LONG TERM SAFETY AND EFFICACY OF ALPHA BLOCKERS FOR LUTS/BPH: THE CARDIOLOGISTS PERSPECTIVE

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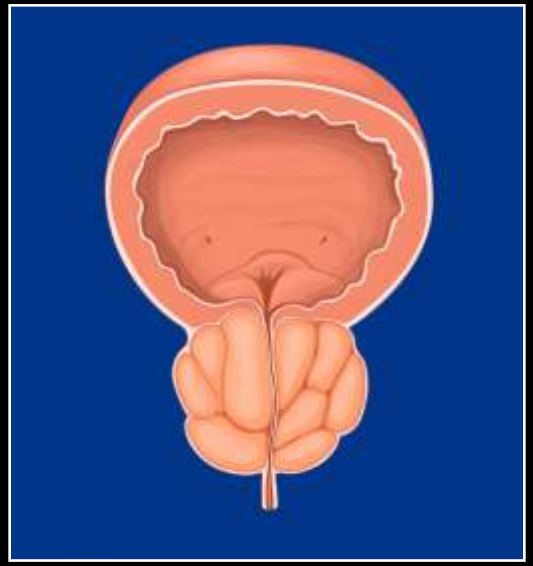
Introduction

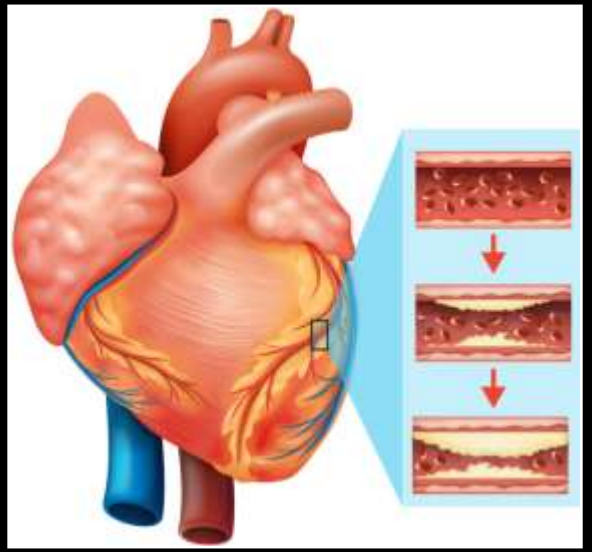
- Benign Prostatic Hyperplasia is a chronic condition that clinically manifests with LUTS (lower urinary tract symptoms).

- BPH causes bladder outlet obstruction by:
  - Spasm of the urethral muscles
  - Mechanical compression of the urethra due to enlarged prostate

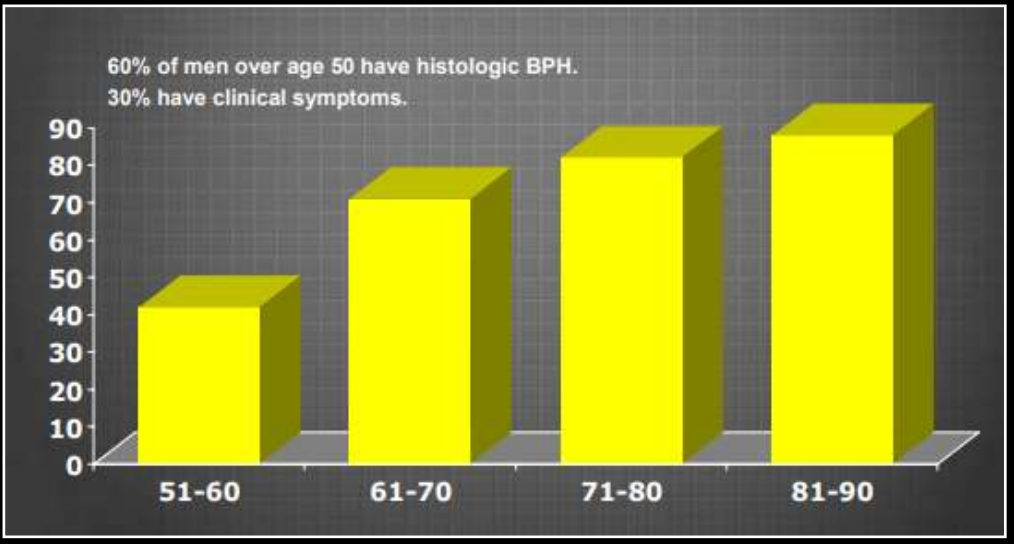
Age - A common factor for both the conditions

