Drug Class Review
Beta Adrenergic Blockers

Preliminary Scan Report #2

October 2013

Last Report: Update #4 Final Report (July 2009)

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations’ consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #4, July 2009 (searches through January 2009)

Date of Last Preliminary Update Scan Report

October 2010

Scope and Key Questions

Key Questions

1. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in effectiveness?
2. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices

Interventions

Interventions include an oral beta blocker compared with another beta blocker, another drug (such as calcium channel blocker), or placebo. (Oral beta blockers: acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, carvedilol phosphate, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, penbutolol, pindolol, propranolol, propranolol LA, timolol)
Table 1. Effectiveness outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1. All-cause and cardiovascular mortality</td>
</tr>
<tr>
<td></td>
<td>2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure)</td>
</tr>
<tr>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>4. Quality-of-life</td>
</tr>
<tr>
<td>Chronic stable angina (treatment duration ≥ 2 months)</td>
<td>1. Exercise tolerance</td>
</tr>
<tr>
<td></td>
<td>2. Attack frequency</td>
</tr>
<tr>
<td></td>
<td>3. Nitrate use</td>
</tr>
<tr>
<td>Post-coronary artery bypass graft (long-term treatment)</td>
<td>1. All-cause mortality</td>
</tr>
<tr>
<td></td>
<td>2. Ischemic events (MI, unstable angina, need for repeat CABG and PTCA)</td>
</tr>
<tr>
<td>Recent myocardial infarction (with and without LV dysfunction)</td>
<td>1. All-cause and cardiovascular mortality</td>
</tr>
<tr>
<td></td>
<td>2. Cardiovascular events (usually, development of heart failure)</td>
</tr>
<tr>
<td>Symptomatic chronic heart failure</td>
<td>1. All-cause or cardiovascular mortality</td>
</tr>
<tr>
<td></td>
<td>2. Symptomatic improvement (heart failure class, functional status, visual analogue scores)</td>
</tr>
<tr>
<td></td>
<td>3. Hospitalizations for heart failure</td>
</tr>
<tr>
<td>Asymptomatic LV dysfunction</td>
<td>1. All-cause and cardiovascular mortality</td>
</tr>
<tr>
<td></td>
<td>2. Cardiovascular events (usually, development of heart failure)</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>1. Rate control</td>
</tr>
<tr>
<td></td>
<td>2. Relapse into atrial fibrillation</td>
</tr>
<tr>
<td>Migraine</td>
<td>1. Attack frequency</td>
</tr>
<tr>
<td></td>
<td>2. Attack intensity/severity</td>
</tr>
<tr>
<td></td>
<td>3. Attack duration</td>
</tr>
<tr>
<td></td>
<td>4. Use of abortive treatment</td>
</tr>
<tr>
<td>Bleeding esophageal varices</td>
<td>1. All-cause mortality</td>
</tr>
<tr>
<td></td>
<td>2. Fatal/non-fatal rebleeding</td>
</tr>
</tbody>
</table>

Harms
- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events reported
- Specific adverse events

Study designs
1. For effectiveness, randomized controlled trials and good-quality systematic reviews
2. For harms, controlled clinical trials and observational studies
METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from September 2010 through October 2013 using terms for included drugs. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

We did not identify any new drugs in this or the previous scan.

New Indications

We did not identify any new indications in this or the previous scan.

New Black Box Warnings

We did not identify any new black box warnings in this or the previous scan.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

We did not identify any new potentially relevant comparative effectiveness reviews in this or the previous scan.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches from this scan resulted in 212 citations. Of those, there were 7 potentially relevant new trials (see Appendix A for abstracts). Together with the 10 potentially relevant trials identified in the last scan (Appendix B), now there are a total of 17. Characteristics of these trials are shown in Table(s) 2 and 3, below.
Table 2. Characteristics of head-to-head trials

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Beta Blockers</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliuta 2009</td>
<td>Betaxolol vs metoprolol</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>Jabbour 2010</td>
<td>Carvedilol vs metoprolol succinate vs bisoprolol</td>
<td>Heart failure and chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Shahzamani 2011</td>
<td>Carvedilol vs metoprolol</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>Ulimoen 2013</td>
<td>Carvedilol vs metoprolol</td>
<td>Permanent atrial fibrillation</td>
</tr>
<tr>
<td>Udelson 2009</td>
<td>Carvedilol vs carvedilol phosphate</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Marazzi 2011</td>
<td>Nebivolol vs carvedilol</td>
<td>Hypertensive heart failure</td>
</tr>
<tr>
<td>Espinola-Klein 2011</td>
<td>Nebivolol vs metoprolol</td>
<td>Hypertension with intermittent claudication</td>
</tr>
<tr>
<td>Sen 2009</td>
<td>Nebivolol vs metoprolol</td>
<td>Cardiac syndrome X</td>
</tr>
</tbody>
</table>

Among the publications of placebo-controlled trials, all involved patients with heart failure and 7 of 9 provide results from subanalyses of previously included trials (Table 2).

