
Oregon Health Resources Commission



Draft

Beta Adrenergic Blockers

Pharmaceutical Subcommittee Report

Update #3 March 2008

This report is an update of the initial
 β -Blocker Subcommittee Report of March 2004.
All revisions are highlighted.

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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission to advise the Department of Human Services on this Plan.

Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed. The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

In the fall of 2003 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of Beta Adrenergic Blocker drugs. Members of the subcommittee consisted of a cardiologist, internists, pharmacists, a registered nurse, and a consumer advocate. The subcommittee had five meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The original OHSU EPC draft report, “Drug Class Review on Beta Adrenergic Blockers” was completed on September 26, 2003, circulated to subcommittee members and posted on the web. The Beta Blocker (β -Blocker) Subcommittee met on October 13, 2003 to review the document and additional evidence. By consensus, the subcommittee members agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. The subcommittee’s final meeting was held on March 11, 2004 to review the draft subcommittee report. All available sources of information including the EPC report, information submitted by pharmaceutical manufacturers, and public testimony were considered. The conclusions drawn by the β -blocker Subcommittee comprise the body of this report.

The HRC Pharmaceutical Subcommittee performs evidence-based reviews based on DERP reports as they become available. The *Drug Class Review on Beta Adrenergic Blockers Update Report #3* was completed in August, 2007. Members of the pharmaceutical subcommittee consisted of one HRC physician member, two subcommittee physicians, one nurse practitioner, one PhD. RPh, and a PharmD. The committee had one meeting held in public with appropriate notice provided.

The pharmaceutical subcommittee met on March 4, 2008 to review the document and additional evidence. By consensus, the committee members agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. All available sources of information from the EPC’s report *Drug Class Review on Beta Adrenergic Blockers Update Report #3* that included information submitted by pharmaceutical manufacturers and public testimony, were considered. The Update Committee presented its findings to the HRC and the revisions were approved at its meeting on March 21, 2008.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Pharmaceutical Subcommittee or the Health Resources Commission. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the Health Resources Commission in providing recommendations to the Department of Human Services.

The Pharmaceutical Subcommittee of the Health Resources Commission, working together with the EPC and the Center for Evidence-based Policy (Center), will

monitor medical evidence for new developments in this drug class. Within a year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration (FDA) changes in indications and safety recommendations will be evaluated. The β -Blocker report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a β -blocker Subcommittee.

The full OHSU EPC's Updated Final Report #3, *Drug Class Review on Beta Adrenergic Blockers*, is available on the Office for Oregon Health Policy & Research, PMPDP website:

http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website:

<http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/process.shtml>

You may request more information including copies of the draft report, and minutes of subcommittee meetings, from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the Center by contacting:

Alison Little, MD
OHSU Center for Evidence-based Policy
2611 SW 3rd Avenue, MQ280
Portland, OR 97201-4950
E-mail: littleal@ohsu.edu

There will be a charge for copying and handling in providing documents both from the Office for Oregon Health Policy & Research and from the Center for Evidence-based Policy.

Critical Policy:

■ *Senate Bill 819*

- "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The

purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

■ *Health Resources Commission*

- “Clinical outcomes are the most important indicators of comparative effectiveness”;
- “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Inclusion Criteria:

■ *Populations*

- Adult patients with hypertension (blood pressure $\geq 140/90$ mm Hg), stable angina pectoris, post-coronary artery bypass graft (CABG), recent myocardial infarction, congestive heart failure, atrial arrhythmias, migraines, or bleeding esophageal varices.

■ *Interventions*

- Interventions include an oral B-Blocker compared with another B-Blocker, another drug (such as calcium channel blocker), or placebo. (Oral beta blockers: acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, carteolol, labetalol, metoprolol tartrate (IR), metoprolol succinate (ER), nadolol, penbutolol, pindolol, propranolol, propranolol LA, and timolol.

■ *Effectiveness*

- For effectiveness, study is a randomized controlled trial. Crossover trials will be included.

■ *Efficacy Measures are dependent on clinical conditions as noted in Table 1:*

Table 1

Hypertension	<ol style="list-style-type: none"> 1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure) 3. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance) 4. Quality-of-life
Stable angina (treatment \geq 2 months' duration)	<ol style="list-style-type: none"> 1. Exercise tolerance 2. Attack frequency 3. Nitrate use
Post-coronary artery	<ol style="list-style-type: none"> 1. All-cause mortality

bypass graft (long-term treatment)	2. Ischemic events (MI, unstable angina, need for repeat CABG and PTCA)
Recent myocardial infarction (with and without LV dysfunction)	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Symptomatic chronic heart failure	1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure
Asymptomatic LV dysfunction	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Atrial fibrillation/flutter	1. Rate control 2. Relapse into atrial fibrillation
Migraine	1. Attack frequency 2. Attack intensity/severity 3. Attack duration 4. Use of abortive treatment
Bleeding esophageal varices	1. All-cause mortality 2. Fatal/non-fatal re-bleeding

■ *Safety and Adverse Effects.*

- Exacerbation of peripheral vascular disease, exacerbation of reactive airway disease, hypoglycemia, depression, fatigue, and sexual dysfunction. Intermediate measures of efficacy (such as blood pressure control) and of adverse events (such as airway resistance measures or ejection fraction) are not included.
- Adverse effects that may be dose-related will only be assessed in head-to-head trials where dose can be taken into account.
- For adverse effects, studies will be a controlled clinical trial or population-based observational study. Drug-drug interaction studies of shorter duration will be included.