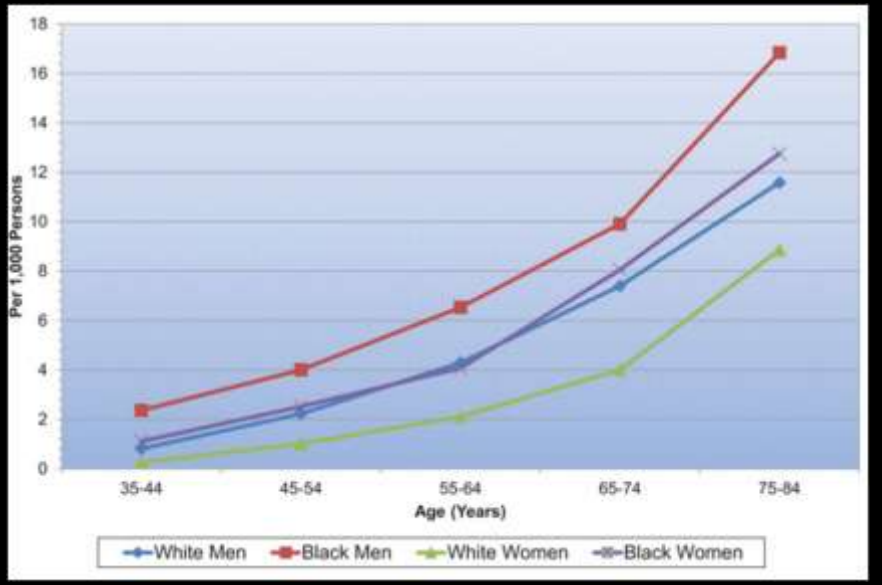


OLD MAN'S DISEASE



How Common is benign prostatic hyperplasia and Ischemic heart disease?





Berry et al. J Urol. 1984;132:474-479

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BPH and Heart Attack - Two sides of the same coin

Common Urological Problem

Common Cardiovascular Problem

A Positive Correlation between BPH and CAD

Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2017/420

Original Article

Correlation between Benign Prostatic Hyperplasia and Coronary Artery Disease

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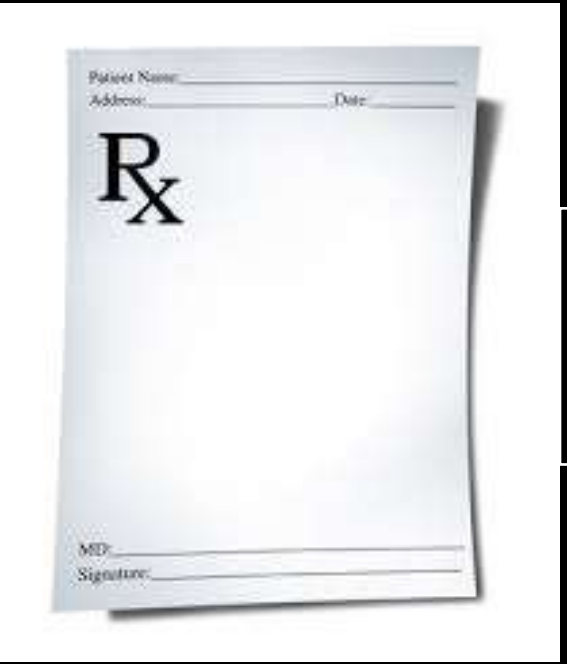
Materials and Methods: A total of 150,75 subjects with BPH (lower urinary tract symptoms with ultrasonography [USG] evidence/raised age-specific serum prostate-specific antigen [PSA]) and 75 subjects without BPH were included. PSA was measured by chemiluminescence method, prostate volume with transabdominal USG. CAD was diagnosed with the help of electrocardiogram, 2D-ECHO, Tread Mill Test (TMT), and documented history of angioplasty.

