

# Beta-blockers in Cardiovascular Medicine



Aijaz H Mansoor, Upendra Kaul\*

## Abstract

Beta-blockers are among the proven medication in Cardiovascular Medicine, reducing both the morbidity as well as the mortality. Most beta-blockers are well-absorbed after oral intake. The third generation beta-blockers (carvedilol, nebivolol) are non-selective and have additional properties of vasodilatation. Currently, beta-blockers are employed in a number of cardiovascular conditions. The strongest evidence for their use (evidence level A) is in systolic heart failure, post-myocardial infarction (myocardial protection) and in prevention and treatment of ventricular arrhythmias in post MI patients. In acute myocardial infarction, current recommendation (based on COMMIT/CCS-2 trial) are to avoid early use of beta blockers in patients with hemodynamic instability or who are at risk of cardiogenic shock. Once stable, beta blockade is strongly recommended in patients of myocardial infarction. Beta-blockers are not currently favoured as the first line anti-hypertensive therapy, particularly in the elderly, unless there are specific indications. For patients undergoing non-cardiac surgery, risk stratification should be performed, and beta-blockers prescribed to patients at high cardiac risk.

## Introduction

Beta-blockers were first developed by Sir James Black at the Imperial chemical industries in the United Kingdom in 1962. They are considered one of the most important contributions to clinical medicine and pharmacology in the 20<sup>th</sup> century, and Sir James Black was awarded the Nobel prize in 1988 for advances in medicine.

This review briefly discusses the pertinent clinical pharmacology of beta-blockers followed by their clinical use in cardiovascular medicine.

Beta-blockers are one of the 4 oral medications proven in randomized control trials to decrease cardiovascular morbidity and mortality. The other three agents being ACE-inhibitors, antiplatelets and statins. This quadruple therapy reduces 6 months mortality by 90% in ACS compared with treatment by none of these.<sup>1</sup>

The approximate life-saving potential of these agents have been estimated;<sup>2</sup> Beta-blockers 33%, Aspirin 23%, ACE inhibitors 20% and Statins 15%.

## Clinical Pharmacology

Although more than 100 beta-blockers have been developed, only about 30 are available for clinical use.<sup>3</sup> Water-soluble beta-blockers (Atenolol, Nadolol) tend to have longer half-lives and are eliminated via the kidney. Lipid-soluble beta-blockers (metoprolol, propranolol) are metabolized mainly in the liver and have shorter half-lives.<sup>4</sup>

Most of the drugs in the class are well absorbed after oral

administration. The biologic half-life of Beta-blockers exceeds the plasma half life considerably. (e.g. propranolol, dosage twice a day despite a plasma half-life of 3 hours). Clearly, the higher the dose, the longer the biologic effect. Longer acting compounds and preparations are preferred for angina and hypertension (metoprolol XL, atenolol, nadolol, sotalol, inderal LA). esmolol (I/V) has the shortest half life (10 min).

Three types of Beta-receptors ( $\beta_1$ ,  $\beta_2$ ,  $\beta_3$ ) are variably distributed in tissues<sup>5</sup>.  $\beta_1$  receptors are mainly located in the heart while  $\beta_2$  receptors are found in vascular and bronchial smooth muscle.  $\beta_3$  receptors are located in the adipocytes and heart<sup>3</sup>.

Cardioselective Beta-blockers (metoprolol, atenolol) exhibit greater affinity for  $\beta_1$  versus  $\beta_2$  receptors at usual drug levels<sup>6</sup>. This selectivity is lost at higher drug doses. Most Beta-blockers in clinical use are pure antagonists. A few (acebutalol, pindolol) are partial agonists. The relative density of  $\beta_1$  and  $\beta_2$  receptors changes with disease. In heart failure,  $\beta_1$  receptors are down-regulated.<sup>6,7</sup> Beta-blockers are also grouped in generations (Table 1). Third generation beta-blockers (carvedilol, bucindolol, nebivolol) are non-selective and vasodilatory.