Exclusion Criteria:

- No original data: the paper does not contain original data (e.g., non-systematic review, editorial, letter with no original data). Good quality systematic reviews will be used as appropriate to inform the current review.
- Studies of multiple interventions where the effect of the β -blocker cannot be delineated.

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- Studies conducted entirely in the inpatient setting are excluded.
 - For hypertension, studies in which blood pressure lowering was the only endpoint.
 - For angina, studies less than 2 months.
 - For post-CABG patients, studies of short-term β -blockers to suppress atrial arrhythmias.

Definition of β -Blockers

Beta-Adrenergic receptor blocking drugs (β -Blockers) are competitive, pharmacologic antagonists that compete with norepinephrine for adrenoreceptors. They are a heterogeneous group of compounds that inhibit the chronotropic, inotropic and vasoconstrictive responses to adrenaline. Two subfamilies of adrenoreceptors for the neurotransmitter norepinephrine— α and β are further subdivided into subtypes α_1 or α_2 , and β_1 or β_2 . Clinically, β -Blockers are usually classified into subgroups on the basis of β_1 vs. β_2 selectivity, partial agonist activity (concurrent α receptor blockade), intrinsic sympathomimetic activity (ISA), and lipid solubility.

Several characteristics of β -Blockers may be related to their clinical effectiveness such as cardioselectivity and ISA. Historically, the term “cardioselective,” has been used to describe β_1 -adrenoreceptor antagonists; however, these agents will affect any tissues that express β_1 adrenoreceptors. Cardioselective β -Blockers (atenolol, bisoprolol, and metoprolol) preferentially inhibit β_1 receptors that are principally found in the myocardium. Non-cardioselective β -Blockers inhibit both β_1 and β_2 receptor sites. Pindolol is further distinguished as the only β -Blocker marketed in the United States with ISA that involves simultaneous weak stimulation of receptors and catecholamine blockage. Carvedilol and labetalol block α receptors as well as β_1 and β_2 receptor sites.

In 1965 Snow reported that treatment with propranolol reduced the mortality rate in patients with acute MI.¹ Since then a wide range of β -Blockers have appeared on the market and have become one of the most extensively investigated of all drugs.

β -Blockers are an example of a class of drugs that have been avoided for the treatment of heart failure for decades because of the theoretical risks and the pharmacologic profile not fitting the understanding of the pathophysiology of disease. It had been assumed that activation of the sympathetic nervous system in patients with heart failure was an important compensatory mechanism, giving

¹ Snow PJ, Effect of propranolol in acute myocardial infarction. *Lancet* 18;2(7412):551-553, Sept. 18, 1965
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inotropic support to the heart and helping maintain blood pressure. It was assumed that blocking this supporting mechanism would be harmful. The detrimental effects of chronic sympathetic activation on the heart appear, however to outweigh any short-term benefit. From this pathophysiologic perspective there is a sound theoretical rationale for the use of β -Blockers. Over the past several years, understanding the effect of activation of the renin-angiotensin system and the sympathetic nervous system on the pathophysiology of heart failure has resulted in the development of drugs that have improved morbidity and mortality associated with heart failure.

This review covers all the 15 oral β -Blockers currently marketed in the United States. Please note we define metoprolol tartrate IR (immediate release) and propranolol as short acting, and metoprolol succinate ER (extended release) and propranolol LA and Carvedilol Phosphate as the extended release forms.

<u>Generic</u>	<u>Brand</u>
1. Acebutolol	Sectral
2. Atenolol	Tenormin
3. Betaxolol	Kerlone
4. Bisoprolol	Zebeta
5. Carvedilol	Coreg
6. Carvedilol Phosphate (ER)	Coreg CR
7. Labetalol	Normodyne
8. Metoprolol Tartrate (IR)	Lopressor
9. Metoprolol Succinate (ER)	Toprol XL
10. Nadolol	Corgard
11. Penbutolol	Levatol
12. Pindolol	Visken
13. Propranolol	Inderal
14. Propranolol LA (long acting)	Inderal LA
15. Timolol	Blocadren

Quality of the Evidence

For quality of evidence the Pharmaceutical Subcommittee took into account the number of studies, the total number of patients in each study, the length of the

study period, and the end points of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency and power of the body of evidence relevant to that question.

The subcommittee's task was to identify β -Blockers that would offer the greatest likelihood of success for the treatment of cardiovascular disease including hypertension, angina, post MI, CHF, and atrial arrhythmias. Additionally, it was our task to identify β -Blockers used to prevent migraine headaches or to treat bleeding esophageal varices.