Results: The occurrence of CAD among 75 subjects with BPH (30.66%) was significantly higher than 75 subjects without BPH (12%) ($P < 0.05$) and even after excluding subjects with risk factor/factors (22.5% versus 7.4%: $P < 0.05$, respectively). Among subjects with CAD (32/150), occurrence of BPH was 27.81% more as compared to subjects without CAD (118/150). Mean serum PSA level and mean prostatic volume were also significantly higher in subjects with CAD as compared to subjects without CAD.

Conclusion: The occurrence of CAD was found to be significantly higher among subjects with BPH (even after excluding subjects with risk factors). Occurrence of BPH was also significantly higher among subjects with CAD along with mean serum PSA and mean prostatic volume. Thus, a significant correlation can exist between CAD and BPH.

Prescription of common medications for the treatment of both conditions



For IHDs

- **Statin**
- **Antiplatelet**
- **Antihypertensive**

For BPH

- **Alpha blockers**
- **5-alphareductase inhibitor**

Actions Of Catecholamines And Sympathomimetic Agents :

1) A peripheral excitatory action on certain types of smooth muscle, such as those in blood vessels supplying skin, kidney, and mucous membranes; and on gland cells, such as those in salivary and sweat glands.
2) A peripheral inhibitory action on certain other types of smooth muscle, such as those in the wall of the gut, in the bronchial tree, and in blood vessels supplying skeletal muscle.
3) A cardiac excitatory action that increases heart rate and force of contraction.
4) Metabolic actions, such as an increase in the rate of glycogenolysis in liver and muscle and liberation of free fatty acids from adipose tissue.
5) Endocrine actions, such as modulation (increasing or decreasing) of the secretion of insulin, renin, and pituitary hormones.
6) Actions in the central nervous system (CNS), such as respiratory stimulation, an increase in wakefulness and psychomotor activity, and a reduction in appetite.
7) Prejunctional actions that either inhibit or facilitate the release of neurotransmitters, the inhibitory action being physiologically more important.

Drug Effects and Indications: Alpha Blockers

- Cause both arterial and venous dilation, reducing peripheral vascular resistance and BP
- Used to treat hypertension
- Effect on receptors on prostate gland and bladder decreases resistance to urinary outflow, thus reducing urinary obstruction and relieving effects of benign prostatic hyperplasia (BPH)

ALLHAT

Background

- Randomized, double-blind, multicenter trial
- Determined whether fatal CHD or nonfatal MI was lower for high-risk hypertensives treated with amlodipine (CCB), lisinopril (ACEI), doxazosin (alpha blocker) vs chlorthalidone (diuretic)
- Atrial fibrillation (AF) is the most common serious arrhythmia affecting morbidity and mortality.

DOUGLAS S. PAULL, MD

Alpha-blockers and congestive heart failure: Early termination of an arm of the ALLHAT trial

■ ABSTRACT

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a large, randomized, double-blind study comparing four antihypertensive agents: chlorthalidone, diuretic; amlodipine; and lisinopril, angiotensin-converting enzyme (ACE) inhibitor; and doxazosin, alpha-blocker. Patients were 55 years or older and had hypertension plus at least one other risk factor for coronary heart disease. The trial's safety and monitoring board (SMB) recently found a higher incidence of congestive heart failure in patients receiving doxazosin than in those receiving chlorthalidone (8.7% vs 6.0%; relative risk, 1.79; 95% confidence interval, 1.63–1.96; $P < .001$).