Mechanism of vasodilation is direct vasodilation via nitric oxide (carvedilol, nebivolol) and via  $\alpha$  receptor blockade (labetalol, carvedilol).<sup>8</sup> Carvedilol is also antiproliferative, antioxidant and blocks the expression of several genes involved in myocardial damage.<sup>9</sup>

## Mechanism of Action of Beta-blockers<sup>10</sup>

All Beta-blockers occupy the  $\beta$  receptor and counter the effects of catecholamines on the cardiovascular tissues.  $\beta_1$  receptors are located on the cardiac sarcolemma and belong to the G-protein coupled adenylyl cyclase system. When catecholamines stimulate the receptor, Gs protein couples the activated receptor to adenylyl cyclase and generates cAMP. cAMP, the second messenger, activates protein kinase A (PKA) which phosphorylates the membrane calcium channel and increases calcium entry into the cytosol. PKA also increases calcium release from the sarcoplasmic reticulum. This calcium loading accounts for the positive inotropic effect. PKA also phosphorylates Troponin I (decreases affinity of myosin head to actin) and phospholamban (increased calcium reuptake by sarcoplasmic reticulum). This accounts for the lusitropic effect. increased  $I_f$  in the sinus node

Table 1<sup>10</sup> : 3 Generations of beta-blockers

	Properties	Drugs
1 <sup>st</sup> Generation	Non-selective No vasodilatation	Propranolol, Timolol, Pindolol, Nadolol, Sotalol
2 <sup>nd</sup> Generation	$\beta_1$ -selective without vasodilation $\beta_1$ selective with vasodilation	Atenolol, Bisoprolol, Metoprolol Nebivolol, Acebutolol
3 <sup>rd</sup> Generation	Non-selective with vasodilation	Carvedilol, Bucindolol

\*Executive Director, Department of Cardiology, Escorts Heart Institute and Research Centre, New Delhi

Table 2 : Indications for use of beta-blockers (in cardiovascular medicine)

Strongly indicated (level A)	Systolic heart failure Post MI Ventricular arrhythmias (Post MI)
Other indications (level B)	Other arrhythmias STEMI, UA/NSTEMI/Chronic stable angina Hypertension Hypertrophic cardiomyopathy Mitral stenosis, MVP Dissecting aortic aneurysm Marfan's syndrome (aortic root involvement) Neurocardiogenic syncope Fallot's tetralogy Inherited arrhythmogenic disorders (LQTS, CPVT)

Table 3<sup>10</sup> : Mechanism of beta-blockade in heart failure

- Upregulation of  $\beta$  receptors and improved  $\beta$  adrenergic signaling.
- Reducing the hyperphosphorylation of calcium release channels of sarcoplasmic reticulum and normalizing their function
- Bradycardia ( $\uparrow$  coronary blood flow and decreased myocardial oxygen demand).
- Protection from catecholamine myocyte toxicity.
- Suppression of ventricular arrhythmias.
- Anti-apoptosis.  $\beta_2$  receptors, which are relatively increased, are coupled to inhibitory G protein & block apoptosis.
- Inhibition of RAAS. When added to prior ACE-I or ARB, metoprolol augments RAAS inhibitors

leads to positive chronotropic effect. Accelerated conduction across AVN and conduction tissue causes the positive dromotropic effect.

## Clinical Uses of Beta-blockers

Indications for use are listed in Table no. 2

### Heart failure (HF)

Beta-blockers are now the Cornerstone of systolic heart failure therapy. The mechanisms involved are summarized in Table 3.

#### Evidence

Several meta-analyses of beta-blocker trials have conclusively shown that beta-blocker use is associated with a consistent 30% reduction in mortality, 40% reduction in hospitalizations and 38% reduction in sudden death in patients with chronic heart failure.<sup>11,12</sup> It was estimated that 26 patients would need to be treated to avoid one death.<sup>13</sup> Table 4 depicts the trials of Beta-blockers in heart failure.

Clinical use: Patients are stabilized first (no acute or recent deterioration; no volume overload) and then evidenced-based beta-blockers (carvedilol, metoprolol succinate XL, bisoprolol and nebivolol) are slowly introduced and gradually up-titrated.

## Acute Myocardial Infarction (MI)

Beta blockers significantly reduce morbidity and mortality in patients with acute MI.

