Paresthesia	-	<1	✓	-	-	✓	<1	✓
Psychosis	<1	-	-	-	✓	-	-	-
Sedation	-	-	-	1	-	-	-	-
Sleep disturbance	-	<1	≥1	-	-	-	-	-
Somnolence	-	<1	≥1	-	✓	-	-	-
Vertigo	2	<1	≥1	-	✓	✓	✓	✓
Dermatologic								
Acne	-	<1	-	-	-	-	-	-
Alopecia	<1	<1	✓	-	✓	-	-	<1
Cutaneous ulcers	-	-	-	-	✓	-	-	-
Dermatitis	-	<1	-	-	✓	-	-	-
Ecchymosis	-	-	-	-	-	✓	-	-
Eczema	-	<1	-	-	-	-	-	-
Eczematous eruptions	-	-	-	-	✓	-	-	-

Adverse Event	β-blockers					Diuretics		
	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Bendroflumethiazide	Chlorthalidone	HCTZ
Erythema multiforme	-	-	-	-	✓	-	-	✓
Exfoliative dermatitis	-	-	-	-	✓	✓	-	✓
Hyperkeratosis	-	-	-	-	✓	-	-	-
Nail changes	-	-	-	-	✓	-	-	-
Oculomuocutaneous reactions	-	-	-	-	✓	-	-	-
Photosensitivity	-	-	≥1	-	-	✓	1 to 10	1 to 10
Pruritus	-	<1	5	-	✓	✓	-	-
Pseudopemphigoid	-	-	-	-	-	-	-	-
Psoriasisiform rash	<1	<1	-	-	✓	-	-	-
Psoriasis (exacerbated)	-	<1	≥1	-	-	-	-	-
Purpura	-	<1	-	-	-	✓	<1	✓
Rash	-	<1	5	-	0 to 2	✓	<1	✓
Stevens-Johnson syndrome	-	-	-	-	✓	-	-	<1
Sweating, excessive	-	1	✓	-	2	-	-	-
Toxic epidermal necrolysis	-	-	-	-	✓	-	✓	<1
Ulcers	-	-	-	-	✓	-	-	-
Urticaria	-	-	✓	-	✓	✓	<1	✓
Endocrine and Metabolic								
Alkaline phosphatase increased	-	-	✓	-	✓	-	-	-
Diabetes (exacerbated)	-	-	≥1	-	-	-	-	-
Glycosuria	-	-	-	-	-	✓	✓	✓
Gout	-	<1	-	-	-	-	<1	-
Hypercalcemia	-	-	-	-	-	-	<1	<1
Hyperglycemia	-	<1	-	-	✓	-	<1	✓
Hyperkalemia	-	<1	-	-	✓	-	-	-
Hyperlipidemia	-	-	-	-	✓	-	-	-
Hypernatremia	-	-	-	-	-	-	<1	-
Hypertriglyceridemia	-	<1	-	-	-	-	-	-
Hyperuricemia	-	-	-	-	-	✓	✓	✓
Hypoglycemia	-	-	-	-	✓	✓	-	-
Hypoglycemia masked	-	-	-	-	-	-	-	-
Hypokalemia	-	-	-	-	-	-	1 to 10	1 to 10
Libido decreased	-	-	≥1	-	-	-	-	-
Gastrointestinal								
Abdominal bloating	-	-	-	-	-	✓	-	-
Abdominal discomfort	-	<1	-	1 to 10	-	-	-	-

