

# The Black and Whyte of Beta Blockers

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## ABSTRACT

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The role of beta blockers in the management of systemic hypertension is discussed in detail. The major indications for its use, its side effects and adverse effects are discussed in detail. The newer vasodilatory beta blockers are introduced. The present status of beta blockers in the latest guidelines for the management of hypertension is also mentioned.

**Keywords:** Systemic hypertension, Beta blockers, Propranolol

\*See End Note for complete author details

The discovery and development of the beta adrenoceptor antagonists represents one of the most significant advances in the history of cardiovascular pharmacology and therapeutics. Sir James Whyte Black (Figure 1) is credited with leading the team that discovered the first clinically useful beta adrenoceptor antagonist, propranolol, which was developed specifically for the treatment of angina. For his discovery, he was awarded the Nobel prize in 1998.

In this article we will discuss the uses of beta adrenoceptor blockade in the treatment of cardiovascular diseases.

The main use of betablockers in cardiovascular diseases are in

1. Coronary artery disease
2. Systemic Hypertension
3. Arrhythmias
4. LV Dysfunction and Heart Failure
5. MVP and HOCM.

Beta blockers (BB) in the management of coronary artery disease (CAD)

## I. Acute Coronary Syndromes

### 1. ST Elevation myocardial Infarction (STEMI)

#### *Intravenous betablockers*

Early studies in 1980s have shown that intravenous beta-blockers exhibited clinical benefits (ISIS1, MIAMI)<sup>1,2</sup> in STEMI. But data derived from large trials in the current era of reperfusion (TIMI IIb, GUSTO I and



Figure 1. Sir James Whyte Black

COMMIT CCS)<sup>3,4,5</sup> have shown that early aggressive beta blockade poses a substantial net hazard in haemodynamically unstable patients. This has made this therapy unpopular among physicians.

#### *Oral betablockers*

Initiation of oral BB is found to have benefit in NST EMI patients. Based on this, ACC-AHA guidelines have proposed that beta blockers should be initiated within the first 24 hours in all STEMI patients who do not have any contraindication

### 2. Non-ST elevation MI (NST EMI) or Unstable angina

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In NSTEMI also betablocker therapy was found to be beneficial as reported in the HINT<sup>6</sup> trial and the CRUSADE<sup>7</sup> registry.

*Current Recommendations - BB usage in Myocardial Infarction* (ACC – AHA 2007 STEMI and NSTEMI Guidelines)

*Oral Beta Blockers*

Oral beta-blocker therapy should be initiated in the first 24 hours for patients without contraindications\*.

*Intravenous Beta Blockers*

The prudent approach is to use intravenous beta blockers selectively in patients with lower Killips class (no features of LV dysfunction), hypertension or continuing angina.

*\*Contraindications to BB*

1. Signs of heart failure.
2. Evidence of a low cardiac output state,
3. Increased risk for cardiogenic shock,
  - a. Age greater than 70 years,
  - b. Systolic blood pressure less than 120 mm Hg,
  - c. Sinus tachycardia greater than 110 bpm or
  - d. Heart rate less than 60 bpm,
4. Other relative contraindications to betablockade (PR interval greater than 0.24 seconds, second- or third-degree heart block, active asthma.)

**II. Beta Blockers in Secondary Prevention of CAD**

The metaanalysis of 23 trials by Salim Yusuf<sup>9</sup> and the data from beta blocker pooling<sup>10</sup> project have shown 22-24% reduction in mortality with BB. But the robust data regarding the benefit of BB in secondary prevention of CAD was obtained from the Cooperative Cardiovascular Project<sup>11</sup> where BB was found to be beneficial in patients after primary angioplasty or thrombolysis, irrespective of the usage of concomitant drugs like statins, ACE inhibitors and aspirin.

**Secondary prevention – ACC Guidelines – 2007<sup>8</sup>**

Beta blocker therapy should be started and continued indefinitely (unless contraindicated) in all patients who have had

1. myocardial infarction,
2. acute coronary syndrome, or
3. left ventricular dysfunction with or without heart failure symptoms.

BB should be considered in all post MI settings—along with new drugs like statins, ACEIs, or whether the patient undergoes reperfusion – either medical or mechanical.