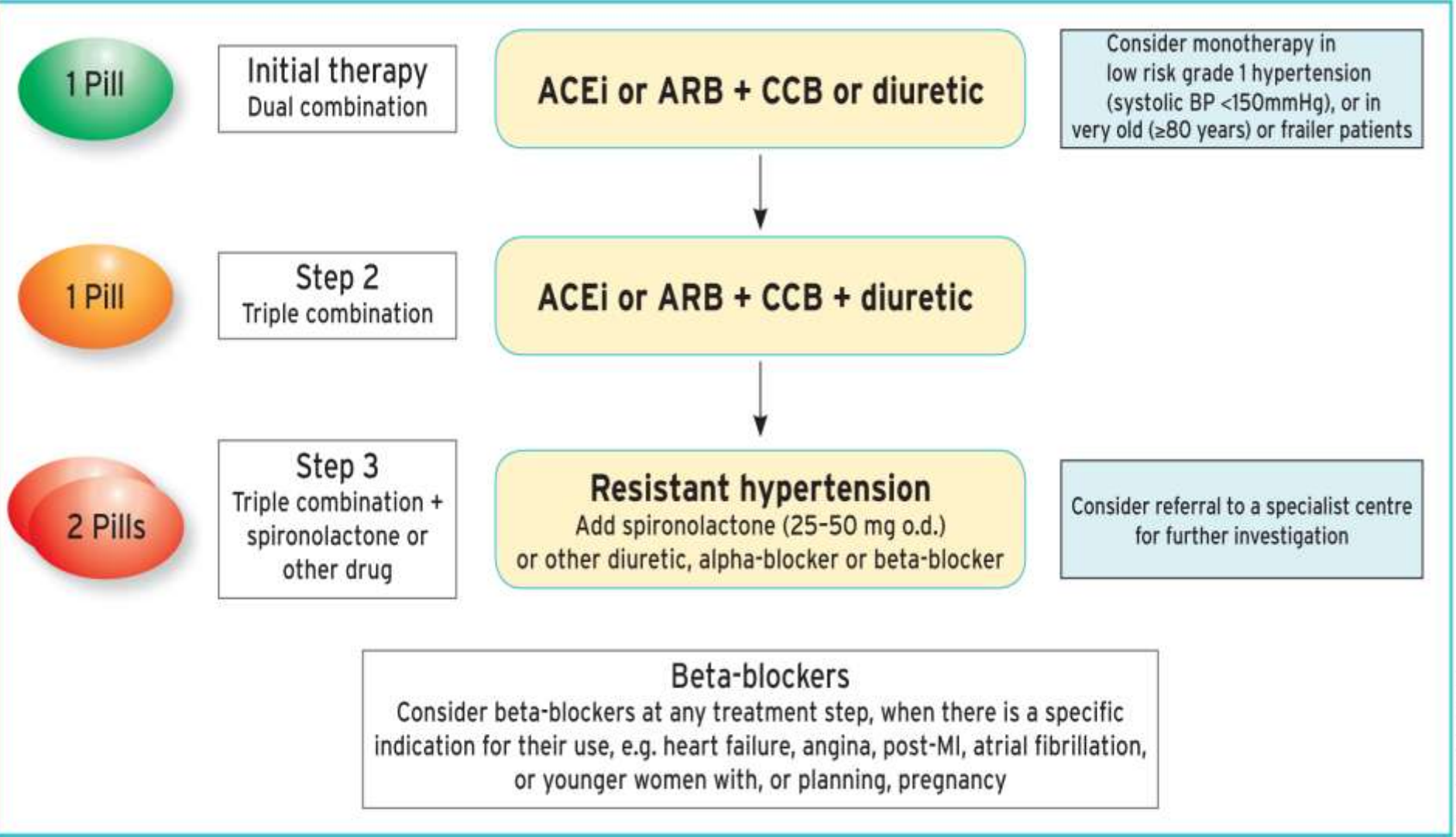
Current guidelines will need to be changed

■ WHAT IS THE BEST FIRST-LINE ANTIHYPERTENSIVE AGENT?

ALLHAT

Additional Comments

- ALLHAT does not allow an assessment of the effect of doxazosin compared with placebo on the incidence of CVD.
- The use of doxazosin as a step-up drug for treating hypertension was not tested in this trial.
- These findings are likely to apply to all alpha-blockers.