Adverse Event	β-blockers					Diuretics		
	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Bendroflumethiazide	Chlorthalidone	HCTZ
Abdominal pain	-	-	1	-	1	-	-	-
Angioedema	-	<1	-	-	-	-	-	-
Anorexia	-	-	-	-	✓	✓	1 to 10	1 to 10
Constipation	1 to 10	<1	1	1 to 10	0 to 2	✓	✓	✓
Cramping	-	-	-	-	✓	✓	✓	✓
Diarrhea	1 to 10	3 to 4	5	1 to 10	2 to 7	✓	✓	✓
Dry mouth	-	1	1	-	-	-	-	-
Dyspepsia	-	<1	-	-	1 to 7	-	-	-
Epigastric distress	-	-	-	-	-	✓	1 to 10	1 to 10
Flatulence	-	-	1	-	4	-	-	-
Gastritis/gastric irritation	-	<1	-	-	-	-	✓	✓
Heartburn	-	-	1	-	-	-	-	-
Ischemic colitis	-	-	-	-	✓	-	-	-
Nausea	1 to 10	2	1	1 to 10	1 to 6	✓	-	✓
Peptic ulcer	-	<1	-	-	-	-	-	-
Retroperitoneal fibrosis	-	-	✓	-	-	-	-	-
Sialadenitis	-	-	-	-	-	✓	-	✓
Stomach discomfort	-	-	-	-	✓	-	-	-
Taste disorder	-	<1	✓	-	-	-	-	-
Vomiting	-	1 to 2	≥1	1 to 10	✓	✓	<1	✓
Weight gain	-	<1	✓	-	-	-	-	-
Genitourinary								
Cystitis	-	<1	-	-	-	-	-	-
Impotence	1 to 10	<1	✓	-	1	-	✓	✓
Libido decreased	-	<1	-	-	-	-	-	-
Micturition (frequency)	-	-	-	-	1	-	-	-
Oliguria	-	-	-	-	✓	-	-	-
Polyuria	-	<1	-	-	-	-	-	-
Proteinuria	-	-	-	-	✓	-	-	-
Sexual ability decreased	-	-	-	>10	-	-	-	-
Hematologic								
Agranulocytosis	-	-	✓	-	✓	✓	<1	<1
Anemia (aplastic/hemolytic)	-	-	-	-	-	✓	<1	<1
Claudication	-	<1	≥1	-	-	-	-	-
Leukopenia	-	<1	-	<1	-	✓	<1	<1
Purpura	-	-	-	-	✓	-	-	-

Adverse Event	β-blockers					Diuretics		
	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Bendroflumethiazide	Chlorthalidone	HCTZ
Thrombocytopenia	<1	<1	✓	<1	✓	✓	<1	<1
Hepatic								
Hepatic impairment	-	-	-	-	-	-	-	<1
Hepatitis	-	-	✓	-	-	✓	-	-
Increase liver enzymes	<1	-	-	-	-	-	-	-
Jaundice, cholestatic	-	-	-	-	-	✓	✓	✓
Transaminases increase	-	<1	✓	-	✓	-	-	-
Neuromuscular and Skeletal								
Arthralgia	-	1 to 10	✓	-	1	-	-	-
Arthritis	-	-	✓	-	-	-	-	-
Arthropathy	-	-	-	-	✓	-	-	-
Asthenia	-	≤2	-	-	-	-	-	-
Back pain	-	<1	-	-	-	-	-	-
Carpal tunnel syndrome	-	-	-	-	✓	-	-	-
Hyper/hypoesthesia	-	<1	-	-	-	-	-	-
Muscle cramps	-	<1	-	-	-	-	-	-
Muscle pain	-	<1	≥1	-	-	-	-	-
Muscle spasm	-	-	-	-	-	✓	✓	✓
Myalgia	-	-	-	-	1	-	-	-
Myasthenia gravis exacerbated	-	-	-	-	-	-	-	-
Myotonus	-	-	-	-	✓	-	-	-
Paresthesia	-	-	-	1	✓	-	-	-
Polyarthrits	-	-	-	-	✓	-	-	-
Restlessness	-	<1	-	-	-	✓	✓	✓
Toxic Myopathy	-	-	-	-	-	-	-	-
Tremor	-	<1	-	-	-	-	-	-
Twitching	-	<1	-	-	-	-	-	-
Weakness	-	2	-	-	1	✓	✓	✓
Ocular								
Abnormal/blurred vision	-	-	≥1	-	3	✓	-	✓
Corneal sensitivity decrease	-	-	-	-	-	-	-	-
Cystoid macular edema	-	-	-	-	-	-	-	-
Diplopia	-	-	-	-	-	-	-	-
Dry eyes	-	-	✓	-	✓	-	-	-
Eye irritation	-	-	-	-	-	-	-	-
Eye pain	-	<1	-	-	-	-	-	-