Table 3. Characteristics of placebo-controlled trials

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Beta Blockers</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkins 2009</td>
<td>Bisoprolol</td>
<td>Heart failure and moderate to severe chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Silberstein 2012</td>
<td>Propranolol</td>
<td>Migraine</td>
</tr>
<tr>
<td>Ambrosio 2011</td>
<td>Nebivolol</td>
<td>Ischemic events</td>
</tr>
<tr>
<td>Cohen-Solal 2009</td>
<td>Nebivolol</td>
<td>Influence of renal dysfunction</td>
</tr>
<tr>
<td>de Boer 2010</td>
<td>Nebivolol</td>
<td>Influence of diabetes</td>
</tr>
<tr>
<td>Mulder 2012</td>
<td>Nebivolol</td>
<td>Influence of atrial fibrillation</td>
</tr>
<tr>
<td>van Veldhuisen 2009</td>
<td>Nebivolol</td>
<td>Influence of impaired and preserved left ventricular ejection fraction</td>
</tr>
<tr>
<td>Castagno 2010</td>
<td>Bisoprolol</td>
<td>Patients with heart failure and renal impairment (CIBIS-II)</td>
</tr>
<tr>
<td>Ghali 2009</td>
<td>Metoprolol CR</td>
<td>Patients with heart failure and deceased renal function (MERIT-HF)</td>
</tr>
</tbody>
</table>
Appendix A. Abstracts of potentially relevant new trials of Beta Adrenergic Blockers from current scan

**Head-to-head trials**


A number of elective coronary artery bypass graft (CABG) surgery patients have impaired underlying left ventricular function (poor ejection fraction). This study was performed to compare the effect of postoperative oral carvedilol versus metoprolol on left ventricular ejection fraction (LVEF) after CABG compared with metoprolol. In a double-blind clinical trial, 60 patients with coronary artery disease, aged 35 to 65 years, who had an ejection fraction of 15% to 35% were included. Either carvedilol or metoprolol was administered the day after CABG. The patients were evaluated by the same cardiologist 14 days before and 2 and 6 months after elective CABG. The results demonstrated better improvements in LVEF in the carvedilol group. No difference regarding postoperative arrhythmias or mortality was detected. The results suggest that carvedilol may exert more of an improved myocardial effect than metoprolol for the low ejection fraction patients undergoing CABG in the early postoperative months. Copyright 2011 American Society of PeriAnesthesia Nurses. Published by Elsevier Inc. All rights reserved.


Rate control of atrial fibrillation (AF) is a main treatment modality. However, data are scarce on the relative efficacy of calcium channel blockers and blockers or between drugs within each class. The purpose of the present study was to compare the effect of 4 rate-reducing, once-daily drug regimens on the ventricular heart rate and arrhythmia-related symptoms in patients with permanent AF. We included 60 patients (mean age 71 +/- 9 years, 18 women) with permanent AF in an investigator-blind cross-over study. Diltiazem 360 mg/day, verapamil 240 mg/day, metoprolol 100 mg/day, and carvedilol 25 mg/day were administered for 3 weeks in a randomized sequence. The 24-hour heart rate was measured using Holter monitoring, and arrhythmia-related symptoms were assessed using the Symptom Checklist questionnaire before randomization and on the last day of each treatment period. The 24-hour mean heart rate was 96 +/- 12 beats/min at baseline (no treatment), 75 +/- 10 beats/min with diltiazem, 81 +/- 11 beats/min with verapamil, 82 +/- 11 beats/min with metoprolol, and 84 +/- 11 beats/min with carvedilol. All drugs reduced the heart rate compared to baseline (p <0.001 for all). The 24-hour heart rate was significantly lower with diltiazem than with any other drug tested (p <0.001 for all). Compared to baseline, diltiazem significantly reduced both the frequency (p <0.001) and the severity (p= 0.005) of symptoms. In contrast, verapamil reduced symptom frequency only (p=0.012). In conclusion, diltiazem 360 mg/day was the most effective drug regimen for reducing the heart rate in patients with permanent AF. Arrhythmia-related symptoms were reduced by treatment with the calcium channel blockers diltiazem and verapamil, but not by the blockers. Copyright 2013 Elsevier Inc. All rights reserved.

