NPTC Drug Class Review: Beta Blockers

Introduction

The purpose of this review is to support the IHS National P&T Committee in making recommendations for the IHS National Core Formulary (NCF) regarding the clinical effectiveness of the available beta blocker agents. The agents included are outlined in Table 1.

Table 1: Beta Blockers

Drug	Usual Hypertension Dosage (TDD)	Daily dosage frequency	Half-life (hours)	Cardioselective	Partial agonist activity (ISA)	Alpha agonist effect
Acebutolol	200-1200 mg	Twice	3-4	Yes	Yes	No
Atenolol	50-100 mg	Once	6-9	Yes	No	No
Betaxolol	5-40 mg	Once	14-22	Yes	No	No
Bisoprolol	5-20 mg	Once	9-12	Yes	No	No
Carteolol	2.5-10 mg	Once	6	No	Yes	Yes
Carvedilol	12.5-50 mg	Twice	7-10	No	No	Yes
Cavedilol phosphate (extended release)	10-80 mg	Once	10-11	No	No	Yes
Labetalol	200-1200 mg	Twice	3-6	No	No	Yes
Metoprolol tartrate	50-200 mg	Twice	3-7	Yes	No	No
Metoprolol succinate (extended release)	50-400 mg	Once	3-7	Yes	No	No
Nadolol	20-240 mg	Once	10-20	No	No	No
Nebivolol	5-40 mg	Once	12-19	Maybe	No	No
Penbutolol	20 mg	Once	5	No	Yes	No
Pindolol	10-60 mg	Twice	3-4	No	Yes	No
Propranolol	40-240 mg	Twice	3-4	No	No	No
Propranolol long-acting	60-240 mg	Once	8-11	No	No	No
Timolol	10-40 mg	Twice	4-5	No	No	No

This review specifically excludes esmolol, an ultra-short acting beta blocker available only in intravenous form. Esmolol is used primarily as an antiarrhythmic drug for intraoperative and other acute arrhythmias. It also excludes sotalol, a nonselective beta blocker with Class III antiarrhythmic activity that is used exclusively for arrhythmias.

FDA-Approved Indications and Off-Label Uses

All beta blockers are FDA-approved for the treatment of essential hypertension. Most of the beta blockers carry additional indications for the treatment of other disorders, such as; chronic stable angina, atrial arrhythmia, migraine headaches, bleeding esophageal varices, heart failure, post myocardial infarction, and decreased LV function after recent MI. Table 2 shows which agent carries which of these additional indications.

Table 2: Beta Blocker Approved indications

Drug	HTN	Chronic Stable Angina	Atrial Arrhythmia	Migraine	Bleeding Esophageal Varices	Heart Failure	Post MI	Decreased LV function after recent MI
Acebutolol	Yes	Yes						
Atenolol	Yes	Yes					Yes	
Betaxolol	Yes							
Bisoprolol	Yes							
Carteolol	Yes							
Carvedilol	Yes					Mild to severe		
Cavedilol phosphate (extended release)	Yes					Mild to severe		Yes
Labetalol	Yes							Yes

Metoprolol tartrate	Yes	Yes					Yes	
Metoprolol succinate (extended release)	Yes	Yes				Stable, symptomatic Class II-III		
Nadolol	Yes	Yes						
Nebivolol	Yes							
Penbutolol	Yes							
Pindolol	Yes							
Propranolol	Yes	Yes	Yes	Yes				
Propranolol long-acting	Yes	Yes	Yes	Yes				
Timolol	Yes			Yes			Yes	

Adapted from Drug Facts and Comparisons®

Pharmacology, Dosing, and Administration

Beta blockers inhibit the chronotropic, ionotropic, and vasoconstrictor responses to the catecholamines, epinephrine and norepinephrine. Most beta blockers have half-lives over six hours. These agents differ in their effects on the 3 adrenergic receptors (β_1, β_2, and α) and in their duration. Cardioselective beta blockers preferentially inhibit β_1 receptors that are principally found in the myocardium. Non-cardioselective beta blockers also inhibit β_2 receptor sites, which are found in smooth muscle in the lungs, blood vessels, and other organs. Beta blockers with intrinsic sympathomimetic activity (ISA) act as partial adrenergic agonists and would be expected to have less bradycardic and bronchoconstrictor effects than other beta blockers. Carvedilol and labetalol block α-adrenergic receptors and would be expected to reduce peripheral vascular resistance more than other beta blockers.