Adverse Event	β-blockers					Diuretics		
	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Bendroflumethiazide	Chlorthalidone	HCTZ
Hyperemia of conjunctiva	-	-	-	-	✓	-	-	-
Keratitis	-	-	-	-	-	-	-	-
Lacrimation, abnormal	-	<1	-	-	-	-	-	-
Mydriasis	-	-	-	-	✓	-	-	-
Ocular discharge	-	-	-	-	-	-	-	-
Ocular pain	-	-	-	-	-	-	-	-
Ptosis	-	-	-	-	-	-	-	-
Refractive changes	-	-	-	-	-	-	-	-
Visual acuity decreased	-	-	-	-	✓	-	-	-
Visual disturbances	-	<1	≥1	-	✓	-	-	-
Xanthopsia	-	-	-	-	-	✓	✓	✓
Otic								
Hearing decreased	-	<1	-	-	-	-	-	-
Tinnitus	-	<1	≥1	-	-	-	-	-
Renal								
Blood urea nitrogen increased	-	<1	-	-	✓	-	-	-
Creatinine increase	-	<1	-	-	-	-	-	-
Glomerulonephritis (allergic)	-	-	-	-	-	✓	-	-
Interstitial nephritis	-	-	-	-	✓	-	-	<1
Renal colic	-	<1	-	-	-	-	-	-
Renal failure/dysfunction	-	-	-	-	-	-	-	✓
Respiratory								
Bronchitis	-	<1	-	-	-	-	-	-
Bronchospasm	-	<1	1	1 to 10	✓	-	-	-
Cough	-	3	-	-	1	-	-	-
Dyspnea	<1	1 to 2	1 to 3	<1	1 to 6	-	-	-
Eosinophilic pneumonitis	-	-	-	-	-	-	-	<1
Laryngospasm	-	-	-	-	✓	-	-	-
Nasal congestion	-	-	-	-	-	-	-	-
Pharyngitis	-	2	-	-	✓	-	-	-
Pulmonary edema	-	-	-	-	✓	-	-	-
Rales	-	-	-	-	-	-	-	-
Respiratory failure/distress	-	-	-	-	✓	-	-	<1
Rhinitis	-	3 to 4	≥1	-	1	-	-	-
Sinusitis	-	2	-	-	-	-	-	-
Upper respiratory infection	-	5	-	-	5	-	-	-

Adverse Event	β-blockers					Diuretics		
	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Bendroflumethiazide	Chlorthalidone	HCTZ
Wheezing	<1	-	1	-	✓	-	-	-
Other								
Allergy/allergic reaction	-	-	-	-	-	-	-	<1
Anaphylactoid reaction	-	-	-	-	✓	✓	-	✓
Cholecystitis	-	-	-	-	-	-	<1	-
Cutaneous vasculitis	-	<1	-	-	-	-	<1	-
Electrolyte imbalance	-	-	-	-	-	-	✓	✓
Lactate dehydrogenase increased	-	-	✓	-	-	-	-	-
Lupus syndrome	<1	-	-	-	✓	-	-	-
Metabolic acidosis	-	-	-	-	-	✓	-	-
Necrotizing angiitis	-	-	-	-	-	✓	<1	✓
Pancreatitis	-	-	-	-	-	✓	<1	<1
Peyronie's disease	<1	<1	<1	-	✓	-	-	-
Positive antinuclear antibody test	<1	<1	-	-	-	-	-	-

*Defined as <40 beats per minute.

†Defined as <50 beats per minute.

- Event not reported or incidence <1%.

✓ Percent not specified.