1 Pill
Initial therapy
Dual combination
ACEi or ARB + CCB or diuretic
Consider monotherapy in low risk grade 1 hypertension (systolic BP <150mmHg), or in very old (≥80 years) or frailer patients
1 Pill
Step 2
Triple combination
ACEi or ARB + CCB + diuretic
2 Pills
Step 3
Triple combination + spironolactone or other drug
Resistant hypertension
Add spironolactone (25–50 mg o.d.) or other diuretic, alpha-blocker or beta-blocker
Consider referral to a specialist centre for further investigation
Beta-blockers
Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning, pregnancy
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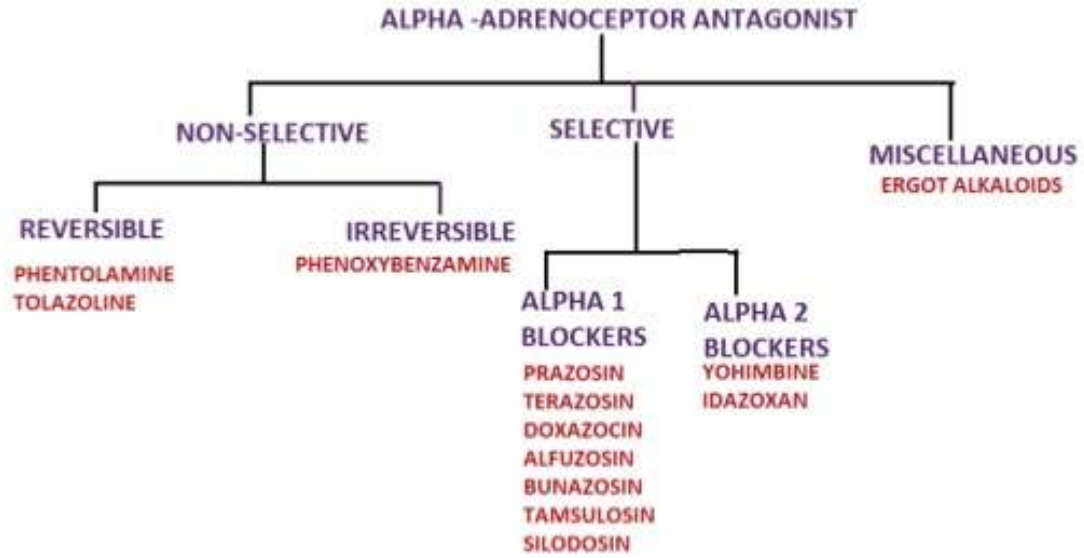
Anti-hypertensive Drugs Market: Revenue Share (%), By Product, Global, 2018

- Diuretics
- Angiotensin Converting Enzyme (ACE) Inhibitors
- Angiotensin Receptor Blockers (ARBs)
- Beta Blockers
- Alpha Blockers
- Renin Inhibitors
- Calcium Channel Blockers
- Others