Efficacy/Effectiveness

The OHSU Evidenced-Based Practice Center published a drug class review in September 2007 of the beta adrenergic blockers[28]. They conducted a Cochrane review of randomized controlled trials and good-quality systematic reviews to evaluate efficacy. Unless otherwise cited, the following data came from this review.

Hypertension

Beta blockers are equally efficacious in controlling blood pressure in patients with hypertension. No beta blocker has been demonstrated to be more efficacious or to result in better quality of life than other beta blockers, either as initial therapy or when added to a diuretic, ACE inhibitor, or ARB. Evidence from long-term trials is mixed; overall, beta blockers are generally more effective than diuretics and usually no better than placebo, in reducing cardiovascular events. There was one exception: in one large trial, treatment with metoprolol resulted in lower all-cause mortality than treatment with a thiazide diuretic.

A Cochrane review was published in 2007 to look specifically at the issue of the use of beta blockers in hypertension. The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension[25]. This conclusion is based on the relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared to placebo or no treatment. More importantly, it is based on the trend towards worse outcomes in comparison with calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics. Most of the evidence for these conclusions comes from trials where atenolol was the beta-blocker used (75% of beta-blocker participants in this review). However, it is not known at present whether beta-blockers have differential effects on younger and elderly patients or whether there are differences between the different sub-types of beta-blockers.

Chronic stable angina

There were no differences in exercise tolerance or attack frequency in head to head trials of carvedilol vs. metoprolol, pindolol vs. propranolol, and betaxolol vs. propranolol in patients with chronic stable angina. Atenolol and bisoprolol were equivalent in angina patients with COPD. Atenolol and labetalol (when combined with chlorthalidone) were equivalent in angina patients with hypertension.

Beta blockers that have ISA reduce the resting heart rate less than other beta blockers, a potential disadvantage in patients suffering from angina pectoris. For this reason, experts recommend against using beta blockers with ISA in patients with angina.

Recent Myocardial Infarction

Timolol was the first beta blocker shown to reduce total mortality, sudden death, and reinfarction outcomes, all in the Norwegian Multicenter Study[1]. Subsequently, similar total mortality reductions were reported across trials of acebutolol[2], metoprolol tartrate, and propranolol in comparable populations. In addition, similar benefits in sudden death were reported for propranolol[3] and metoprolol tartrate[4, 5] and in reinfarction for metoprolol tartrate[5].

Carvedilol reduced reinfarction rates in the CAPRICORN trial, which recruited stable inpatients with recent myocardial infarction and a left ventricular ejection fraction of 40% or less. Carvedilol is the only beta blocker shown to reduce mortality in post-MI patients who are already taking an ACE inhibitor.

Indirect comparisons of beta blockers across these trials must be done with caution because the study populations differed in duration, the presence or absence of left ventricular dysfunction, the dose and timing of therapy, and the use of other medications.

Heart Failure

The main findings from placebo-controlled trials in patients with mild to moderate heart failure are summarized in Table 3. Reductions in mortality, sudden death, cardiovascular deaths, and death due to heart failure were similar for bisoprolol, metoprolol succinate, and carvedilol. Because several carvedilol trials performed in the US had significant mortality reductions, the evidence for carvedilol may be more relevant to a US population. When titrated gradually in stable patients, there is no difference in tolerability among the drugs.