Contraindications/Precautions

Atenolol is contraindicated in sinus bradycardia, sinus node dysfunction, heart block greater than first degree, cardiogenic shock, uncompensated cardiac failure, pulmonary edema and pregnancy.²⁶ Bisoprolol is contraindicated in cardiogenic shock, overt cardiac failure, marked sinus bradycardia and heart block greater than first degree.²⁷ Metoprolol is contraindicated in severe bradycardia, second and third degree heart block, cardiogenic shock, decompensated heart failure, sick sinus syndrome.²⁸ Nadolol is contraindicated in patients with bronchial asthma, sinus bradycardia, sinus node dysfunction, heart block greater than first degree, cardiogenic shock and uncompensated cardiac failure.²⁹ Propranolol is contraindicated in uncompensated congestive heart failure, cardiogenic shock, severe sinus bradycardia, heart block greater than first degree and severe hyperactive airway disease.³⁰

Chlorthalidone and hydrochlorothiazide are contraindicated in anuria and renal decompensation.³¹⁻³²

β adrenergic blocking agents (β -blockers) should be used with caution in patients with a history of severe anaphylaxis to allergens. Patients receiving β -blockers may become more sensitive to repeated challenges. Treatments of anaphylaxis (e.g., epinephrine) in patients receiving β -blockers may be ineffective or promote undesirable effects.²⁶⁻³⁰

In general, patients with bronchospastic disease should not receive β -blockers. Patients with bronchospastic disease who do not respond to or cannot tolerate other therapies, initial low doses of a β -blocker may be employed and used cautiously with close monitoring. Patients should have an inhaled β_2 -agonist immediately available.²⁶⁻³⁰

Consideration of pre-existing conditions such as sick sinus syndrome should take place before initiating β -blocker therapy.²⁶⁻³⁰

β -blockers with intrinsic sympathomimetic activity are likely to worsen survival in patients with heart failure and should be avoided. β -blockers shown to improve survival in clinical trials should be used for the treatment of heart failure.²⁶⁻³⁰

β -blocker therapy has been associated with induction or exacerbation of psoriasis, but cause and effect have not been firmly established.²⁶⁻³⁰

β -blockade may mask signs of hyperthyroidism (e.g., tachycardia). In addition, abrupt discontinuation may also induce a thyroid storm.²⁶⁻³⁰

β -blockers should be used with caution in patients with diabetes; therapy may potentiate hypoglycemia and/or mask signs and symptoms of the disease.²⁶⁻³⁰

β -blockers can also precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Again, caution should be exercised in these patients and they should be monitored closely for progression of arterial obstruction.²⁶⁻³⁰

β -blockers should be used with caution in patients with a history of psychiatric illness. Use of these agents may cause or exacerbate central nervous system depression. These agents may also precipitate symptoms of Raynaud's disease; therefore, caution should be exercised when the agent is used in patients with this condition.²⁶⁻³⁰

β -blockers should be used with caution in patients with myasthenia gravis.²⁶⁻³⁰

Symptomatic hypotension with or without syncope may occur in patients receiving metoprolol. Close monitoring is required, particularly with initial and increasing dosing. Patients should be advised to avoid driving or other hazardous tasks during initiation of therapy due to the risk of syncope.²⁶⁻³⁰

Use of the thiazide and related diuretics in patients with a sulfonamide allergy is not specifically contraindicated; however, a risk of cross-reaction exists in patients with allergy to sulfonamide-derived

drugs. Concurrent use should be avoided in patients with a previously severe reaction, and therapy should be discontinued if signs of hypersensitivity are noted.³¹⁻³²

Thiazide and related diuretics are associated with electrolyte disturbances including hypokalemia, hypochloremic alkalosis, hyponatremia and hypomagnesemia. Hypokalemia should be corrected before initiating thiazide and related diuretic therapy. These agents may also decrease renal calcium excretion; therefore, should be avoided in patients with hypercalcemia. Because of this reduced renal calcium excretion, pathologic changes in the parathyroid glands have also been observed with prolonged use of these agents.³¹⁻³²

Hypersensitivity reactions may occur in patients receiving thiazide and related diuretics.³¹⁻³²

