ABSTRACT
Sustained elevated blood pressure, unresponsive to lifestyle measures, leads to a critically important clinical question: What class of drug to use first-line? β-Blockers are no longer recommended first-line therapy for primary hypertension, based on data showing that β-blockers are inferior to other antihypertensive and no better than placebo, in spite of provision of blood pressure reduction. However, they still widely used on regular bases may be due to their economic value or just lack of clinical update of guide lines. Emerging evidence reveals physiological differences within the β-blocker class and in comparison to other antihypertensive. These differences provide insight into the diverse clinical effects β-blockers provide in cardiovascular disease. It is important for clinicians to recognize that the recommendation to relegate β-blockers, as a class, to add-on therapy in primary hypertension is largely based on evidence from atenolol. Meritorious arguments can be made that the diversity within β-blockers should limit classwide recommendations. Yet using β-blockers as add-on therapy remains an appropriate recommendation in the absence of long-term trials showing benefit with other β-blockers.

KEYWORDS: Hypertension - Beta blockers - antihypertensive drug - international guidelines.

INTRODUCTION
Hypertension is one of the five leading causes of death by disease in most of the countries which has no symptoms and called slow, silent death. Once the patient complains of being hypertensive it means complication because it has no symptoms as a disease in early stages so the patient can't know that he is hypertensive except by chance in the routine
investigations, sudden visit to a doctor and so on. That’s why we called it as the silent killer. Hypertension has many serious life threatening complications as angina, myocardial infarction, stroke, renal failure and so on. We are then in a great need to initiate treatment to avoid hypertensive complication. There are many groups of drugs which act in different mechanisms to help to delay hypertensive crisis such as: Angiotensin converting enzyme inhibitor, angiotension receptor blockers, calcium channel blockers, beta blockers and so on. In 1962, sir James found the first clinically used beta blockers which are propranolol and pronethanol …. During this time it was amagic effect on angina, myocardial infarction and decreased death mortality rate in this time.

**General Pharmacology**

Beta-blockers are drugs that bind to beta-adrenoceptors and thereby block the binding of norepinephrine and epinephrine to these receptors. This inhibits normal sympathetic effects that act through these receptors. Therefore, beta-blockers are sympatholytic drugs. Some beta-blockers, when they bind to the beta-adrenoceptor, partially activate the receptor while preventing norepinephrine from binding to the receptor. These *partial agonists* therefore provide some "background" of sympathetic activity while preventing normal and enhanced sympathetic activity. These particular beta-blockers (partial agonists) are said to possess intrinsic sympathomimetic activity (ISA). Some beta-blockers also possess what is referred to as membrane stabilizing activity (MSA). This effect is similar to the membrane stabilizing activity of sodium-channels blockers that represent Class I antiarrhythmics. The first generation of beta-blockers were non-selective, meaning that they blocked both beta-1 (β₁) and beta-1 (β₂) adrenoceptors. Second generation beta-blockers are more cardioselective in that they are relatively selective for β₁ adrenoceptors. Note that this relative selectivity can be lost at higher drug doses. Finally, the third generation beta-blockers are drugs that also possess vasodilator actions through blockade of vascular alpha-adrenoceptors.

**Heart**

Beta-blockers bind to beta-adrenoceptors located in cardiac nodal tissue, the conducting system, and contracting myocytes. The heart has both β₁ and β₂ adrenoceptors, although the predominant receptor type in number and function is β₁. These receptors primarily bind norepinephrine that is released from sympathetic adrenergic nerves. Additionally, they bind norepinephrine and epinephrine that circulate in the blood. Beta-blockers prevent the normal
ligand (norepinephrine or epinephrine) from binding to the beta-adrenoceptors by competing for the binding site.