**Monitoring treatment with beta blockers**

Target - HR - 50-60 bpm

It should blunt the HR response to stress and exercise.

**How long to continue treatment in coronary artery disease?**

2-3 years at least. If tolerating at that point treatment may be continued life- long.

**III. Chronic Stable Angina**

Beta blockers – Because of its negative inotropic and chronotropic effects, it reduces heart rate at rest and during exercise. It also reduces blood pressure and myocardial contractility. All this decreases myocardial oxygen demand and moreover increases the diastolic perfusion time.

Of the three major class of drugs used in chronic stable angina, beta blockers provide an equivalent reduction in angina and lead to similar or reduced rates of adverse events compared to calcium channel blockers or nitrates.<sup>12</sup>

**Table 1. Types of adrenoceptors in cardiovascular system and its response to stimulus**

	Type of adreno-receptor	Response to stimulation
Heart	beta 1, beta 2	Increase in heart rate
	beta 1	Increase in conduction velocity
	beta 1	Increase in excitability
	beta 1	Increase in force of contraction
Blood vessels	beta 1	Dilatation of coronary arteries
	beta 1	Dilatation of other arteries

**Which betablocker in Coronary Artery Disease?**

The proven drugs are atenolol and metoprolol. But there is recent data on nebivolol in the management stable angina pectoris. There are few Russian studies demonstrating its benefit for this indication.<sup>13</sup>

**Beta Blockers in Elderly in CAD**

There is apprehension among physicians in the use of betablockers in the elderly. But betablocker treatment has shown much more benefit in the elderly than in younger patients [6% benefit in 65 – 75 yrs Vs 2.1 % at younger ages]. So it should be an essential part of the prescription in the elderly.<sup>14,15</sup>

### Algorithm: Treatment of Newly Diagnosed Hypertension

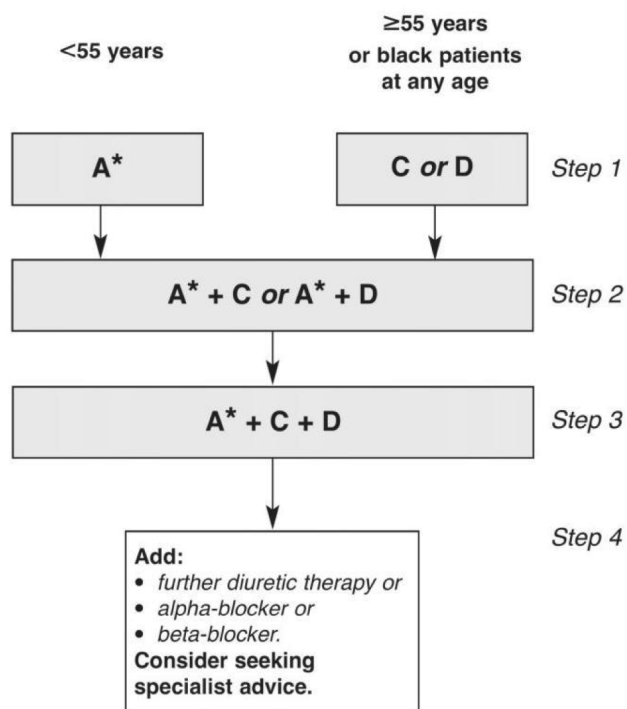


Figure 2. Algorithm. A = ACE inhibitor (\* or ARB if ACEi-intolerant); C = calcium-channel blocker; D = thiazide=type diuretic. Beta-blockers are not a preferred initial therapy for hypertension but are an alternative to A in patients <55 years in whom A is not tolerated, or contraindicated (includes women of child bearing potential). Black patients are only those of African or Caribbean descent. In the absence of evidence, all other patients should be treated according to the algorithm as non-black

#### BB in Systemic Hypertension

Beta-blockers have been used for more than 40 years to treat hypertension. The data from clinical trials that used these agents to manage BP have demonstrated reductions in cardiovascular mortality and this has resulted in recommendations of beta-blockers as first- or second-line antihypertensive agents in the most recent guidelines of the European Society of Hypertension<sup>16</sup> and the Joint National Committee (JNC 7).<sup>17</sup>

The use of BB in patients with uncomplicated hypertension has become increasingly controversial over the past few years.<sup>18,19</sup> The recent data from LIFE<sup>20</sup> study have shown that though atenolol reduces BP and exhibit benefits compared to placebo, it produces worse outcomes when compared to other anti-hypertensive agents. ASCOT-BPLA<sup>21</sup> study evaluated the efficacy of atenolol with a thiazide versus amlodipine with perindopril and found that atenolol based regimen produced worse outcomes.