Thiazide and related diuretics should be used with caution in patients with pre-diabetes and diabetes as a change in glucose control may be seen. In addition, these agents should be used in caution in patients with hepatic impairment, and electrolyte and acid/base imbalances should be avoided as they may lead to hepatic encephalopathy. Gout may be precipitated with a thiazide or related diuretic in patients with a history of gout, a familial predisposition to gout or chronic renal failure.³¹⁻³²

Increased cholesterol and triglyceride levels have been reported in patients receiving thiazide and related diuretics; therefore, caution should be used when these agents are administered to patients with moderate or high cholesterol concentrations.³¹⁻³²

Avoid use of thiazide and related diuretics in patients with severe renal disease, as these agents are ineffective and may precipitate azotemia.³¹⁻³²

The thiazide and related diuretics may cause systemic lupus erythematosus exacerbation or activation.³¹⁻³²

These contraindications/precautions have resulted in the assignment by the Food and Drug Administration of the Black Box Warning outlined below.

Black Box Warning for atenolol³³

WARNING
Advise patients with coronary artery disease who are being treated with atenolol against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in patients with angina following the abrupt discontinuation of therapy with β -blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other β -blockers, when discontinuation of atenolol is planned, observe the patient carefully and advise the patient to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that atenolol be promptly reinstated, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol therapy abruptly, even in patients treated only for hypertension.

Black Box Warning for Lopressor HCT[®] (metoprolol/hydrochlorothiazide)³³

WARNING
Following abrupt cessation of therapy with certain β -blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. Even in the absence of overt angina pectoris, when discontinuing therapy, metoprolol should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Black Box Warning for Corzide[®] (nadolol/bendroflumethiazide)⁴

WARNING
Hypersensitivity to catecholamines has been observed in patients withdrawn from β -blocker therapy;

WARNING

exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Black Box Warning for propranolol/hydrochlorothiazide⁵**WARNING**

There have been reports of exacerbation of angina and, in some cases, myocardial infarction following abrupt discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced and the patient should be carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

Drug Interactions**Table 8. Drug Interactions³³**

Drug(s)	Interaction	Mechanism
β-blockers (atenolol, bisoprolol, metoprolol, nadolol, propranolol)	Nonsteroidal anti-inflammatory drugs	The blood pressure lowering effects of β-blockers may be impaired.
β-blockers (atenolol, bisoprolol, metoprolol, nadolol, propranolol)	Prazosin	Postural hypotension may be increased.
β-blockers (atenolol, bisoprolol, metoprolol, nadolol, propranolol)	Salicylates	The blood pressure lowering effects and the beneficial effects of β-blockers on left ventricular ejection fraction in patients with chronic heart failure may be attenuated.
β-blockers (atenolol, metoprolol, nadolol, propranolol)	Clonidine	Potentially life-threatening increases in blood pressure may occur.
β-blockers (atenolol, metoprolol, nadolol, propranolol)	Lidocaine	Increased plasma concentrations of lidocaine, resulting in lidocaine toxicity.
β-blockers (atenolol, metoprolol, nadolol, propranolol)	Verapamil	The effects of β-blockers and verapamil may be increased.
β-blockers (atenolol, metoprolol, propranolol)	Diltiazem	The pharmacologic effects of certain β-blockers may be increased, resulting in symptomatic bradycardia.
β-blockers (atenolol, metoprolol, propranolol)	Quinidine	The effects of certain β-blockers may be increased in extensive metabolizers.
β-blockers (atenolol, bisoprolol, metoprolol)	Rifamycins	The pharmacologic effects of β-blockers may be reduced. A three to four washout period for the enzyme induction effect to disappear may be required.
β-blockers (metoprolol,	Barbiturates	Pharmacokinetic effects of certain β-blockers may be