Beta-adrenoceptors are coupled to a Gs-proteins, which activate adenylyl cyclase to form cAMP from ATP. Increased cAMP activates a cAMP-dependent protein kinase (PK-A) that phosphorylates L-type calcium channels, which causes increased calcium entry into the cell. Increased calcium entry during action potentials leads to enhanced release of calcium by the sarcoplasmic reticulum in the heart; these actions increase inotropy (contractility). Gs-protein activation also increases heart rate (chronotropy). PK-A also phosphorylates sites on the sarcoplasmic reticulum, which lead to enhanced release of calcium through the ryanodine receptors (ryanodine-sensitive, calcium-release channels) associated with the sarcoplasmic reticulum. This provides more calcium for binding the troponin-C, which enhances inotropy. Finally, PK-A can phosphorylate myosin light chains, which may contribute to the positive inotropic effect of beta-adrenoceptor stimulation. Because there is generally some level of sympathetic tone on the heart, beta-blockers are able to reduce sympathetic influences that normally stimulate chronotropy (heart rate), inotropy (contractility), dromotropy (electrical conduction) and lusitropy (relaxation). Therefore, beta-blockers cause decreases in heart rate, contractility, conduction velocity, and relaxation rate. These drugs have an even greater effect when there is elevated sympathetic activity.

**Blood vessels**

Vascular smooth muscle has β2-adrenoceptors that are normally activated by norepinephrine released by sympathetic adrenergic nerves or by circulating epinephrine. These receptors, like those in the heart, are coupled to a Gs-protein, which stimulates the formation of cAMP. Although increased cAMP enhances cardiac myocyte contraction (figure 1), in vascular smooth muscle an increase in cAMP leads to smooth muscle relaxation. The reason for this is that cAMP inhibits myosin light chain kinase that is responsible for phosphorylating smooth muscle myosin. Therefore, increases in intracellular cAMP caused by β2-agonists inhibits myosin light chain kinase thereby producing less contractile force (i.e., promoting relaxation).

Compared to their effects in the heart, beta-blockers have relatively little vascular effect because β2-adrenoceptors have only a small modulatory role on basal vascular tone. Nevertheless, blockade of β2-adrenoceptors is associated with a small degree of vasoconstriction in many vascular beds. This occurs because beta-blockers remove a small
β₂-adrenoceptor vasodilator influence that is normally opposing the more dominant alpha-adrenoceptor mediated vasoconstrictor influence.

![Diagram of β₂-adrenoceptor system](image)

**Figure 1: Effect on blood vessels**

**Indications**
- Angina pectoris
- Myocardial infarction
- Hypertension
- Prophylaxis of migraine
- Congestive heart failure
- Essential tremors "as it decrease potassium levels"
- Some types of arrhythmias
- Glaucoma"primary and secondary"
- Atrial fibrillation
* These days' beta blockers are used also into:
- Marfan syndrome "propranolol for aortic dilatation"
- Anxiety disorders
- Acute aortic dissection (with sodium nitroprusside)
- Hypertrophic obstructive cardiomyopathy.
- Reduction of preoperative mortality.
- Reduction of weight by effect on B3

**Adverse effects**
nausea, vomiting, diarrhea, dyspnea, bronchospasm, hypotension, cold extremities, acute exacerbation of Reynaud's syndrome, bradycardia, heart failure, heart block, fatigue,
dizziness, alopecia, hallucination, insomnia, abnormal vision, sexual and erectile dysfunction and alteration of lipid and glucose metabolism in long use. Mixed alpha 1 and beta blockers like labetalol may associated with postural hypotension (sudden fall of one's blood pressure on standing). Alpha and beta mixed blocker like carvedilol may cause edema, through it's effect by higher penetration across blood brain barrier. A common serious effect that may lead to death from beta blocker is indication in diabetic persons as they can mask the hypoglycemic precautions of this person and lead to silent death. It can precipitate acute attacks of bronchial asthma through it's action on B2 found in the lung causing bronchospasm.