In 2,289 patients with severe heart failure (COPERNICUS), carvedilol clearly reduced mortality and the combined endpoint of mortality and hospitalizations. Carvedilol has the most direct, strongest evidence. In a post-hoc subgroup analysis of 795 patients from the good-quality MERIT-HF trial, metoprolol succinate demonstrates a mortality reduction similar to that for carvedilol in patients who had a similar mortality risk. This is a weaker level of evidence than that for carvedilol, but the lack of direct comparator and the difficulty of comparing subjects from the different trials makes it uncertain whether one of these drugs is superior in patients with the various degrees of heart failure.

In COMET, a head-to-head trial conducted in patients with mild to moderate failure, carvedilol reduced mortality compared with metoprolol tartrate, the immediate-release form of metoprolol. In previous trials, however, metoprolol tartrate had been proven to reduce mortality. COMET does not resolve the question of whether carvedilol is superior to metoprolol succinate or bisoprolol, the preparations that have been shown to reduce mortality.

Table 3: Main findings in placebo-controlled trials of patients with mild-moderate heart failure

Beta Blocker	Mortality reduction	Reduction in sudden cardiac death	Reduction in progressive heart failure	Improvement in NYHA class	Improvement in exercise parameters	Improvement in QOL
Bisoprolol	Yes	Yes	Not proven	Yes	Not significant	Not significant
Carvedilol	Yes	Yes	Mixed results	Not proven	Not significant	Not significant
Carvedilol phosphate	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Metoprolol succinate	Yes	Yes	Yes	Not proven	Not significant	Yes

Atrial arrhythmia

Several beta blockers have been used to reduce the heart rate in patients with atrial tachyarrhythmias and to prevent relapse into atrial fibrillation or flutter. A recent good quality systematic review examined 12 studies of rate control in patients with chronic atrial fibrillation[6]. Atenolol, nadolol, and pindolol were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo.

We found one head-to-head trial comparing bisoprolol 10 mg and carvedilol 50 mg in patients subjected to cardioversion of persistent atrial fibrillation (>7 days)[7]. This fair-quality, 12-month trial enrolled 90 patients (mean age= 65.5; 82% male). Similar proportions of patients relapsed into atrial fibrillation during follow-up in the bisoprolol and carvedilol groups (53.4% vs. 43.6%; p=NS).

Two placebo-controlled trials evaluated beta blockers in patients with persistent atrial fibrillation[8-10]. One placebo-controlled trial found that metoprolol CR/XL 100-200 mg was effective in preventing relapse of atrial fibrillation /flutter after cardioversion[8, 9]. This fair quality trial was conducted in Germany and enrolled 433 patients after cardioversion of persistent atrial fibrillation that were 70% male, with a mean age of 60. Over 6 months, atrial fibrillation or flutter relapse rates were significantly lower in patients taking metoprolol CR/XL (48.7% vs. 59.8%; p=0.005). This trial was not powered to detect differences in rates of mortality as a primary endpoint. Death was reported as an adverse event and rates were not significantly different for the metoprolol CR/XL and placebo groups (3.1% vs. 0).

The other study examined the effects of carvedilol in managing patients with concomitant atrial fibrillation and heart failure[10]. This study was divided into two phases. The first phase involved a 4-month comparison of digoxin alone to the combination of digoxin and carvedilol and the second phase involved a 6-month comparison of digoxin alone to carvedilol alone. Forty-seven patients (mean age=68.5; 61.7% male) with atrial fibrillation (mean duration 131.5 weeks) and heart failure (predominantly NYHA class II-III; mean LVEF=24.1%) were enrolled in this fair-quality study. When added to digoxin, carvedilol significantly lowered the 24-hour ventricular rate (65.2 vs. 74.9bpm; p=<0.0001) and improved mean LVEF scores (30.6% vs. 26%; p=0.048) and severity of symptoms/functional capacity on a 33-point scale (6 vs. 8; p=0.039). There were no differences between monotherapies with either carvedilol or digoxin in the second phase, however.