#### Efficacy

Studies in the Pre-thrombolytic era showed a 10-15% mortality benefit with beta-blockers in acute MI.<sup>14,15</sup> and benefits were confirmed in studies performed in the reperfusion era (upto 40% reduction in mortality).<sup>16,17</sup> Beta-blockers reduced the odds of death by 23%.<sup>16</sup> Retrospective analysis of the CADILLAC trial showed that beta-blockers were also beneficial in patients undergoing primary PCI.<sup>18</sup> In the PCI era however, the large

Table 4 : Heart failure trials

Trial	Agent	N	F. up period	Pr. End Pt	Results
MDC (1993)	Metoprolol Tartrate	383	12-18 months	Death	EF increase
CIBIS (1994)	Bisoprolol vs Placebo	341	23 months	Death	20% $\downarrow$ P=0.22
US Carvedilol HF Trial program (1996)	Carvedilol	1094	6 months	Death	65% $\downarrow$
CIBIS II (1999)	Bisoprolol Vs Placebo	2647	16 months	Death	34% $\downarrow$
MERIT HF (2000)	Metoprolol CR/CL vs Placebo	3991	12 months	Death	34% $\downarrow$
BEST (2001)	Bucindolol vs Placebo	2708	2 years	Death	10% $\downarrow$
COPERNICUS (2001)	Carvedilol vs Placebo	2289	10 months	Death	35% $\downarrow$
CAPRICORN (2001)	Carvedilol vs Placebo	1959	1.3 yrs	Death or CV hospitalization	8% $\downarrow$
COMET (2003)	Carvedilol vs Metoprolol	3029	58 months	Death	17% $\downarrow$
SENIORS	Nebivolol vs Placebo	2128	21 months	Death or CV admission	14 % $\downarrow$

COMMIT/CCS-2<sup>19</sup> Metoprolol trial found no difference in mortality and no difference in the composite end point of death, re-infarction and VF between metoprolol and placebo groups. Mortality was increased in Patients presenting with hemodynamic compromise.

Current recommendations are to avoid early (<24 hr) beta-blocker use in patients with hemodynamic instability, or risk of cardiogenic shock (age > 70 yrs, systolic blood pressure <120 mmHg, heart rate >110 bpm, killip class III on presentation). Early metoprolol can be given in the setting of ongoing ischaemia with tachycardia or hypertension.

## Post-MI Myocardial Protection

Beta-blocker use in Post MI patients reduces CV events by 23% in prospective studies and upto 40% in observational studies.<sup>14,20</sup> The benefits are greatest in patients at high risk<sup>20</sup> (advanced age, LV dysfunction, large anterior infarction, complex ventricular ectopy). In fact, the only medications proven to reduce SCD in Post MI patients are beta blockers. 42 patients treated for 2 years prevents 1 death. The number needed to treat to achieve mortality reduction in post MI patients is fewer for beta-blockers when compared with antiplatelets or statins.<sup>16</sup> As noted earlier, early(<24 hr) use is avoided per the COMMIT/CCS-2 trial. The SAVE trial<sup>21</sup> demonstrated that ACE inhibitors and beta-blockers are additive in reducing post MI mortality.

Beta-blockers also confer a survival benefit in patients with COPD, DM and peripheral vascular disease.<sup>22,23</sup> Cardio-selective beta blockers (bisoprolol most cardioselective) are tolerated and effective in patients with mild pulmonary disease, although no beta-blocker is completely safe in bronchial asthma.

Analysis of diabetic subgroups in several Post MI beta-blocker trials demonstrate overall benefit of beta blocker use. Similarly, cardio-selective beta blockers do not worsen claudication symptoms and in fact improve survival in patients with PAD.<sup>24</sup>

Current recommendations are that beta-blockers must

be a part of standard therapy in Post MI patients unless contraindicated.

## Chronic Stable Angina

Beta-blockers are first line therapy in effort-induced chronic stable angina for all patients in the absence of a contraindication (ACC/AHA focused update 2007).<sup>25</sup>

Beta-blockers reduce myocardial oxygen demand, mainly via reduction of exertional heart rate.

No randomized trials have proven the effect of beta-blockers on improving survival in chronic stable angina. Certain subgroups, however, have shown improved survival. (Patients with prior MI and Patients with LV systolic dysfunction)

Adequate dosage is important. e.g. for atenolol, all doses improve angina, but only 100-200 mg/day improves exercise capacity.<sup>26</sup>

Non-selective beta-blockers should be avoided in Prinzmetal's angina as they may exacerbate vasospasm<sup>34</sup>

## Silent Ischemia and Syndrome X

Beta blockers are very effective in reducing the frequency and number of episodes of silent ischemia as well as in reducing cardiovascular events.<sup>27</sup> Beta blockers are effective in syndrome X and superior to calcium channel blockers.