The results of a recent meta-analysis showed no difference between atenolol and placebo in risk reduction for mortality, myocardial infarction, or stroke<sup>22</sup> and an increased risk of mortality and stroke with atenolol or propranolol in comparison to other antihypertensive drug classes, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs).<sup>22,23</sup>

The recently updated NICE guidelines<sup>24</sup> in UK reflected this concern, having changed the indication for beta-blockers from use as first-line agents for hypertension treatment to consideration as a fourth-line add-on therapy in patients requiring multiple drugs. In the most recent guidelines, the European Society of Hypertension / European Society of Cardiology<sup>16</sup> recommend that beta-blockers should not be preferred in hypertensives with multiple metabolic risk factors including metabolic syndrome, abdominal obesity, high normal or impaired fasting glucose, and impaired glucose tolerance, conditions that make the risk of incident diabetes higher.

#### Are all BB equal?

No. Eventhough they have a class effect, each BB shows different properties. Although the above data on beta-blockers and CVD risk reduction cannot be overlooked, one must always bear in mind that most of the studies on the field included “traditional” agents (such as propranolol and atenolol).

#### Problems with atenolol

1. Hydrophilic – so cannot cross blood brain barrier – So no reduction in sympathetic output – so no reduction in SCD
2. Left ventricular hypertrophy reduction lesser
3. Newer onset DM more
4. Control of BP inadequate in the majority,
5. No reduction in peripheral vascular resistance.
6. No improvement in endothelial dysfunction
7. Reduction in central aortic pressure (which is an important prognostic factor) is less compared to other drugs (pseudohypertensive effect)
8. Half life is short – so 24 hour protection is not provided.

Now we have to see the data about other beta-blockers. We have the metoprolol extended release (succinate salt) – and Bisoprolol. Both of them have the advantage of being lipophilic. The other class of BB are the vasodilatory betablockers.

**Figure 1**  
Proposed use of beta blockers for hypertension. In patients with uncomplicated hypertension beta blockers should not be used as first line agents. However, in patients with uncontrolled hypertension on various other anti-hypertensive agents and in those with complicated hypertension, betablockers should be considered in the armamentarium of treatment.

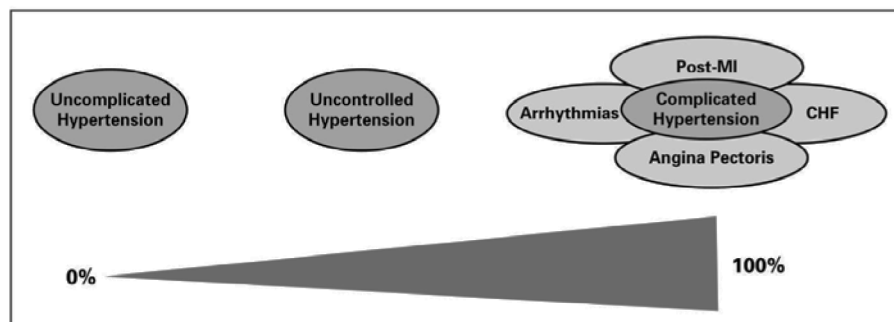


Figure 3. NICE – UK Guidelines in the management of hypertension 2006<sup>24</sup>

### Vasodilatory BB

**Nebivolol**– Lipophilic, vasodilatory (nitric oxide mediated), antioxidant.

**Carvedilol** – Lipophilic, vasodilatory (alpha blocking), antioxidant.

Their favorable hemodynamic profile includes reduction of peripheral vascular resistance (PVR) while maintaining or improving cardiac output (CO), stroke volume, and left ventricular function, whereas nonvasodilating beta-blockers tend to raise PVR and reduce CO and left ventricular function.