Key Questions:

1. For adult patients with hypertension (blood pressure $\geq 140/90$ mm Hg), stable angina pectoris, post-coronary artery bypass graft (CABG), recent myocardial infarction, congestive heart failure, atrial arrhythmias, migraines, or bleeding esophageal varices do β -Blockers differ in efficacy?
2. Do β -Blockers differ in safety or adverse effects?
3. Are there subgroups of patients based on demographics (race, ethnicity, gender), use of other medications, or co-morbidities, for which one β -Blocker is more effective or associated with fewer adverse effects?

New Findings

- No new information was obtained from pharmaceutical dossiers for this update.
 - There were 7 new publications identified that met inclusion criteria.

Amended Summary of Results

Key Question 1A. For adult patients with hypertension do β -blockers differ in efficacy?

Information to compare the efficacy of different β -Blockers for treatment of blood pressure is poor. All β -Blockers studied by the EPC have been found to be effective in lowering blood pressure when compared to placebo. However, there are no head to head trials for long term (>6 months) health outcomes, survival, or quality of life.

The Joint National Committee on the Prevention, Detection, evaluation and Treatment of High Blood Pressure (**JNC-7**) recommends a diuretic as the first-line treatment for most patients who have Stage 1 (systolic blood pressure 140-149 and diastolic blood pressure 90-99) without compelling indications.² It recommends a β -Blocker usually in conjunction with a diuretic or an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in patients with Stage 1 or 2 hypertension who also have heart failure, recent myocardial infarction, high risk of coronary artery disease, or diabetes.

By the time β -Blockers became available; diuretics had already been shown to prevent cardiovascular events, primarily strokes. It was considered unethical to compare a β -Blocker to placebo in patients who were likely to benefit from a diuretic. Unlike diuretics, β -Blockers have not been clearly demonstrated to be more effective than placebo in reducing cardiovascular events when used as initial hypertensive therapy.

Of the trials that compared a β -Blocker with a diuretic, only one (**MAPHY**) had even a suggestion that the β -Blocker was more effective than hydrochlorothiazide

² Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. JAMA 2003; 289: (19):2560-2572.

or bendroflumethiazide.³ A good quality meta-analysis of 10 trials published in 1998 or earlier, β -Blockers were less effective than comparator drugs in preventing coronary heart disease cardiovascular mortality, and all-cause mortality (ORs, 1.01, 0.98, and 1.05, respectively).⁴

KQ 1A. The Pharmaceutical Subcommittee agrees by consensus:

- **For adult patients with hypertension there is no evidence to suggest that one β -Blocker is more effective in the treatment of hypertension than another.**
- **No mortality benefit has been found with the use of β -Blockers in otherwise healthy patients with essential hypertension.**

Key Question 1B. For adult patients with angina pectoris do β -Blockers differ in efficacy?

Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol tartrate (IR), metoprolol succinate (ER), nadolol, penbutolol, pindolol, propranolol, propranolol LA and timolol reduce anginal attacks. Five fair-quality head-to-head trials of different β -blockers found no significant differences in exercise tolerance, attack frequency or use of nitrates after two months of treatment. These trials made 5 comparisons— betaxolol vs. propranolol, carvedilol vs. metoprolol tartrate (IR); pindolol vs. propranolol, atenolol vs. bisoprolol, or in combination with chlorthalidone (atenolol vs. labetalol) had no significant differences in any exercise tolerance, attack frequency or use of nitrates. Numerous short-term placebo-controlled trials did not provide sufficient evidence to identify any β -Blocker as clinically superior.

³ Wikstrand J, Warnold I, Olsson G et al. Primary prevention with metoprolol in patients with hypertension. JAMA 1988;259(13):1976-82.

⁴ Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279(23):1903-7

β -Blockers that have intrinsic sympathomimetic activity (acebutolol, carteolol, penbutalol, and pindolol) reduce the resting heart rate less than other β -Blockers, a potential disadvantage in patients suffering from angina pectoris. For this reason, expert opinion recommends against using β -Blockers with ISA in patients with angina.⁵

KQ 1B. The Pharmaceutical Subcommittee agrees by consensus that for adult patients with angina:

- **Acebutolol atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol tartrate (IR), metoprolol succinate (ER), nadolol, penbutolol, pindolol, propranolol, propranolol LA, or timolol reduced anginal attacks in patients with stable angina in short term studies which did not allow mortality evaluation.**
- **The current evidence does not identify any β -Blocker as clinically superior.**

Key Question 1C. For adult patients post coronary bypass surgery do β -Blockers differ in efficacy?

Use of β -Blockers after coronary artery bypass graft (CABG) surgery has not been shown to improve mortality or prevent other ischemic events such as MI, unstable angina, need for additional CABG or percutaneous transluminal coronary angioplasty (PTCA). Evidence is insufficient to determine whether β -blockers differ in their efficacy after coronary bypass surgery.

KQ 1C. The Pharmaceutical Subcommittee agrees by consensus that for adult patients with coronary artery bypass surgery β -Blockers following coronary artery bypass surgery do not reduce mortality or prevent adverse cardiovascular events.