Drug(s)	Interaction	Mechanism
propranolol)		reduced by concurrent treatment with barbiturates.
β-blockers (metoprolol, propranolol)	Cimetidine	Pharmacologic effects of β-blockers metabolized by the cytochrome P450 pathway may be increased.
β-blockers (metoprolol, propranolol)	Diphenhydramine	Increased plasma concentrations and cardiovascular effects of β-blockers.
β-blockers (metoprolol, propranolol)	Hydralazine	Serum levels of both drugs may be increased, resulting in enhanced pharmacologic effects.
β-blockers (metoprolol, propranolol)	Propafenone	The pharmacologic effects of β-blockers metabolized by the liver may be increased.
β-blockers (metoprolol, propranolol)	Thioamines	The pharmacokinetic profiles of certain β-blockers may be altered and pharmacologic effects may be increased.
β-blockers (nadolol, propranolol)	Sympathomimetics (β-agonists)	Pharmacologic effects of sympathomimetic β-agonists may be antagonized, possibly resulting in bronchospasm.
β-blockers (nadolol, propranolol)	Ergot derivatives	Concurrent administration may lead to peripheral ischemia manifested by cold extremities, resulting in possible peripheral gangrene.
β-blockers (nadolol, propranolol)	Insulin	Concurrent administration may produce prolonged hypoglycemia with masking of hypoglycemic symptoms.
β-blockers (atenolol)	Ampicillin	Antihypertensive and Antianginal effects of atenolol may be impaired.
β-blockers (propranolol)	Digoxin	Serum digoxin concentrations may be increased by coadministration of carvedilol. Synergistic bradycardia may occur in some patients.
β-blockers (propranolol)	Phenothiazines	Patients may experience increased effects from either or both drugs, including increased risk of life-threatening cardiac arrhythmias with thioridazine.
β-blockers (propranolol)	Rizatriptan	Rizatriptan plasma concentrations may be elevated, increasing the pharmacologic effects and adverse reactions.
Thiazide diuretics (chlorthalidone, bendroflumethiazide, HCTZ)	Cisapride	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Thiazide diuretics (chlorthalidone, bendroflumethiazide, HCTZ)	Diazoxide	Hyperglycemia, often with symptoms similar to frank diabetes, may occur.
Thiazide diuretics (chlorthalidone, bendroflumethiazide, HCTZ)	Digitalis glycosides	Thiazide-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias.
Thiazide diuretics (chlorthalidone, bendroflumethiazide, HCTZ)	Dofetilide	Hypokalemia may occur, increasing the risk of torsades de pointes.
Thiazide diuretics (chlorthalidone, bendroflumethiazide, HCTZ)	Lithium	Thiazide and related diuretics increase serum lithium levels, resulting in lithium toxicity.
Thiazide diuretics (chlorthalidone, bendroflumethiazide, HCTZ)	Loop diuretics	Both classes of medications have synergistic effects that may result in profound diuresis and serious electrolyte abnormalities.

Drug(s)	Interaction	Mechanism
Thiazide diuretics (chlorthalidone, bendroflumethiazide, HCTZ)	Sulfonylurea	Thiazide and related diuretics increase fasting blood glucose and may decrease sulfonylurea hypoglycemia. Hyponatremia may also occur.