**Hypertension**

Studies in late 1990s shown that it has a great efficacy in lowering morbidity and mortality rates. Beta-blockers decrease arterial blood pressure by reducing cardiac output. Many forms of hypertension are associated with an increase in blood volume and cardiac output. Therefore, reducing cardiac output by beta-blockade can be an effective treatment for hypertension, especially when used in conjunction with a diuretic. Acute treatment with a beta-blocker is not very effective in reducing arterial pressure because of a compensatory increase in systemic vascular resistance. This may occur because of baroreceptor reflexes working in conjunction with the removal of β₂ vasodilatory influences that normally offset, to a small degree, alpha-adrenergic mediated vascular tone. Chronic treatment with beta-blockers lowers arterial pressure more than acute treatment possibly because of reduced renin release and effects of beta-blockade on central and peripheral nervous systems. Beta-blockers have an additional benefit as a treatment for hypertension in that they inhibit the release of renin by the kidneys (the release of which is partly regulated by β₁-adrenoceptors in the kidney). Decreasing circulating plasma renin leads to a decrease in angiotensin II and aldosterone, which enhances renal loss of sodium and water and further diminishes arterial pressure.

Beta blocker are known, since it was discovered, by their reductive effect on the heart by it's sympatholytic effect on B1 receptor found on the heart muscle as mentioned before, and by the same action on the kidney through the same receptor it can reduce the activity of rennin angiotensin system because it can reduce the rennin secretion, by the afferent arteriole from the kidney from certain cells called granular cells of the juxtagromular apparatus, which has the ability to reduce cardiac demand of oxygen by lowering extra-cellular volume and
increasing the carrying capacity of the blood to oxygen that will lead to better nutrition for cardiac muscles, that may explain to some extent their action on prolonging life and decrease morbidity and mortality, and so they can increase the ejection fraction of the heart despite the initial reduction at the beginning of the treatment.

ACEI, nowadays, is the drug of choice in treatment of hypertension. Doctors prefer to use it as a monotherapy in hypertensive people because it has many effects over beta blockers that would be summarized in the (table 2). On the other hand, β-Blockers have low economic value and in developing countries it is appropriate to use it especially that hypertension is a lifelong disease and it represents burden on the economy of the country.
DISCUSSION
The common belief that all antihypertensive drugs can lower the blood pressure to the same degree. We know that different antihypertensive drugs lower blood pressure by different mechanisms of action and so their efficacy would be different. Thiazide and beta blockers can reduce the systolic blood pressure to the same degree but when we talk about diastolic and pulse pressure it would be slightly different by 1-2 mmHg. Beta blockers can reduce diastolic pressure to a larger degree and reduce the pulse pressure to a lower degree. The reduction of beta blocker with thiazide at doses as low as 0.25 times if the recommended manufactured starting dose. The blood pressure lowering level during using of Beta blocker as a second drug was 6/4 mmHg at the starting dose and 8/6 at twice the starting dose. But on the other hand thiazide can lower pressure to a much greater degree. Comparing to beta blocker, which has low effect on pulse pressure, thiazide can cause a significant dose-related reduction in pulse pressure. So beta blocker become less effective at reducing the adverse cardiovascular outcomes than thiazide, especially in older (Table1).

CONCLUSION
β-blockers are effective antihypertensive agents and, together with diuretics, have been the cornerstone of pioneering studies showing their benefits on cardiovascular morbidity and mortality as a consequence of blood pressure reduction in patients with hypertension. However, Beta-blockers have been found not to be effective for primary prevention of cardiovascular disease in patients with primary hypertension. The problem was first recognized by Messerli et al.[11], they declare that “The time has come to admit that beta-blockers should no longer be considered appropriate for first-line therapy of uncomplicated hypertension.” On the other hand, in Egypt B-blockers is one of the most used drugs in the field of hypertension. More studies needed focusing on b-blockers and its efficacy over many years especially it is one of hypertension drugs and didn’t become obsolete yet, they are still resisting distinction.

REFERENCES