BACKGROUND: Beta-blockers improve left ventricular (LV) systolic function and prognosis in patients with chronic heart failure (CHF), but their different pleiotropic properties may influence their cardiovascular effects. This open-label study compared the effects of long-term treatment with nebivolol versus carvedilol on LV ejection fraction (LVEF), in hypertensive CHF patients. Secondary end points were to assess the effect of the 2 beta-blockers on exercise capacity and clinical outcome.

METHODS AND RESULTS: A total of 160 hypertensive CHF patients, with LVEF <40% and in New York Heart Association (NYHA) functional class I, II, or III, were randomly assigned to receive nebivolol or carvedilol for 24 months. At baseline and at the end of treatment, all patients underwent clinical evaluation, echocardiography, and 6-minute walking test. The target doses were 10 mg/d for nebivolol and 50 mg/d for carvedilol. Compared with baseline values, LVEF increased by a similar extent in the carvedilol (C) and nebivolol (N) groups (C from 36.1% (SD 1.5%) to 40.9% (SD 1.9%), P < .001; N from 34.1% (SD 1.8%) to 38.5% (SF 2.2%), P < .001). Heart rate and NYHA functional class decreased significantly in both groups, and the 6-minute walking distance increased (C from 420 m (SD 104 m) to 490 m (SD 115m), P < .001; N from 421 m (SD 118 m) to 487 m (SD 138 m), P < .001). During 24 months, 21 carvedilol recipients (26%) and 18 nebivolol recipients (22%) had cardiac events, including 3 and 4 deaths, respectively.

CONCLUSION: In the long term, nebivolol and carvedilol appear to be similarly effective in the treatment of hypertensive patients with CHF. Copyright 2011 Elsevier Inc. All rights reserved.


The use of -receptor blockers in peripheral arterial disease is controversial for their impact on vasomotor tone. The -blocker nebivolol possesses vasodilating, endothelium-dependent, NO-releasing properties that might be beneficial in peripheral arterial disease. The aim of the study was to evaluate the effects and tolerability of nebivolol in comparison with metoprolol in these patients. A total of 128 patients with intermittent claudication and essential hypertension were included and double-blind randomized to receive 5 mg of nebivolol (N=65) or 95 mg of metoprolol (N=63) once daily. End points were changes in ankle-brachial index, initial and absolute claudication distance, endothelial function assessed by flow-mediated dilatation of the brachial artery, blood pressure, and quality of life using the claudication scale questionnaire. End point analysis was possible in 109 patients (85.2%). After the 48-week treatment period, ankle-brachial index and absolute claudication distance improved significantly in both patient groups (P<0.05 for both), with no difference across treatments. A significant increase of initial claudication distance was found in the nebivolol group. Adjusted mean change of initial claudication distance was 33.9% after nebivolol (P=0.003) and 16.6% after metoprolol (P=0.12) treatment. Quality of life was not influenced by either treatment, and there was no relevant change in flow-mediated dilatation in patients treated with nevidol or metoprolol (P=0.16). Both drugs were equally effective in lowering blood pressure. In conclusion, -blocker therapy
was well tolerated in patients with intermittent claudication and arterial hypertension during a treatment period of 1 year. In the direct comparison, there was no significant difference between nebivolol and metoprolol.
**Placebo-controlled trials**


**OBJECTIVE:** To assess the efficacy and safety of adding propranolol to topiramate in chronic migraine subjects inadequately controlled with topiramate alone.

**METHODS:** This was a double-blind, placebo-controlled, randomized clinical trial conducted through the National Institute of Neurological Disorders and Stroke Clinical Research Collaboration, expected to randomize 250 chronic migraine subjects inadequately controlled (>=10 headaches/month) with topiramate (50-100 mg/day) to either propranolol LA (long acting) (240 mg/day) or placebo. Primary outcome was 28-day moderate to severe headache rate reduction at 6 months (weeks 16 to 24) compared with baseline (weeks -4 to 0).

**RESULTS:** A planned interim analysis was performed after 48 sites randomized 171 subjects. The data and safety monitoring board recommended ending the trial after determining that it would be highly unlikely for the combination to result in a significant reduction in 28-day headache rate compared with topiramate alone if all 250 subjects were randomized. No safety concerns were identified. At study closure, 191 subjects were randomized. The 6-month reduction in moderate to severe 28-day headache rate and total 28-day headache rate for combination therapy vs topiramate alone was not significantly different: 4.0 vs 4.5 days (moderate to severe 28-day headache rate; p = 0.57) and 6.2 vs 6.1 days (total 28-day headache rate; p = 0.91).