HCTZ=hydrochlorothiazide

Dosage and Administration

Table 8. Dosing and Administration¹⁻⁵

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Atenolol/ chlorthalidone	<u>Hypertension:</u> Tablet: initial, 50/25 mg Daily; maintenance, if optimum response is not achieved, may increase to 100/25 mg Daily	Safety and efficacy in children have not been established.	Tablet: 50/25 mg 100/25 mg
Bisoprolol/ HCTZ	<u>Hypertension:</u> Tablet: initial, 2.5/6.25 mg Daily; maintenance: may titrate dose every 14 days up to 20/12.5 mg Daily; maximum, 20/12.5 mg Daily	Safety and efficacy in children have not been established.	Tablet: 2.5/6.25 mg 5/6.25 mg 10/6.25 mg
Metoprolol/ HCTZ	<u>Hypertension:</u> Tablet: initial, 100/25 mg/day in single or divided doses; maintenance, may titrate dose gradually until desired effect is achieved; usual doses of metoprolol and HCTZ are 100 to 450 mg/day and 12.5 to 50 mg/day; may be administered in single or divided doses	Safety and efficacy in children have not been established.	Tablet: 50/25 mg 100/25 mg 100/50 mg
Nadolol/ bendro- flumethiazide	<u>Hypertension:</u> Tablet: initial, 40/5 mg Daily; maintenance, if desired effect is not achieved, may increase dose to 80/5 mg Daily	Safety and efficacy in children have not been established.	Tablet: 40/5 mg 80/5 mg
Propranolol/ HCTZ	<u>Hypertension:</u> Tablet: initial, 40/25 mg BID; maintenance, may gradually increase dose until desired response is achieved up to 160 to 480 mg/day; maximum, 160 mg of propranolol is the maximum recommended dose for the combination product, since maximum dose of HCTZ will have been reached	Safety and efficacy in children have not been established.	Tablet: 40/25 mg 80/25 mg

BID=twice-daily, HCTZ=hydrochlorothiazide

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute: The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and	<ul style="list-style-type: none"> Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with another class (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], β-blockers, calcium channel blockers) demonstrated to be beneficial in randomized controlled outcome trials. Certain high-risk conditions are compelling reasons for initiating

Clinical Guideline	Recommendation
<p>Treatment of High Blood Pressure (JNC 7) (2004)⁸</p>	<p>therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs or calcium channel blockers. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications.</p> <ul style="list-style-type: none"> • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with two antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), post-myocardial infarction (β-blockers, ACE inhibitors and aldosterone antagonists), high coronary disease risk (diuretics, ACE inhibitors, β-blockers and calcium channel blockers), diabetes (diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers), chronic kidney disease (ACE inhibitors and ARBs) and recurrent stroke prevention (diuretics and ACE inhibitors). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting calcium channel blockers may also be used. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to microalbuminuria. • Patients with chronic kidney disease often require treatment with three or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs and β-blockers compared to calcium channel blockers and diuretics. The incidence of ACE-inhibitor-induced angioedema is two to four times higher in African Americans. • Calcium channel blockers may be useful in Raynaud’s syndrome and certain arrhythmias. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.

Clinical Guideline	Recommendation
<p>World Health Organization/ International Society of Hypertension: 2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)⁹</p>	<ul style="list-style-type: none"> • When used as monotherapy, a diuretic or a calcium channel blocker may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine calcium channel blockers), renal disease (ACE inhibitors and ARBs), post-myocardial infarction (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors and diuretics), left ventricular hypertrophy (ARBs) and cerebrovascular disease (diuretics and ACE inhibitors).
<p>European Society of Hypertension/European Society of Cardiology: 2007 Guidelines for the Management of Hypertension (2007)¹⁰, Reappraisal of Guidelines on Hypertension Management (2009)¹¹</p>	<ul style="list-style-type: none"> • In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which must include a search for subclinical organ damage. • In general, early introduction of blood pressure lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, is recommended. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs and calcium channel blockers), asymptomatic atherosclerosis (calcium channel blockers and ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers and ARBs), angina (calcium channel blockers and β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors and ARBs), permanent atrial fibrillation (β-blockers and nondihydropyridine calcium channel blockers), end stage renal disease/proteinuria (ACE inhibitors, ARBs and loop diuretics), metabolic syndrome (ACE inhibitors, ARBs and calcium channel blockers), diabetes (ACE inhibitors and ARBs), pregnancy (methyldopa, calcium channel blockers and β-blockers) and African American patients (calcium channel blockers and diuretics). • Available evidence justifies the use of aliskiren in hypertension, particularly in combination with other agents. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, consider medications which have different and complementary mechanisms of action, and that there is evidence that the antihypertensive effect of the combination is greater than that of either combination component and the combination is likely to be well tolerated. <ul style="list-style-type: none"> • Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a diuretic with an ACE inhibitor, ARB or calcium channel blocker and an ACE inhibitor with a calcium channel blocker.