### Nebivolol

Nebivolol is a third generation beta-blocker. It is highly selective for the beta1-adrenoceptor, and has additional nitric oxide-mediated vasodilating and antioxidant properties, along with a favourable metabolic profile. It was approved in Dec 2007 by FDA for the treatment of HTN. A recent meta-analysis<sup>25</sup> showed that nebivolol 5 mg achieved similar or better rates of treatment response and BP normalization than other drug classes and other antihypertensive drugs combined, with similar tolerability to placebo and significantly better tolerability than losartan, CCAs, other beta-blockers, and all antihypertensive drugs combined.

### Carvedilol

Carvedilol, a vasodilating non-cardioselective beta-blocker has shown benefits in hypertension and has a favourable metabolic profile even compared to Metoprolol.

### What is the present status of BB in HTN?

The current data regarding use of BB in hypertension suggest that it may not be an ideal drug especially to start as the firstline therapy<sup>26</sup> (Figure 1). Atenolol with all the unfavourable data may be avoided. The

newer BB especially vasodilatory BB– Nebivolol and Carvedilol shows promise, but should be validated in large studies.

### Beta Blockers in Heart Failure

We now know that sustained adrenergic stimulation produce harmful effects in heart failure. The main mediator is beta1 receptor. Beta blockers by competitively antagonising the beta receptors prevent the damage induced by adrenergic stimulation. BB when given along with ACEI reverse the process of LV remodeling, improve patient symptoms, prevent hospitalisation and prolong life.<sup>27-30</sup> So BB are indicated in patients with EF <40% irrespective of whether they are symptomatic or asymptomatic.

There are four beta blockers which showed benefits in heart failure

1. Bisoprolol
2. Sustained release metoprolol succinate
3. Carvedilol
4. Nebivolol is licensed for heart failure in elderly in Europe

### Whom to start on Beta Blocker therapy in heart failure?

All patients of stable mild, moderate or severe heart failure should be started on betablockers as soon as LV dysfunction is identified. Ischemic & non-ischemic heart failure has shown benefits. Even patients in NYHA Class IV without fluid retention (once adequate diuresis have been achieved) can also be started on BB.

Recent trials have shown that beta blocker therapy is tolerated in 85% of patients with HF including patients with co-morbidities like DM, COPD and POVD.<sup>27,30</sup> But there is a subgroup of patients (15%) who will remain intolerant to beta blockers due to worsening fluid retention and symptomatic hypotension.

It is very important to up-titrate the dosage of BB till it reaches the target doses as shown in the table as maximum clinical benefit is obtained at the maximum tolerated levels. DOSAGE CHART –

Drug	Initial dose (mg)	Max dose (mg)
Bisoprolol	1.25	5-10
Metoprolol Succinate	12.5	200
Carvedilol	3.125	50-100

Dose doubling should be done no sooner than at 2 weeks interval as this may precipitate fluid retention and lead to worsening of CHF. Monitor for bradycardia, fluid retention (monitor for weight gain) and hypotension. If there is worsening of HF, increase diuretics. If not able to control HF, reduce or consider withdrawing beta blockers.

### BB in Arrhythmias

Beta-blockers are extensively used antiarrhythmics. The most commonly used BB are metoprolol, atenolol, propranolol and esmolol. Esmolol has the advantage that it is extremely short acting. Supraventricular arrhythmias

### Atrial fibrillation and Atrial Flutter

BB cannot convert chronic AF to SR, and cannot slow the atrial rate, but can reduce the ventricular response because beta blockade prolongs the AVNodal conduction time and refractoriness. I/V esmolol can be used to rapidly control the ventricular rate if required.

PSVT - AVNRT and WPW Syndrome (orthodromic reciprocating tachycardias)

In these tachyarrhythmias, AVNode acts as one of the re-entrant pathways BB can slow or terminate the tachycardia and can be used prophylactically to prevent recurrence.

Betablockers are also useful in inappropriate sinus tachycardia. Patients with infrequent episodes of automatic atrial tachycardia may also get benefited with BB therapy.

### Ventricular arrhythmias

#### Ventricular Premature Contractions (VPCs)

In the absence of heart disease, premature ventricular complexes are associated with little or no increased risk of developing a dangerous arrhythmia. If they

are asymptomatic no treatment is required. If patients with multiple premature ventricular complexes have severe, disabling symptoms, beta blockers are the safest initial choice.

In patients with structural heart disease, the occurrence of premature ventricular complexes in patients with has been shown to significantly increase the risk of subsequent morbidity and mortality.