Migraine headache

Five head to head trials show no difference in efficacy in reduction of attack frequency, severity, headache days or acute tablet consumption, or in improvement in any subjective or composite index in any of the comparisons made (atenolol or metoprolol durules or metoprolol or timolol vs. propranolol). Results from placebo controlled trials on similar outcome measures generally supports those for atenolol, metoprolol durules, and propranolol seen in head to head trials. Placebo controlled trial results also show that bisoprolol had a significant effect on attack frequency reduction and that pindolol had no appreciable effects.

Bleeding esophageal varices

One small head to head trial showed no difference between atenolol and propranolol in rates of non-fatal/fatal rebleeding and all-cause mortality. Results of one trial of nadolol and eight small placebo controlled trials of immediate release and two formulations of extended release propranolol do not provide any additional indirect evidence of the comparative efficacy across beta blockers in these clinical outcomes. The somewhat mixed results across the placebo-controlled trials of propranolol suggest that treatment initiation interval may have an effect on rebleeding rates.

Safety / Tolerability

Side effects are common among patients taking beta blockers. In longer-term trials (12-58 months) directly comparing beta blockers in patients with hypertension (atenolol vs. bisoprolol vs. propranolol), heart failure (carvedilol vs. metoprolol), bleeding esophageal varices (atenolol vs. propranolol), or atrial fibrillation (bisoprolol vs. carvedilol), a few differences in specific adverse events were noted. But, overall, no particular beta blocker stood out from the others as being consistently associated with a significantly less favorable adverse effect profile.

In everyday practice, weight gain, fatigue, dizziness, and dyspnea are the most common side effects in patients with heart failure. About 1 in 5 patients require discontinuation of the initial beta blocker choice. In a retrospective review of one series of 268 patients seen in a U.S. heart failure clinic, 54% were started on carvedilol and 46% on metoprolol succinate or metoprolol tartrate[11]. Overall, about 1 in 5 patients (51 total) could not tolerate the initial choice of treatment. Forty of the 51 patients who could not tolerate the initial choice were switched to another beta blocker. Twenty two of these 40 patients tolerated the second choice, with equal proportions tolerating a switch to carvedilol from metoprolol and to metoprolol from carvedilol.

A higher rate of beta blocker intolerance was reported in another trial that enrolled 90 consecutive patients in a heart failure clinic in Denmark[12]. This trial compared bisoprolol and carvedilol and was designed to measure treatment failure rates under conditions that mimic daily clinical practice. The eligibility criteria were lax and

the dosing regimen was flexible. Overall, 40% of patients (35 of 87) did not tolerate beta blocker therapy. Intolerance rates were similar in the bisoprolol and carvedilol groups (39% vs. 40%). This trial had some important methodological flaws, however. The trial used an inadequate method of randomization. Between-group differences at baseline confirm the inadequacy of the randomization method. The bisoprolol group was comprised of a significantly higher proportion of females (31% vs. 17%) and a numerically lower proportion of patients with an LVEF < 25% (27% vs. 43%). Further, the team that treated and assessed the patients was not blinded to beta blocker assignment and the analysis excluded 3 patients that died prior to completing 2 months of follow-up. Group assignment of the 3 excluded patients was not reported. For these reasons, we rated this trial as poor quality and recommend a cautious interpretation of these potentially unreliable results.

Specific adverse effects

Bradycardia

Rates of bradycardia were reported in short-term hypertension trials and in longer-term heart failure trials[13-17]. Overall, no significant differences between beta blockers were reported.