Clinical Guideline	Recommendation
	<ul style="list-style-type: none"> • Avoid β-blocker/diuretic combination unless required for other reasons. • If triple therapy is needed, the most rational combination is a blocker of the rennin-angiotensin system, a calcium channel blocker and a diuretic at effective doses. • A β- or α-blocker may be included in a triple therapy approach depending on clinical circumstances. • Antihypertensive treatment is highly beneficial in elderly patients and treatment may be initiated with a thiazide diuretic, ACE inhibitor, calcium channel blocker, ARB or β-blocker. • Blood pressure lowering drugs should be continued or initiated in patients 80 years of age, starting with monotherapy and adding a second drug, if needed. The decision to treat should be made on an individual basis and patients should be carefully monitored. • Calcium channel blockers, ARBs and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. • Antihypertensive treatment should always be initiated in diabetic patients when blood pressure is 140/90 mm Hg or higher; however, there is evidence in favor of initiating treatment with high normal blood pressure. • The blood pressure goal of <130/80 mm Hg is not supported by outcome evidence from trials and is difficult for the majority of patients to achieve; therefore, its realistic to recommend only to pursue a sizeable blood pressure reduction without indicating a goal that is unproven. • In hypertensive diabetic patients, tight blood glucose control (glycosylated hemoglobin to 6.5%) is beneficial, particularly in combination with effective blood pressure control, on improving microvascular complications. Tight glucose control should not be pursued abruptly and patients should be monitored closely due to the increased risk of severe hypoglycemic episodes.
<p>National Institute for Health and Clinical Excellence/British Hypertension Society: Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)¹²</p>	<ul style="list-style-type: none"> • Initial therapy in patients ≥ 55 years of age should be a calcium channel blocker or a thiazide diuretic. • Initial therapy in patients <55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • If a second medication is required and initial therapy was with a calcium channel blocker or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a calcium channel blocker or a diuretic should be added. • If three medications are required, a combination of calcium channel blocker, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.

Conclusions

The β -adrenergic blocking agent (β -blocker)/diuretic combination products are all Food and Drug Administration approved for the treatment of hypertension and are all available generically.¹⁻⁵ These products contain a β -blocker and a thiazide and related diuretic. These two medication classes are well established in the management of hypertension.

The safety and efficacy of these combination products for the treatment of hypertension has been demonstrated in several clinical trials. Many of the trials compared a β -blocker/diuretic combination product to placebo, other antihypertensive medication, one of the drug components of the combination

product or both of the components given concurrently. In general, the combination product resulted in additional blood pressure lowering when compared to one of the drug components. There are currently no head-to-head trials comparing the various combination products or any trials to demonstrate differences in clinical outcomes when the drug components are administered as separate agents concurrently vs the combination product.¹³⁻²⁵

Many patients with hypertension may require more than one antihypertensive medication to achieve blood pressure goals. As mentioned previously both the β -blockers and thiazide and related diuretics are well established therapies in the management of hypertension, with the thiazide and related diuretics are typically recommended as initial therapy.⁸⁻¹² Little guidance on the use of fixed dose combination products are available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to favor compliance. With regards to the β -blocker/diuretic combination products, these agents should be avoided unless required for other reasons.^{10,11}

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Atenolol/HCT	58	112	53%	\$1,820.26	\$16.25
Bisoprolol/HCT	41	71	33%	\$1,778.88	\$25.05
Metoprolol/HCT	15	29	14%	\$2,281.96	\$78.69
Class Total:	----	212	100%	\$5,881.10	\$27.74

Recommendations

No changes to the Department of Vermont Health Access (DVHA) approval criteria for beta-adrenergic blocking agent/diuretic combination products (see below) are proposed. At this time, all available generic combination products, with the exception of propranolol/hydrochlorothiazide, are preferred agents.

Non-preferred drugs:

- The patient has had a documented side effect, allergy, or treatment failure to at least three preferred drugs. (If a medication has an AB rated generic, one trial must be the generic formulation.)

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