⁵ Drug Class Review on Beta Adrenergic Blockers, Sept. 2004, p 11.

Key Question 1D. For adult patients post myocardial infarction do β -Blockers differ in efficacy?

The subcommittee decided to focus on post myocardial infarction (MI) following discharge from the hospital. Twenty five years ago, timolol was the first β -Blocker shown to reduce total mortality, sudden death, and reinfarction outcomes.⁶ Acebutolol, atenolol, metoprolol tartrate (IR) and propranolol slightly reduced mortality in several older short-term studies conducted before the advent of thrombolysis and coronary artery catheter intervention. One fair quality head-to-head trial found no difference between atenolol, propranolol, and placebo after one year. A second head-to head trial⁷, a fair quality open label study evaluated atenolol vs. carvedilol for change in LVEF (primary outcome) at one year and time to first serious cardiovascular event (secondary outcome). There was no significant difference found between the two interventions, but the authors acknowledge that the study is underpowered to evaluate the secondary outcome so no conclusion can be drawn.

Twenty longer-term placebo controlled studies of >100 patients evaluated atenolol (2 trials), carvedilol (2), metoprolol tartrate (IR) (7), pindolol (2), and propranolol (7). Among these trials, difference in mortality rates between β -blockers and placebo were statistically significant in three: Carvedilol Post-Infarct Survival Control in LV Dysfunction (**CAPRICORN**), the Goteborg Metoprolol Trial (metoprolol tartrate [IR]) and the Beta-Blocker Heart Attack Trial (**BHAT**) (propranolol).

CAPRICORN is the only trial to demonstrate the added benefit of a β -Blocker in post-MI patients with mild or asymptomatic LV dysfunction already taking ACE inhibitors or having undergone thrombolytic therapy or angioplasty. Additional information from the FDA website about the recruitment of patients and the centers at which the CAPRICORN was conducted raise concern that of the 1949 subjects in this multi-center trial, only 83 were enrolled in the US and 5 were from Canada. Five of the top 6 recruiting sites were in Russia and that country accounted for 600 of the total subjects. In fairness to this study, recruitment was slow in some countries where it was widely perceived that the case for β -Blockers in all patients with myocardial infarction was proven.⁸

⁶ Anonymous. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *NEJM* 1981; 304(14):801-7

⁷Jonsson G, Abdelnoor M, Muller C, Kjeldsen SE, Os I, Westheim A. A comparison of the two beta-blockers carvedilol and atenolol on left ventricular ejection fraction and clinical endpoints after myocardial infarction. a single-centre, randomized study of 232 patients. *Cardiology*. 2005;103(3):148-155

⁸ Anonymous, Effect of carvedilol on outcome after MI in patients with LV dysfunction: the CAPRICORN randomized trials. *Lancet* 2001;351(9266)1385-1390.

A more recent review (Freemantle, 1999) used meta-regression to examine the relationship of characteristics of different β -Blockers with the outcome of treatment.⁹ Acebutolol, carvedilol, metoprolol tartrate, propranolol and timolol significantly reduced mortality. However, there was a trend towards decreased benefit in β -Blockers with intrinsic sympathomimetic activity.

Evidence on the effect of beta blockers on post-myocardial infarction arrhythmias is unclear based on the available evidence. No significant difference in occurrence of post-MI arrhythmia (defined as cardiac arrhythmia, fibrillation, or tachycardia) was found in placebo-controlled trials of acebutolol (1 trial) or propranolol (1 trial), while one placebo-controlled trial of propranolol found a small, but significantly higher, percentage of withdrawals due to serious ventricular arrhythmia in the placebo group (0.3% propranolol vs. 1.0% placebo; $p < 0.025$).¹⁰ One trial of timolol found a significantly higher proportion of patients experiencing ventricular tachycardia with placebo use (20% placebo versus 8.5% timolol; $p = 0.05$) while the number of episodes of ventricular tachycardia (55 placebo versus 10 timolol) was not statistically significant (data not provided)¹¹.

Two publications comparing carvedilol to placebo presented mixed results. One older trial found no significant difference between the two drugs in the rate of cardiac arrhythmias among all enrolled patients¹². In a subgroup analysis of patients ($n = 49/151$; 32%) with baseline LVEF $< 45\%$, carvedilol was associated with a significant decrease in serious cardiac events, a combined endpoint that included death, reinfarction, unstable angina, congestive heart failure, and ventricular tachycardia ($p = 0.04$). The second publication, a post-hoc analysis of data from the CAPRICORN trial, compared rates of atrial and ventricular arrhythmias¹³. As stated above, patients enrolled in the CAPRICORN trial had baseline LVEF $\leq 40\%$. Atrial and ventricular arrhythmias were found to be less common with carvedilol use relative to placebo: HR 0.48 95% CI 0.30-0.76; $p = 0.0015$ and HR 0.37 95% CI 0.24-0.58; $p < 0.0001$, respectively. These values remained significant when controlling for history of arrhythmias. Carvedilol was also found to reduce the risk of all analyzed combinations of death and arrhythmia outcomes

⁹ Freemantle N, Cleland J, Young P, et al. Beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;318(7200):1730-7

¹⁰ Anonymous, A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247(12):1707-1714

¹¹ Roque F, Amuchastegui LM, Lopez Morillos MA, et al. Beneficial effects of timolol on infarct size and late ventricular tachycardia in patients with acute myocardial infarction. *Circulation* 1987;76(3):610-617

¹² Basu S, Senior R, Raval U, Van der Does R, Bruckner T, Lahiri A. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction: A placebo controlled randomized trial. *Circulation* 1997;96(1):183-191.