**CONCLUSIONS:** This study does not provide evidence that the addition of propranolol LA to topiramate adds benefit when chronic migraine is inadequately controlled with topiramate alone. Classification of evidence: This study provides Class II evidence that propranolol LA, added to topiramate, is ineffective in chronic migraine patients who fail topiramate monotherapy.


**OBJECTIVES:** This subanalysis of the Study of the Effects of Nebivolol Intervention on Outcomes and Hospitalisation in Seniors with Heart Failure (SENIORS) investigates whether treatment with nebivolol, a -blocker with nitric oxide-releasing properties, can provide additional benefits besides its effects on heart failure (HF), by reducing cardiac ischaemic events in patients with HF of ischaemic aetiology.

**DESIGN:** A double-blind, randomised, placebo-controlled, multicentre trial of nebivolol in 2128 elderly patients.

**PATIENTS AND INTERVENTIONS:** For this analysis, data were extracted for 2128 elderly (>= 70 years) HF patients in whom coronary artery disease (CAD) was the underlying aetiology (68.2%; 717 placebo-treated patients and 735 assigned to nebivolol).

**MAIN OUTCOME MEASURES:** The main endpoint was the composite of cardiac ischaemic events at 2 year follow-up: death/hospitalisation for myocardial infarction, unstable angina or sudden death, as originally identified in the case report form.

**RESULTS:** At follow-up, nebivolol treatment was associated with a one-third reduction in the risk of ischaemic events, the composite endpoint occurring in 15.9% of placebo and
10.7% of nebivolol-treated patients (HR 0.68; 95% CI 0.51 to 0.90; p=0.008). This effect was independent of age, gender and ejection fraction. No difference in this composite endpoint was observed in the subgroup of patients of non-ischaemic aetiology. CONCLUSIONS: Nebivolol was effective in reducing cardiac ischaemic events in patients with HF of ischaemic aetiology. The prevention of ischaemic events can be an additional beneficial effect of beta-blockade in HF patients with underlying CAD.


AIMS: Beneficial effects of beta-blockade remain unclear in heart failure patients who have atrial fibrillation (AF), especially in the elderly. We evaluated the effect of nebivolol on cardiovascular outcomes in elderly patients with heart failure and AF.

METHODS AND RESULTS: The SENIORS trial showed an overall benefit of nebivolol compared with placebo in 2128 heart failure patients >70 years of age. At baseline, AF was present in 738 (34.7%) patients. The primary outcome was all-cause mortality or cardiovascular hospitalizations. After 21 months, the cumulative incidence of the primary outcome was significantly more common in patients with AF compared with those with sinus rhythm (38.5% vs. 30.4%, respectively, P < 0.001). In patients with AF, nebivolol had no beneficial effect on the primary outcome [nebivolol vs. placebo, 37.1% vs. 39.8%, hazard ratio (HR) 0.92, 95% confidence interval (CI), 0.73-1.17, P = 0.46], in contrast to patients with sinus rhythm (28.1% vs. 32.9%, respectively, HR 0.82, 95% CI 0.67-0.99, P = 0.049). In patients with AF, the primary outcome was similar in the impaired and preserved left ventricular ejection fraction (LVEF) groups (39.0% with LVEF <= 35% vs. 37.3% in patients with LVEF > 35%). There was also no evidence of benefit of nebivolol in AF patients stratified by LVEF.

CONCLUSION: Nebivolol failed to improve outcomes in elderly patients with stable heart failure and co-existing AF, irrespective of LVEF. Furthermore, in patients with AF, outcome was comparable between patients with preserved and impaired LVEF.
Appendix B. Abstracts of potentially relevant new trials of Beta Adrenergic Blockers from previous scan in October 2010

Head-to-head trials


In this study, we tried to compare the efficacy and safety of betaxolol vs. metoprolol immediately postoperatively in coronary artery bypass grafting (CABG) patients and to determine whether prophylaxis for atrial fibrillation (AF) with betaxolol could reduce hospitalization and economic costs after cardiac surgery. Our trial was open-label, randomized, multicentric enrolling 1352 coronary surgery patients randomized to receive betaxolol or metoprolol. The primary endpoints were the composites of 30-day mortality, in-hospital AF (safety endpoints), duration of hospitalization and immobilization, quality of life, and the above endpoint plus in-hospital embolic event, bradycardia, gastrointestinal symptoms, sleep disturbances, cold extremities (efficacy plus safety endpoint). At the end of the study the incidence and probability of early postoperative AF with betaxolol was lower than with metoprolol in coronary surgery (P<0.0001). In the two study groups minor side effects were similar and no major complication was reported (P<0.001). Patient compliance was good and the general condition improved due to shortened hospitalization and immobilization with subsequent improvement in the psychological status, less arrhythmias and lack of significant side effects. In conclusion, because of its efficacy and safety, betaxolol was superior to metoprolol for the prevention of the early postoperative AF in coronary surgery.