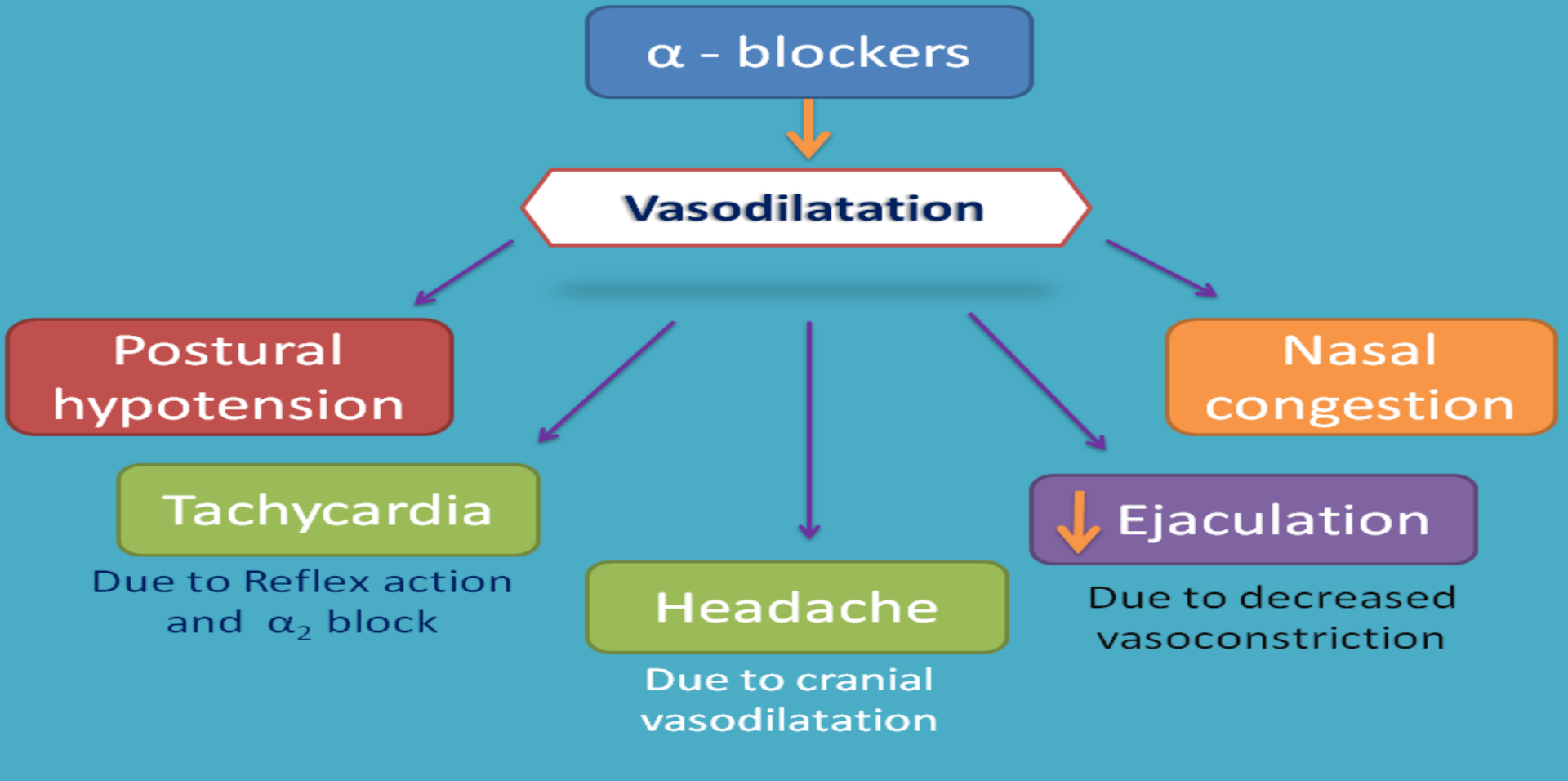
Source: Mordor Intelligence

CLASSIFICATION



Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS neurons	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibits lipolysis

Non-selective α blockers – Side effects



To Reduce Postural Hypotension…

- Give at bed time
- Measure supine and standing BP at baseline
- Avoid with prazosin/doxazosin
- Careful with diuretics/SGLT2I
- First sit before standing, cross leg posture
- Elastic stockings
- Avoid dehydration

Most commonly used alpha blockers for BPH treatment

Tamsulosin	selective irreversible nor-adrenergic (NA) antagonist to iris dilator smooth muscle [18]. $\alpha 1_A + \alpha 1_D$ and $\alpha 1_L$ NA receptors [11] dopaminergic (D) receptors	potent affinity for D receptors greater affinity for $\alpha 1_A + \alpha 1_D$ receptors than other $\alpha 1$ blockers $\alpha 1_L$ receptor might mediate iris dilatation tamsulosin is more potent antagonist of 1L receptor
Terazosin	non-selective competitive receptor subtype - $\alpha 1_A$, $\alpha 1_B$ and $\alpha 1_D$ receptors	no selectivity towards α1A receptor which is thought to predominate in Iris $\alpha 1_A + \alpha 1_D$ – uroselective $\alpha 1_B$ – vascular epithelium
Doxazosin	competitive non-selective antagonist	$\alpha 1_A$ – uroselective $\alpha 1_B$ – vascular epithelium
Prazosin	competitive antagonist in iris dilator smooth muscle [19]	$\alpha 1_A$ – uroselective $\alpha 1_B$ – vascular epithelium
Alfuzosin	competitive antagonist effect on iris dilator muscle has not been studied similar structure to prazosin and behaves as prazosin little /no affinity for S/D receptors [17] balanced binding affinity for the $\alpha 1$ receptor subtypes	similar uroselectivity to tamsulosin but behaves as competitive antagonist like terazosin and prazosin [20]

Most commonly used alpha blockers for BPH treatment

	Tamsulosin	Silodosin	Alfuzosin
Metabolism Enzymes involved	**CYP3A4 and CYP2D6**	**CYP3A4**	**CYP3A4**
Clinical Trials	87	20	31
Renal dysfunction	Safe above CLcr <10 mL/min/1.73m2	CCr 30-50 mL/min), the dose should be reduced to 4 mg, s contraindicated in patients with severe renal impairment (CCr < 30 mL/min)	Caution should be exercised in patients with severe renal insufficiency
Hepatic dysfunction	Patients with moderate hepatic dysfunction do not require an adjustment	Patients with severe hepatic impairment (Child-Pugh score > 10)	Contraindicated moderate or severe hepatic insufficiency