Patients who have coronary heart disease, cardiomyopathy or congestive heart failure are the ones associated with unfavorable outcomes if they develop premature ventricular complexes. In such patients betablockers are beneficial.

### Ventricular tachycardia

All patients who demonstrate sustained and non-sustained ventricular tachycardia associated with ischemic heart disease should receive chronic therapy with beta blockers. Beta-blockers has also demonstrated benefit in non-ischemic cardiomyopathy.

### Prevention of sudden cardiac death (SCD)

Betablockers stabilize autonomic imbalance and reduce ischemic episodes. The most well established treatment for the prevention of SCD is BB. Singh et al<sup>31</sup> has shown that beta blockers reduce SCD by 30%. Beta blockers are effective in the setting of ventricular arrhythmias provoked by high sympathetic tone, as in patients with Long QT syndrome and ARVD –arrhythmogenic right ventricular dysplasia. Benefit is found maximum in those with high risk of SCD like those in heart failure, post-MI patients and diabetes mellitus.

### BB in Mitral valve prolapse

BB are useful in patients with palpitations secondary to ventricular ectopics. In patients who have chest discomfort due to regional ischemia secondary to MVP, BB are useful

### BB in Hypertrophic Obstructive Cardiomyopathy

In patients with obstructive HCM and symptoms, BB are the initial treatment of choice. The advantages of BB are 1) decreased HR response to exercise, 2) decreased outflow tract gradient with exercise, 3) relief of angina by decreasing myocardial oxygen demand, 4) improved diastolic filling. There is no data to prove that BB reduces SCD in HCM. Only about 40% of the patients show improvement with BB. Here also dosage of the BB should be titrated.

## Adverse Effects with Beta Blockers

### Beta Blocker Withdrawal Syndrome

Chronic exposure to BB will lead to beta-receptor up-regulation - increase in the number of beta receptors and increase in receptor sensitivity. It is most common with BB with short half life like propranolol and at high doses. Sudden withdrawal will lead to very high levels of adrenergic stimulation which can precipitate unstable angina and myocardial infarction. This usually occurs within 48 hrs of discontinuation. To prevent this - avoid abrupt discontinuation, taper the drug over 2 weeks by decreasing the dose by 50% every 3-4 days.

### BB and Peripheral Occlusive Vascular Disease

Beta adrenergic-antagonist drugs have been thought to exacerbate symptoms in patients with PAD because of fears that B-blockade would lead to unopposed alpha receptor vasoconstriction and deterioration in peripheral arterial circulation, and cause worsening of intermittent claudication and development of critical limb ischemia. A meta-analysis and a critical review of published studies concluded that b-adrenergic antagonists are safe in patients with PAD and do not adversely affect walking capacity or symptoms of intermittent claudication in patients with mild-to-moderate PAD.<sup>32</sup>

### BB and COPD

Beta-blockers are known to precipitate and exacerbate bronchial asthma. Cardioselective blockers do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease. The results were similar for patients with concomitant chronic airways obstruction. Given their demonstrated benefit in such conditions as heart failure, cardiac arrhythmias, and hypertension, cardioselective beta blockers should not be withheld from patients with mild to moderate reactive airway disease.<sup>33</sup> But in severe disease we have to exercise caution.

### Other Major side effects of Beta Blockers

1. Bradycardia, AV Nodal blocks
2. Fatigue is often reported with BB, may be due to the central and peripheral effects
3. Impotence is often reported in patients with BB, usually in middle-aged men with atherosclerotic arterial disease. (In one study 11% with BB Vs 26% with diuretics vs 3% with placebo)
4. Effects on lipid parameters – Decrease in HDL by 7-10% and rise in Triglycerides by 10-20%.

## CONCLUSIONS

The current data regarding use of BB in hypertension suggest that it may not be an ideal drug to start as a first line therapy. Atenolol with all the unfavourable data may be avoided. The newer vasodilatory beta-blockers – Nebivolol and Carvedilol show promise, but should be validated in larger studies.

But beta-blockers have shown significant mortality benefit in other situations like post-MI patients, LV dysfunction and prevention of SCD. So they should be essential prescriptions in such situations. Beta-blockers are also beneficial in other situations like HOCM and MVP.

## END NOTE

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