¹³ McMurray J, Kober L, Robertson M, et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. *J Am Coll Cardiol*. Feb 15 2005;45(4):525-530

KQ 1D. The Pharmaceutical Subcommittee agrees by consensus that for adult patients with myocardial infarction:

- **The following drugs when compared to placebo decreased mortality: Acebutolol, carvedilol, metoprolol tartrate (IR), propranolol, and timolol however there is insufficient data to distinguish among the β -Blockers .**
- **Evidence is unclear as to the efficacy of beta blockers for controlling post MI dysrhythmias.**

Key Question 1E. For adult patients with heart failure (HF) do β -Blockers differ in efficacy?

Recognition of the deleterious effects of activated sympathetic nervous system neurohumoral agents in HF has prompted investigation of β -Blockers use in patients with this disorder. Many studies have confirmed that β -Blockers reduce death, improve symptoms, and increase exercise capacity in patients with HF due to systolic left ventricular dysfunction. Acceptance of β -Blocker treatment in HF has developed slowly over the last two decades, in part because of concern that the negative inotropic effects of these medications can worsen heart failure symptoms. Because of this potential it is important that β -Blockers be given to HF patients only after they have been stabilized hemodynamically with ACE inhibitors or angiotensin receptor blockers (ARBs) or hydralazine with isosorbide dinitrate and diuretics. Lower doses of β -Blockers should be used to initiate therapy and gradually increased to the target dose.

Four large trials have been completed in the last 5 years and, in general, they support the concept that β -blockers are beneficial in heart failure. These trials found that bisoprolol, carvedilol, and metoprolol succinate (ER) reduce mortality, preventing 3.8 deaths/100 patients in the first year of treatment. The initial US Carvedilol Heart Failure Trials Program, which was not designed to assess mortality, was followed by The Cardiac Insufficiency Study (**CIBIS-II**), a trial powered to study the mortality benefit of used in patients with heart failure. The largest β -Blocker trial, Metoprolol CR/XL Randomized Intervention Trial in patients with heart failure (**MERIT-HF**) was reported shortly after the first 2 trials. The Carvedilol Prospective Randomized Cumulative Survival

(**COPERNICUS**) provided additional insight into the mortality benefits of β -blocker use in patients with heart failure. No studies of carvedilol phosphate (ER) were identified. The FDA approval for this drug for use in patients with Heart failure was based on pharmacokinetic and pharmacodynamic data which showed bioequivalence with carvedilol.

Reductions in mortality, sudden death, cardiovascular deaths and deaths due to heart failure were similar for bisoprolol, metoprolol succinate and carvedilol. Because several carvedilol trials performed in the U.S. had significant mortality reductions, the evidence for carvedilol may be more relevant to a U.S. population. The EPC and subcommittee will continue ongoing evaluation of data from these trials.

A large (3029), lengthy (58 months) good-quality head-to-head trial, Carvedilol Or Metoprolol European Trial (**COMET**), showed evidence that carvedilol is superior to metoprolol tartrate (IR) in patients with mild-moderate chronic heart failure (carvedilol mortality was 34% vs. metoprolol tartrate (IR) 40%; NNT=18; $p<0.0017$). **COMET** attempted to answer the question of whether to use a selective β -Blocker (metoprolol tartrate [IR]) vs. a non-selective agent with alpha-adrenergic blocking effects (carvedilol), but there continues to be debate as to whether the inadequate dosing of metoprolol tartrate (IR) may have influenced the difference in results. Metoprolol tartrate (IR) studied in **COMET** has been found to be of no mortality benefit in HF by metanalysis and in individual placebo-controlled trials. No study to date has compared carvedilol to metoprolol succinate (ER) or for moderate-severe HF and hence the question of whether carvedilol is superior to these other useful agents remains unknown.

Numerous secondary outcomes from the **COMET** trial were recently published. Carvedilol was superior to metoprolol-IR in reducing rates of cardiovascular death, sudden death, and stroke and similar to metoprolol-IR in reducing death due to circulatory failure and other CV deaths¹⁴ as well as in reducing days lost due to impaired well-being.¹⁵

Another combined endpoint of days of life lost due to death, hospitalization, impaired well-being, or need to increase diuretic use (deemed the ‘patient journey’) found carvedilol to be superior to metoprolol over four years when compared to baseline composite scores ($p=0.0068$).¹⁴ It is important to note however, that this combined endpoint considered all factors to be equal; days lost due to death were considered equivalent to days lost due to hospitalization.