## Anti-arrhythmic Effects<sup>10</sup>

Mechanisms: beta-blockers negate the arrhythmogenic influence of excessive catecholamine states.  $I_{CaL}$  and  $I_f$  ionic currents are inhibited at the level of action potentials. (class II effect). Sotalol, specifically, prolongs APD (class III anti-arrhythmic effect). Membrane stabilization effect (class I effect) is usually not seen at the therapeutic dosages of beta blockers employed

Efficacy & clinical use: in post-MI patients, beta-blockers are superior to other anti-arrhythmics for ventricular tachyarrhythmias and reduce arrhythmic cardiac deaths.<sup>10</sup>

The ESVEM study<sup>28</sup> showed that sotalol was more effective than a variety of class I anti-arrhythmics for ventricular tachyarrhythmias in post MI patients. Beta-blockers can slow, terminate or prevent supraventricular tachycardias (SVTs).

## Inherited Arrhythmogenic Disorders

ACC/AHA/ESC guidelines (2006)<sup>29</sup>

Beta-blockers are recommended for patients with a clinical diagnosis of Long QT syndrome 1 (LQTS 1). ICD + Beta blockers are recommended for patients with LQTS and h/o resuscitated cardiac arrest and who have a good functional status and reasonable expectation of survival for more than 1 year.

Beta-blockers are also the drugs of choice for patients with a clinical diagnosis of catecholaminergic Polymorphic VT (CPVT). Mutation carriers of CPVT should also receive beta blockers even in the absence of documented VT.

## Hypertension

In recent years, controversy has surrounded the use of beta blockers as initial therapy in Hypertension.

Concept of efficacy equivalence

Trial data suggest that, for the same degree of blood pressure control, most anti-hypertensive drugs provide the same

degree of cardiovascular protection.<sup>30</sup> e.g. trials like CAPPP, STOP-Hypertension-2, NORDIL, UKPDS, and INSIGHT found little overall difference in outcomes between older (diuretics/beta-blockers) and newer (ACE inhibitors, ARB's) antihypertensives.<sup>31,32</sup> Where outcome differences were noted, the drug providing better outcomes had better blood pressure control. e.g. in the ASCOT trial, amlodipine arm was superior to atenolol, the mean blood pressure being significantly lower in patients taking amlodipine.<sup>33</sup>

The largest meta-analysis so far on anti-hypertensives has been published (BMJ 2009).<sup>56</sup> The effect of blood pressure lowering drugs in reducing the risk of disease is entirely or largely due to blood pressure reduction, with one main exception, a special extra effect of  $\beta$  blockers in people who have had a recent myocardial infarction. The proportional reduction in coronary heart disease events and stroke for a given reduction in blood pressure, (an approximate halving in risk for each 10 mm Hg diastolic reduction), is the same in people with and without a history of vascular disease and in people without high blood pressure as well as in those with high blood pressure.

## The Beta-blocker Setback

In 1992, a large MRC outcomes trial conducted on British elderly patients (inderal vs a diuretic) found little benefit of beta-blockers against stroke and none against coronary events.<sup>34</sup> In 1998, Messerli<sup>35</sup> showed in a systematic review of trials that in the elderly, beta-blockers gave worse outcomes than did the diuretics.

Beta-blockers were also found to increase new-onset diabetes.<sup>36</sup> Lindholm et al (2005)<sup>37</sup> concluded in their meta-analysis that beta-blockers (as a group, but mainly atenolol) should not remain the first choice in the treatment of hypertension, failing to provide adequate protection against cardiovascular disease. The mechanism proposed was that central aortic systolic pressure decreased less as compared to brachial pressure.

In another met-analysis by Messerli et al, an intriguing finding was that greater the reduction of heart rate with beta-blockers, the high was the risk of CV events.<sup>38</sup>

On balance, it seems that rather than increasing CV events, beta blockers are less effective than other anti-hypertensives. Pooled analyses report a 16-22% reduction of stroke by beta-blockers, compared to 38% stroke reduction by other anti-hypertensives.<sup>39</sup>

The newer agents carvedilol and nebivolol have better metabolic and hemodynamic profiles, but their outcome data on hypertension are lacking.

Until further data become available,  $\beta$  blockers are not currently favoured as first line antihypertensive therapy,<sup>58</sup> particularly in the elderly, unless there are specific indications. (Post MI, class II or III systolic HF, or rate control for AF). An ACE inhibitor is usually co-prescribed in such settings.

