

MHA Clinical Spotlight: Bystolic®

Forest Labs has recently released its newest product, Bystolic® (nebivolol), a unique β -blocker indicated for the treatment of hypertension. Bystolic's mechanism of action includes both highly selective β_1 blockade and enhancement of endothelial mediated vasodilation. It promises clinical advantages over the other currently available β -blockers as it effectively lowers blood pressure yet has a low incidence of side effects common to other β -blockers such as fatigue, bradycardia, dyspnea, depression and erectile dysfunction. Studies have shown Bystolic® to be an effective antihypertensive in a wide patient population, including African Americans who have historically been resistant to β -blockers. The following are some important facts about Bystolic® which may be useful in your practice.

- Approximately 60% of patients studied showed a positive response (systolic blood pressure of <90mm Hg or decrease in systolic blood pressure of greater than 10mm Hg) or at doses of 5-10mg/day nebivolol.
- A head to head study comparing nebivolol with metoprolol immediate release showed a 79% normalization of blood pressure in the nebivolol group compared with 66% in the metoprolol group. The nebivolol group showed no increase in side effects reported from the initial placebo period, the metoprolol group showed a 15% increase in reported side effects.
- In pooled data from 3 clinical trials, only 2.8% of patients treated with nebivolol stopped treatment due to side effects compared with 2.2% with placebo. Headache, fatigue and dizziness were the most commonly reported adverse effects
- A study targeting the effectiveness of nebivolol in African-Americans showed a >50% response rate at all doses with adverse effects similar to placebo. The effectiveness of nebivolol compared with other β -blockers is most likely due to its enhancement of vasodilation therefore decreasing peripheral vascular resistance.
- A study assessing nebivolol as add-on therapy to existing anti-hypertensive regimens (ACE inhibitor, ARB and/or diuretic) showed significant additional reductions in blood pressure (-7.1mm Hg to -8.6mm Hg diastolic and -6.0 to -8.6mm Hg systolic)
- Nebivolol undergoes metabolism by CYP2D6. The manufacturer recommends caution in patients on medications that either inhibit or induce this enzyme. In particular, fluoxetine and cimetidine have led to increases in exposure to nebivolol. Coadministration of sildenafil and nebivolol decreased exposure to both drugs by about 20%.
- Recommended starting dose is 5mg once-a-day as monotherapy or in combination with other agents. Doses can be increased at two week intervals to a maximum of 40mg daily. β_1 selectivity is preserved in extensive metabolizers and at doses less than or equal to 10mg/day. At higher doses and in poor metabolizers, nebivolol can inhibit both β_1 and β_2 receptors. In patients with renal or hepatic impairment, the recommended starting dose is 2.5mg/day. No dosage adjustment is necessary in CYP2D6 poor metabolizers. Nebivolol can be given without regards to meals.

SOURCES

Bystolic Product Information

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Guidelines for Treating Hypertension

In 2003 the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure released its seventh set of guidelines for the treatment of hypertension (JNC-7). In mid-2007 the American Heart Association published its most recent statement regarding the treatment of hypertension, which is slightly more aggressive and does not favor one class for the initial treatment of uncomplicated hypertension. Both reports have lowered the goal blood pressure for control of hypertension to prevent heart disease. Following is a summary of the guidelines:

- Goal blood pressure should be <140/90 or <130/80 for patients with diabetes or chronic kidney disease. AHA recommendations also include recommending BP <130/80 for patients with known coronary artery disease, at high risk for coronary artery disease or with a Framingham Risk Score of >10%.
- Many patients will need 2 or more medications to meet goal. In general, patients with uncomplicated hypertension should have a regimen which includes a thiazide diuretic per JNC 7. AHA guidelines don't specify thiazide diuretics but recommend ACEI, ARB, CCB or thiazides as appropriate first line agents. AHA guidelines also don't recommend β -blockers as first line agents without a compelling indication (angina, post MI, heart failure).

JNC 7 Classification of Blood Pressure for adults ≥ 18 Years and Recommended Treatment

JNC 7 BLOOD PRESSURE CATEGORY	SBP (MM HG)	AND/OR	DBP (MM HG)	LIFESTYLE MODIFICATIONS	TREATMENT WITHOUT COMPELLING INDICATIONS	TREATMENT WITH COMPELLING INDICATIONS
Normal	<120	and	<80	Encouraged		
Prehypertension	120-139	or	80-89	Yes	No antihypertensive meds indicated	See medications for compelling indications
Hypertension: Stage 1	140-159	or	90-99	Yes	Thiazide-type diuretics; can consider ARB, β -blocker, CCB or combination	Begin with medications for compelling indication, use other antihypertensive drugs as needed
Hypertension: Stage 2	≥ 160	or	≥ 100	yes	2-drug combination for most cases, usually a thiazide diuretic and ACE inhibitor or ARB or β -blocker or CCB	Begin with medications for compelling indication, use other antihypertensive drugs as needed.

JNC 7 Compelling Indications for Specific Drug Classes

COMPELLING INDICATION	INITIAL THERAPY CHOICES
Heart Failure	diuretic, β -blocker, ACE inhibitor, ARB, aldosterone antagonist
Post MI	β -blocker, ACE inhibitor, aldosterone antagonist
High Cardiovascular Disease Risk	diuretic, β -blocker, ACE inhibitor, CCB
Diabetes	diuretic, β -blocker, ACE inhibitor, ARB, CCB
Chronic Kidney Disease	ACE inhibitor, ARB
Recurrent Stroke Prevention	Thiazide diuretic, ACE inhibitor

AHA Blood Pressure Goals and Treatments

INDICATION	GOAL BP	FIRST LINE AGENTS	SECOND LINE AGENTS	COMMENTS
Primary Prevention of Coronary Artery Disease	<140/90	ACEI, ARB, CCB, or thiazide diuretic (or combination)		Initiate therapy with 2 drugs for sbp>160, dbp>100
High CAD Risk	<130/80	ACEI, ARB, CCB or thiazide diuretic (or combination)		Initiate therapy with 2 drugs for sbp>160, dbp>100
Stable angina	<130/80	B-blocker plus ACEI or ARB	Diltiazem or verapamil if β -blocker contraindicated or not tolerated. Do not use with bradycardia or LVD Dihydropyridine CCB (ie amlodipine) may be added to β -blocker. May add thiazide diuretic	β -blockers are especially effective for symptom relief in pts with prior MI. ARBs and ACEIs are especially effective for pts with diabetes or left ventricular dysfunction
Unstable angina/NSTEMI STEMI	<130/80	B-blocker(if hemodynamically stable) PLUS ACE or ARB	Diltiazem or verapamil if β -blocker contraindicated or not tolerated. Do not use with bradycardia or LVD. Dihydropyridine CCB may be added to β -blocker.	CCBs do not reduce mortality and can increase mortality in depressed Left Ventricular Function.
Left Ventricular Dysfunction/Heart Failure	<130/80	B-blocker, plus ACEI or ARB plus thiazide or loop diuretic, aldosterone antagonist. Hydralazine/isosorbide effective in African Americans.		Avoid verapamil and diltiazem Loop diuretics are more effective than thiazides in severe heart failure.

SOURCES

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