¹⁴ Torp-Pedersen 2005 #12065

¹⁵ Cleland JG, Charlesworth A, Lubsen J, et al. A comparison of the effects of carvedilol and metoprolol on well-being, morbidity, and mortality (the “patient journey”) in patients with heart failure: a report from the Carvedilol Or Metoprolol European Trial (COMET). *J Am Coll Cardiol* 2006;47(8):1603-1611

In patients with mild to moderate heart failure (**CIBIS-II**), carvedilol (**COPERNICUS**), and metoprolol succinate (ER) (**MERIT-HF**) show similar effects on symptoms and all-cause mortality when compared to placebo. Metoprolol succinate (ER) also improves well being and the NYHA functional class. However, metoprolol tartrate (IR) did not reduce mortality in HF in either metanalysis or in individual studies.

In higher risk patients with severe heart failure there is good evidence from **COPERNICUS** (NYHA CHF class not given but patients had symptoms at rest or with minimal exertion and LVEF<25%) that carvedilol reduces mortality and the combined endpoint of mortality and hospitalizations. Patients on carvedilol had 14.0% mortality vs. placebo 20.9% (NNT = 14.5). There is also fair-to-good evidence from a post-hoc subgroup analysis of high-risk patients within a good-quality trial **MERIT-HF** (functional NYHA class III/IV with LVEF < 25%) that metoprolol succinate (ER) is effective in comparable patients. Patients on metoprolol succinate (ER) had 11.3% mortality vs. 18.2% for placebo (NNT = 14.5).

Further breakdown of cause of mortality revealed that bisoprolol and metoprolol succinate (ER) reduce sudden death; whereas, metoprolol tartrate (IR) and carvedilol did not. Mortality due to progressive heart failure was reduced by metoprolol succinate (ER), but not metoprolol tartrate (IR). Carvedilol reduced progressive heart failure deaths in one study in mild CHF; however, metoprolol tartrate did delay the need for heart transplantation.

A small (patients=100) fair quality placebo-controlled study of atenolol in addition to enalapril therapy showed that atenolol significantly reduced the combined endpoint of worsening heart failure or death compared to placebo (26% vs. 55%; p<0.01).

KQ 1E. The Pharmaceutical Subcommittee agrees by consensus that for adult patients with heart failure:

- ◆ Bisoprolol, carvedilol, and metoprolol succinate (ER) are effective in decreasing mortality while treating mild-moderate HF, but there was no significant difference in mortality among these drugs.
- ◆ Only carvedilol and metoprolol succinate (ER) have been shown to reduce mortality in severe HF, but the current evidence does not distinguish a difference between them.
- ◆ Atenolol was more effective than placebo when added to enalapril treatment of HF.
- ◆ Metoprolol tartrate (IR) did not reduce mortality when treating HF.

Key Question 1F. For adult patients with atrial arrhythmia do β -Blockers differ in efficacy?

There were no head-to-head trials and only limited evidence from placebo-controlled trials that atenolol, bisoprolol, nadolol, pindolol, and propranolol but not labetalol, were effective for rate control in atrial fibrillation.

No β -Blocker was clinically effective when compared to placebo in preventing recurrence of atrial fibrillation. In one study metoprolol succinate (ER) was mildly beneficial post cardioversion—(recurrence rate at 6 months, 49% for metoprolol succinate [ER] vs. 60% placebo)

No all cause or cardiovascular mortality benefit has been found with use of β -Blockers in patients with atrial arrhythmia.

In one active controlled trial with patients on digoxin for concomitant AF and HF, the addition of carvedilol improved quality of life.

KQ1F. The Pharmaceutical Subcommittee agrees by consensus that for adult patients with atrial arrhythmias:

- ◆ **There was no clinical superiority among atenolol, metoprolol succinate (ER), nadolol, pindolol, and propranolol for rate control in atrial fibrillation.**
- ◆ **Labetolol was not effective for rate control in atrial fibrillation**
- ◆ **No β -Blocker was very beneficial in preventing recurrence of atrial fibrillation. Metoprolol succinate (ER) was modestly effective in preventing recurrence of atrial fibrillation following cardioversion.**
- ◆ **Carvedilol improved quality of life in patients with AF and HF.**

Key Question 1G. For adult patients with migraine headaches do β -Blockers differ in efficacy?

The overall grade of the evidence is poor for treatment of migraines with β -blockers. Although there were five fair quality head-to-head trials of atenolol, metoprolol tartrate (IR), metoprolol succinate (ER), and timolol each compared to propranolol; the studies didn't clearly differentiate one β -Blocker from another due to variation in measurement methods, dose levels, and treatment durations. Results from placebo controlled trials on similar outcome measures generally supports those for atenolol, metoprolol durules (European slow release formulation) 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. A recent, well-conducted systematic review comparing propranolol to other beta blockers found that there was little difference between propranolol and the comparators (metoprolol, nadolol, timolol) in reducing attack frequency (SMD -0.01 95% CI -0.24-0.22) based on data from four crossover trials.¹⁶

¹⁶ Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database of Systematic Reviews, 2007;1:1

KQ 1G. The Pharmaceutical Subcommittee agrees by consensus that for adult patients with migraines:

- ◆ **The current evidence does not distinguish a difference among atenolol, metoprolol tartrate (IR), metoprolol succinate (ER), propranolol, propranolol LA, nadolol, or timolol in preventing recurrence and diminishing the severity of migraine headaches.**
- ◆ **Bisoprolol reduced migraine attack frequency when compared to placebo.**
- ◆ **Pindolol was not effective in treating migraine headaches.**

Key Question 1H. For adult patients with bleeding esophageal varices do β -blockers differ in efficacy?