## Other Cardiac Indications

Hypertrophic obstructive cardiomyopathy

Symptomatic patients are initiated on negative inotropic agents (beta-blockers, verapamil or disopyramide). Although randomized control trials are not available, beta-blockers are generally the first choice.<sup>40</sup>

Rationale: by slowing the heart rate, diastolic filling time is increased to improve diastolic function. This, together with the direct negative inotropic effect of beta-blockers, reduces the

Table 5 : Absolute Contraindications to Beta-blockers

Severe bradycardia, high grade AV blocks  
cardiogenic shock, frank LVF  
Severe bronchospasm  
Severe depression  
Symptomatic PAD (Rest pain, tissue loss)

LVOT gradient. Slowing the heart rate also decreases myocardial oxygen consumption, improving angina. Exercise-induced tachycardia and increase in LVOT gradient are also blunted by beta-blockers.

Clinical use : beta-blockers are initially effective in 60% to 80% of patients.<sup>41,42</sup> Large doses are usually needed (propranolol 200 to 400 mg/day or equivalent)

## Dissecting Aortic Aneurysm and Other Acute Aortic Syndromes

Anti-impulse therapy i.e. afterload reduction + beta-blockade are initially instituted to all hypertensive and most normotensive patients presenting with an acute aortic dissection.<sup>43</sup>

Rationale: this therapy reduces the risks of rupture or extension of dissection. Beta-blockers help reduce the dp/dt and also lower blood pressure.

Clinical use: I/V beta-blockers (esmolol, propranolol, metoprolol, or labetalol) are initiated, dose being titrated to a heart rate of 55 to 60 bpm. Then sodium nitroprusside is administered to a mean blood pressure of 60 to 70 mm Hg.<sup>44</sup>

Marfan's syndrome with aortic root involvement:

Chronic beta-blockade has been found in prospective trials to protect the aorta. The same applies logically to thoracic and abdominal aortic aneurysms.<sup>45,46</sup>

Mitral Stenosis with NSR.

Beta-blockers slow the heart rate and improve diastolic ventricular filling. In AF, beta-blockers may be added to control ventricular rate.

Neurocardiogenic Syncope

The role of medical therapy is less certain. Based on nonrandomized studies, beta-blockade is used to prevent stimulation of ventricular mechanoreceptors and thereby prevent vasovagal syncope. However, the POST trial found metoprolol to be ineffective.<sup>47</sup>

Fallot's Tetralogy : propranolol is used in cyanotic spells.

## Perioperative Beta-blocker Use

Studies in 1990s indicated that beta-blockers were beneficial perioperatively<sup>48,49</sup> and led various professional societies to endorse them in patients with known or suspected CAD. Then in 2005, Devereaux et al<sup>50</sup> published a meta-analysis of 22 trials of perioperative beta-blockade, with a conclusion that they had no discernible benefit. A very large observational study on perioperative beta-blocker use in noncardiac surgery (Lindenbauer et al 2005)<sup>51</sup> found a 42% reduction in mortality in patients at high cardiac risk. Patients at intermediate cardiac risk derived no benefit whereas patients with no risk factors had more adverse events and a high odds ratio of death. The MaVS study (2006)<sup>52</sup> also found no benefit (of metoprolol) in patients undergoing vascular surgery who otherwise were not at high cardiac risk.

In 2008, the landmark POISE trial,<sup>53</sup> a large prospective randomized control trial of perioperative beta-blockade with

metoprolol in 8351 patients (mostly intermediate risk) showed :

1. Reduced perioperative nonfatal MI (3.6% vs 5.1% P <.001)
2. Increased total perioperative mortality (3.1% vs 2.3% P <0.05)
3. Increased stroke rate (1% vs 0.5% P <0.01)
4. Increased hypotension and bradycardia

The latest 2008 meta-analysis on perioperative betablockade after POISE study<sup>54</sup> concluded that in patients having noncardiac surgery, perioperative beta-blockade provides no clear benefit in preventing short-term cardiovascular events.

The ACC/AHA 2007 guidelines<sup>55</sup> give class I Indication for perioperative beta-blockade only for patients:

1. with known CAD undergoing vascular surgery
2. already on chronic beta-blocker therapy

clearly, it is important to risk-stratify patients before noncardiac surgery, and administer beta-blockers only to patients with high cardiac risk.

## Contra Indications to Beta-blocker Use

Absolute contra-indications are mentioned in Table 5.<sup>10</sup>

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