Dizziness

Seven head to head trials reported dizziness incidence[15, 18-23]. All but one reported no significant differences between beta blockers[19]. Carvedilol was associated with higher rates of dizziness than metoprolol in a 44-month trial of 122 patients with heart failure (14.7% vs. 1.3%; p=0.0046)[19]. This significant difference was not seen in another shorter trial [3 months in 368 patients with angina (4.8% vs. 5.0%)][23], nor was there a significant difference in rates of dizziness in a head to head trial of carvedilol versus atenolol in patients with recent myocardial infarction (36.4% vs. 27.2%; p=0.131)[18]. Reasons for this inconsistency may include differences in definition of dizziness and evaluation techniques between the two trials. This assumption cannot be verified, however, as the methods were not provided. Indirect comparison of the inconsistent head-to-head trial results to available fair-good quality placebo-controlled trials safety data does not offer any additional information as dizziness rates in metoprolol trials were not reported.

Hypotension

Rates of hypotension were similar for carvedilol and metoprolol across two longer-term trials of patients with heart failure[17, 19]. Only 2.7% of patients from either treatment group experienced hypotension in the smaller (n=122), 44-month trial. After 58 months in the COMET trial (n=3029), 14% of patients taking carvedilol and 11% of patients taking metoprolol had hypotensive events.

New-onset diabetes

Retrospective analysis of data from the COMET trial was used to study the development of new-onset diabetes in heart failure patients treated with metoprolol tartrate or carvedilol[24]. New-onset diabetes was identified post-hoc among a cohort of 2,298 patients without diabetes at baseline. The endpoint of new-onset diabetes was based on patient reporting and notes in hospital files and was considered present when there was documentation of a diagnosis of diabetes mellitus or diabetic coma, patients started antidiabetic treatment during the trial, or if patients had two or more random blood glucose readings above 11.1 mmol/l. The main finding of this analysis was that more patients receiving metoprolol tartrate developed new-onset diabetes than those receiving carvedilol (10.1% vs. 8.7%; HR 0.78; 95% CI 0.61 to 0.997). Although noteworthy, this finding should be interpreted with caution, keeping in mind that it is based on a post-hoc analysis and relies on a clinical, rather than guideline-based definition of diabetes.

Tolerability

Reversible airway disease

A Cochrane review published in 2001 concluded that cardioselective beta-blockers given in mild to moderate reversible airway disease or COPD, do not produce adverse respiratory effects in the short term[26]. Given their demonstrated benefit in conditions such as heart failure, cardiac arrhythmias and hypertension,

these agents should not be withheld from such patients. Long term safety (especially their impact during an acute exacerbation) still needs to be established.

Chronic obstructive pulmonary disease

A Cochrane review published in 2002 concluded that cardioselective beta-blockers, given to patients with COPD in the identified studies did not produce adverse respiratory effects[27]. Given their demonstrated benefit in conditions such as heart failure, coronary artery disease and hypertension, cardioselective beta-blockers should not be routinely withheld from patients with COPD.

Conclusions

The results of this review are summarized in the following table:

Table 4: Summary of evidence

Key Question 1: Comparative Efficacy	Grade of Evidence*	Conclusion
a. Hypertension	Overall grade: Poor	No head to head trials of long-term (≥ 6 months) health or QOL outcomes. Reliable indirect comparisons cannot be made by evidence from 3 long-term placebo-controlled trials of propranolol and atenolol.
b. Angina	Overall grade: Fair	No significant differences in 5 head to head trials of carvedilol vs. metoprolol, pindolol vs. propranolol and betaxolol and propranolol in patients with stable angina. Atenolol=bisoprolol in patients with chronic stable angina and COPD. Atenolol=labetalol when added to chlorthalidone in patients with chronic stable angina. One short-term, placebo-controlled trial of propranolol did not add any meaningful evidence of comparative efficacy in the above parameters.
c. Status-post coronary artery bypass graft (CABG)	Overall grade: Poor	Metoprolol did not benefit mortality or ischemic events in a longer-term (> 7 days), placebo-controlled trial (MACB).
d. Recent MI	Overall grade: Fair-good	One fair-quality head to head trial found no differences in mortality after one year between atenolol and propranolol, but this was a relatively small trial; 1 fair-quality head-to-head trial found no differences in time to serious cardiovascular events between carvedilol and atenolol. Similar mortality reductions reported for acebutolol, metoprolol tartrate, propranolol and timolol in placebo controlled trials of patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol. No studies of carvedilol phosphate (extended-release carvedilol) in patients with recent MI were identified.