The overall grade of the evidence is poor for treatment of bleeding esophageal varices with atenolol, nadolol, propranolol, and propranolol LA. The placebo-controlled studies conclude that these drugs are somewhat effective in reducing rates of esophageal variceal re-bleeding; however there was no significant reduction in mortality.

A fair quality head-to-head trial revealed no significant difference between 40-160 mg daily propranolol (non-selective β -Blocker) and 100 mg daily atenolol (selective β -Blocker) for fatal/non-fatal re-bleeding episodes (2.4% vs. 3.1%) or other parameters such as deaths due to re-bleeding, liver failure, or other unrelated causes.

KQ 1H. The Pharmaceutical Subcommittee agrees by consensus that for adult patients with bleeding esophageal varices:

- ◆ **The current evidence does not distinguish a difference among atenolol, nadolol, propranolol, and propranolol LA for reducing esophageal variceal re-bleeding.**

Key Question 2. Do β -Blockers differ in safety or adverse effects?

Adverse events of β -Blockers most commonly reported in randomized controlled trials include cardiovascular symptoms of bradycardia, hypotension, and dizziness. Relatively low rates of withdrawal due to these adverse events suggest that they were only mild to moderate in severity. Other mild adverse events associated with β -blockers that were less commonly reported included sexual dysfunction or various dermatological or gastrointestinal symptoms.

Fourteen head-to-head trials for safety analysis (5 for migraine, 3 for hypertension, 2 for CHF, 2 for angina, 1 for post MI, and 1 for esophageal varices) were reviewed. Only one trial comparing atenolol and pindolol was designed specifically for adverse event assessment and was rated good quality. Safety assessment in the remaining 13 trials was only fair-poor quality due to lack of information regarding the evaluation techniques and much heterogeneity across those trials in specific adverse events reported.

Longer term trials (12-58 months) directly comparing β -Blockers for hypertension (atenolol vs. bisoprolol vs. propranolol), heart failure (carvedilol vs. metoprolol [IR]), and bleeding esophageal varices (atenolol vs. propranolol) showed no differences in any of the safety parameters measured, with one exception. Carvedilol was associated with a higher rate of dizziness than metoprolol tartrate (IR) in patients with CHF in one long-term trial. This significant difference was not seen in another shorter trial in patients with angina. Reasons for this inconsistency may include difference in definition of dizziness and evaluation techniques between the two trials.

Four fair quality short term head-to-head trials directly compared atenolol and, metoprolol CR, or propranolol and assessed changes in quality of life. The strongest evidence of any differences between beta blockers came from a 4-week trial of captopril, enalapril, propranolol, and atenolol that used a parallel design. Patients were all men that were married or living with a significant other. Self-ratings of improvements were greater for atenolol than propranolol in Psychological General Well-Being (PGWB)-measured self-control, distress overall, and that caused by obsessions and hostility symptoms. It remains unclear as to whether these short-term results in men can be generalized to a broader population over a longer time period. The magnitude of the evidence from the

remaining crossover trials is limited by smaller samples sizes and results that were averaged across treatment periods.

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.¹⁷ 158 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.

KQ 2. The Pharmaceutical Subcommittee agrees by consensus there are no significant differences found among β -Blockers in safety or adverse effects.

Key Question 3. Are there subgroups of patients based on demographics (race, ethnicity, gender), use of other medications, or co-morbidities, for which one β -Blocker is more effective or associated with fewer adverse effects?

None of the 14 fair quality head-to-head trials included in our efficacy analyses across all the indications listed, provided any subgroup analyses that differentiated one β -blocker from another in any demographic or comorbidity subgroup.

The Beta-Blocker Pooling Project (BBPP) analyzed mortality in post-infarction patients relative to subgroup risk factors from trials of propranolol and pindolol and found that none of the age, gender, heart failure, and prior diabetes mellitus baseline characteristics interacted significantly with the effect on mortality.

¹⁷ Torp-Pederson C, Metra M, Charlesworth A, et al. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol or Metoprolol European Trial (COMET). *Heart*. Aug 2007;93(8):968-973

However, this analysis does not offer any meaningful information about the comparative efficacy of β -blockers in these subgroups.

A subgroup analysis of the MERIT-HF trial evaluated the influence of comorbid diabetes on the effects of metoprolol CR.¹⁸ This analysis found higher rates of all-cause mortality in the placebo group when compared to metoprolol (12.7% vs. 10.1% per patient year; Risk Reduction 18%; 95% CI 44% to -19%). Metoprolol CR also significantly reduced risks of hospitalizations for worsening heart failure (including those patients identified as having severe heart failure) regardless of diabetic status.