1, https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020579s016lbl.pdf

2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022206s012lbl.pdf

3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021287s013lbl.pdf

International Journal of Urology (2010) 17, 869–875 doi: 10.1111/j.1442-2042.2010.02614.x, 10.1111/j.1442-2042.2010.02624.x

Original Article: Clinical Investigation

Short-term effects of crossover treatment with silodosin and tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia

Table 1 Baseline characteristics of patients

Parameters	Silodosin-preceding group	Tamsulosin-preceding group	*P*-value
Age (years)	68.2 ± 8.6 (34)	70.1 ± 8.9 (31)	NS
Prostate volume (mL)	41.3 ± 25.3 (33)	37.8 ± 16.3 (31)	NS
IPSS total score	16.6 ± 5.2 (34)	18.2 ± 5.8 (31)	NS
QOL score	4.9 ± 0.9 (34)	4.9 ± 0.9 (31)	NS
Maximal urinary flow rate (mL/s)	9.4 ± 3.5 (29)	9.7 ± 4.4 (29)	NS
Residual urine volume (mL)	96 ± 102 (24)	97 ± 113 (27)	NS

Data represents the mean ± standard deviation. Numbers in parenthesis indicates number of subjects. Statistical analyses were performed by unpaired *t*-test. IPSS, International Prostate Symptom Score; NS, not significant; QOL, quality of life.

Conclusions: In BPH/LUTS patients, silodosin exhibits excellent efficacy in improving subjective symptoms in both initial and crossover treatment, and it appears to improve the QOL of patients.

Significant drug interaction between commonly used medications in BPH and IHD

Drugs	Tamsulosin	Alfuzosin	Silodosin
Antiplatelet Therapy			
Aspirin	None	Significant	Significant
Antihypertensive Therapy			
Enalapril	None	Significant	Significant
Ramipril	None	Significant	Significant
Atenolol	None	Monitor closely	Monitor closely
Metoprolol	None	Monitor closely	Monitor closely
Amlodipine	None	Monitor closely	Monitor closely
Nifedipine	Minor	Monitor closely	Serious
Lipid Lowering Agent			
Atorvastatin	None	Monitor closely	Monitor closely

https://www.webmd.com/interaction-checker/default.htm

Medication pairs involved in risk X category drug interactions (to be avoided)

- Azithromycin-silodosin > Increased serum concentration of silodosin
- Atorvastatin-silodosin > Increased serum concentration of silodosin
- Prazosin-tamsulosin > Enhanced antihypertensive effect

Major Drug Drug Interaction of Tamsulosine

- Antiretrovirals
- Antifungals
- Clarithromycin

Moderate Drug Drug Interaction of Tamsulosine

- Erythromycin
- Prazosin/doxazosin
- Amiodarone
- Amitryptiline
- Sildenafil
- SGLT2I
- Verapamil
- Cimetidine
- Alcohol: doesn't directly affect but worsens dizziness

SCIENTIFIC REPORTS

OPEN

Prescription pattern of alpha-blockers for management of lower urinary tract symptoms/benign prostatic hyperplasia

This study investigated trends in the prescription of α-blockers for patients with BPH, focusing on changing patterns of prescriptions during 2002–2013 using National Health Insurance Service-National Sample Cohort data. A total of 65,596 Korean males over 50 years old diagnosed with BPH were identified from the NHIS-NSC database between 2002–2013. Patterns of each α -blocker prescription were analyzed and persistence rate, switch rate, and return rate during a follow-up period of 3 years after the first prescription were calculated. A total of 28,318 men over 50 years old (64.95 ± 9.12), changed medication within six months following the first prescription of α -blocker. (1) Tamsulosin showed the highest persistence rate when compared with other α-blockers (2) Among patients who switched to a second α-blocker, tamsulosin showed the highest return rate when compared with other α-blockers. Tamsulosin has been the most commonly prescribed α1-blocker since the mid-2000s, in line with its demonstrated highest persistence and return rates. These data probably reflect patient satisfaction with α1-blockers in the management of BPH, in which the decision to stop and switch pharmacological treatments is primarily based on changes in symptoms or side effects.

To Solve This Issue - Need A Collaborative Approach Of Medical Fraternity


Thank
you