		Carvedilol reduced mortality and reinfarction in 1 placebo controlled trial of patients with a mean LVEF of < 32.7% (CAPRICORN). 4 systematic reviews were not designed to assess comparative efficacy.
e. Heart failure	Health outcomes in HTH trials: Fair	Carvedilol > metoprolol tartrate in reducing total mortality in COMET in patients with mild-moderate heart failure.
	Symptoms in HTH trials: Good	Carvedilol=metoprolol tartrate in improving symptoms (quality of life; NYHA) and exercise capacity in 4 head to head trials.
	Placebo-controlled trials in mild-moderate HF: Good	Metoprolol succinate reduced total mortality, sudden death, and death due to progressive heart failure and improved quality of life (MERIT-HF). Carvedilol reduced total mortality, sudden death, and death due to pump failure (MOCHA). Bisoprolol reduced total mortality and sudden death No studies of carvedilol phosphate (extended-release carvedilol) in patients with mild-moderate heart failure were identified.
	Placebo-controlled trials in severe HF: Fair+ for carvedilol and Fair- for metoprolol succinate	Carvedilol reduced mortality and the combined endpoint of mortality and hospitalizations in a prospective trial. A post-hoc, subgroup analysis of MERIT-HF suggests that metoprolol succinate is similarly effective in comparable patients. No studies of carvedilol phosphate (extended-release carvedilol) in patients with severe heart failure were identified.
f. Atrial arrhythmia	Overall grade: Fair	Bisoprolol=carvedilol in preventing relapse of atrial fibrillation in a head-to-head trial. Metoprolol succinate reduced incidence of atrial arrhythmia/fibrillation in a placebo-controlled trial. Carvedilol reduced 24-hour ventricular rate in patients with atrial fibrillation and heart failure in one placebo-controlled trial. These placebo-controlled trials do not offer comparative data.
g. Migraine	Overall grade: Fair	Atenolol, slow release metoprolol, immediate release metoprolol, and timolol were all similar to propranolol in their effects on pain outcomes and acute medication use in 5 head to head trials.
h. Bleeding esophageal varices	Overall grade: Poor	Results of 1 head to head trial of atenolol and propranolol, 1 placebo controlled trial of nadolol and 6 placebo controlled trials of immediate release, and 2 formulations of extended release propranolol, all

		fair quality, don't clearly differentiate one beta blocker from another.

*Quality of evidence ratings based on criteria developed by the Third U.S. Preventive Services Task Force.

A few differences in specific adverse event rates were noted across longer-term trials directly comparing one beta blocker to another. But, overall, no particular beta blocker stood out from the others as being consistently associated with a less favorable adverse effect profile.

Evidence showed that age, gender, and race did not impact the effectiveness of carvedilol, immediate and controlled release metoprolol, and propranolol. There was insufficient evidence on the effect of beta blockers on perinatal mortality or preterm birth based on one systematic review. Subgroup analyses of placebo controlled trials showed that a history of MI may reduce the protective effect of bisoprolol on mortality (CIBIS). No risk factor was found to confound the protective effect of carvedilol (COPERNICUS) or controlled release metoprolol (MERIT-HF) on mortality. The MIAMI trial found that metoprolol had the greatest protective effect on mortality in patients with numerous risk factors. The BHAT trial found no variation in propranolol's protective effect on total mortality based on history of heart failure. Subgroup analysis of the SHEP trial found that the addition of atenolol to chlorthalidone did not significantly affect mortality relative to placebo. Metoprolol use reduced all-cause mortality and hospitalizations relative to placebo in a subgroup analysis of the MERIT-HF trial.

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