KQ 3. The Pharmaceutical Subcommittee agrees by consensus that:

There is no evidence of significant differences that one β -Blocker is more effective or associated with fewer adverse effects based on demographics (race, ethnicity, gender), use of other medications or co-morbidities.

CONCLUSION

In a series of public meetings with the opportunity for public questions, comment and testimony, the Pharmaceutical Subcommittee of the Health Resources Commission reviewed the medical evidence comparing β -blockers. The OHSU EPC's report, "Drug Class Review on Beta Adrenergic Blockers Updated Final Report #3," which included appropriate information presented in pharmaceutical manufacturer dossiers was reviewed and public testimony considered.

The charge to the Pharmaceutical Subcommittee to determine the comparative effectiveness and safety of β -Blockers is made most difficult because of the heterogeneity of these compounds and their diverse effects on different clinical indications. A summary of β -Blocker Evidence of Effectiveness is given in the following table:

¹⁸ Deewandia PC, Giles TD, Klibaner M, et al. Efficacy, safety, and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* Jan 2005;149(1):159-167

GENERIC DRUGS	CARDIAC							NON-CARDIAC	
	HTN ¹⁹	Angina	CABG	Recent MI ²⁰	Mild-Mod CHF ²¹	Severe CHF ²²	Atrial Arrhythmia ²³	Migraine	Esophageal varices
Acebutolol	E	E		E+M ²⁴					
Atenolol	E	E					E	E	E
Betaxolol	E	E							
Bisoprolol	E	E			E+L+M		E ²⁵	E	
Carteolol	E								
Carvedilol	E	E		E+M	E+L+M	E+L+M	E ²⁶		
Carvedilol phosphate (ER)									
Labetolol	E	E ²⁷					NE ²⁸		
Metoprolol tartrate (IR)	E	E	NE ²⁹	E+M	NE	NE		E	
Metoprolol succinate (ER)	E	E			E+L+M	E+L+M	E	E	
Nadolol	E	E					E	E	E
Penbutolol	E	E							
Pindolol	E	E					E	NE	
Propranolol	E	E		E+M			E	E	E
Propranolol LA	E	E						E	E
Timolol	E	E		E+M				E	

Empty cells means "no evidence available"

E Effective > placebo

NE Not Effective

L Long-term investigation
> 6 months for CHF
> 2 months for angina
>7days for CABG

M Decreases Mortality

CABG Coronary Artery Bypass Graft (Surgery)

CHF Congestive Heart Failure

MI Myocardial Infarction

19 Effective>placebo

20 Outpatient B-Blocker started <3 months after MI

21 Mild to moderate CHF, NYHA Class 1-3

22 Severe CHF symptoms at rest or with minimal exertion and LVEF<25%

23 Rate control

24 Expert opinion suggests not using this drug because of ISA

25 = carvedilol

26 Rate control with and without digoxin

27 Labetolol with Chlorthalidone

28 No > placebo for atrial fibrillation

29 No mortality or ischemic event differences between metoprolol tartrate (IR) and placebo

CONCLUSION

The Pharmaceutical Subcommittee concludes that:

1. In patients with mild-moderate HF, bisoprolol, carvedilol or metoprolol succinate (ER) reduce mortality. It is important that at least one of these drugs be included in the OHP Prescription Drug Plan (PDL).
2. In patients with severe HF, carvedilol or metoprolol succinate (ER) reduce mortality. It is important that at least one of these drugs be included in the PDL.
3. In patients with recent MI, acebutolol, carvedilol, metoprolol tartrate (IR), propranolol, or timolol reduce mortality. It is important that at least one of these drugs be included in the PDL.
4. All of the β -Blockers reviewed are effective in the treatment of hypertension, but there is no evidence of differences between β -blockers for blood pressure control, survival, or quality of life.
5. All of the β -Blockers reviewed except carteolol reduced anginal attacks in patients in short-term studies that did not allow mortality evaluation.
6. Because of their effectiveness in rate control for atrial fibrillation at least one of either atenolol, bisoprolol, carvedilol, metoprolol succinate (ER), nadolol, pindolol, or propranolol should be included in the PDL.
7. The current evidence does not distinguish a difference among these beneficial β -Blockers that were tested for preventing recurrence and diminishing the severity of migraine headaches: atenolol, bisoprolol, metoprolol tartrate (IR), metoprolol succinate (ER), propranolol, propranolol LA nadolol, or timolol.
8. The current evidence does not distinguish a difference among beneficial β -Blockers that were tested for reducing esophageal variceal re-bleeding: atenolol, nadolol, propranolol, or propranolol LA.
9. There is no evidence of significant differences among β -blockers in safety or adverse effects.
10. There is no evidence of significant differences found for one β -blocker being more effective or associated with fewer adverse effects in subgroups of patients based on demographics (race, ethnicity, gender), use of other medications, or co-morbidities.

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