OBJECTIVES: The purpose of this study was to determine the respiratory, hemodynamic, and clinical effects of switching between beta1-selective and nonselective beta-blockers in patients with chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD). BACKGROUND: Carvedilol, metoprolol succinate, and bisoprolol are established beta-blockers for treating CHF. Whether differences in beta-receptor specificities affect lung or vascular function in CHF patients, particularly those with coexistent COPD, remains incompletely characterized. METHODS: A randomized, open label, triple-crossover trial involving 51 subjects receiving optimal therapy for CHF was conducted in 2 Australian teaching hospitals. Subjects received each beta-blocker, dose-matched, for 6 weeks before resuming their original beta-blocker. Echocardiography, N-terminal pro-hormone brain natriuretic peptide, central augmented pressure from pulse waveform analysis, respiratory function testing, 6-min walk distance, and New York Heart Association (NYHA) functional class were assessed at each visit. RESULTS: Of 51 subjects with a mean age of 66 +/- 12 years, NYHA functional class I (n = 6), II (n = 29), or III (n = 16), and left ventricular ejection fraction mean of 37 +/- 10%, 35 had coexistent COPD. N-terminal pro-hormone brain natriuretic peptide was
significantly lower with carvedilol than with metoprolol or bisoprolol (mean: carvedilol 1,001 [95% confidence interval (CI): 633 to 1,367] ng/l; metoprolol 1,371 [95% CI: 778 to 1,964] ng/l; bisoprolol 1,349 [95% CI: 782 to 1,916] ng/l; p < 0.01), and returned to baseline level on resumption of the initial beta-blocker. Central augmented pressure, a measure of pulsatile afterload, was lowest with carvedilol (carvedilol 9.9 [95% CI: 7.7 to 12.2] mm Hg; metoprolol 11.5 [95% CI: 9.3 to 13.8] mm Hg; bisoprolol 12.2 [95% CI: 9.6 to 14.7] mm Hg; p < 0.05). In subjects with COPD, forced expiratory volume in 1 s was lowest with carvedilol and highest with bisoprolol (carvedilol 1.85 [95% CI: 1.67 to 2.03] l/s; metoprolol 1.94 [95% CI: 1.73 to 2.14] l/s; bisoprolol 2.0 [95% CI: 1.79 to 2.22] l/s; p < 0.001). The NYHA functional class, 6-min walk distance, and left ventricular ejection fraction did not change. The beta-blocker switches were well tolerated. CONCLUSIONS: Switching between beta1-selective beta-blockers and the nonselective beta-blocker carvedilol is well tolerated but results in demonstrable changes in airway function, most marked in patients with COPD. Switching from beta1-selective beta-blockers to carvedilol causes short-term reduction of central augmented pressure and N-terminal pro-hormone brain natriuretic peptide. (Comparison of Nonselective and Beta1-Selective Beta-Blockers on Respiratory and Arterial Function and Cardiac Chamber Dynamics in Patients With Chronic Stable Congestive Cardiac Failure; Australian New Zealand Clinical Trials Registry, ACTRN12605000504617). Copyright (c) 2010 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.


OBJECTIVE: We sought to determine whether nebulol affects coronary endothelial function and exercise induced ischemia in patients with cardiac syndrome X (CSX). METHODS: The study protocol undertaken was based on a single-blind randomized controlled prospective study. After a 2-week washout period, 38 patients with cardiac syndrome X were randomized to receive either nebivolol 5 mg daily (n=19) or metoprolol 50 mg daily (n=19) in a single-blind design for 12 weeks. The control group under study was consisted of 16 age- and gender-matched subjects with negative treadmill exercise tests. Plasma endothelial nitric oxide (NOx), L-arginine, and asymmetric dimethylarginine (ADMA) were measured in all patients at baseline and after 12 weeks of treatment. Statistical differences among groups were tested by one-way analysis of variance and unpaired samples t test for parametric; Kruskal-Wallis and Mann-Whitney U tests for non-parametric variables, respectively. A paired samples t test was used to compare continuous variables before and after drug therapy. RESULTS: At baseline, plasma level of NOx, L-arginine, and L-arginine/ADMA ratio were lower (p<0.001 for all) in patients with CSX than in the control patients. Whereas, the plasma ADMA levels were increased in the patient group (p<0.001). After 12 weeks of drug therapy, the patients taking nebivolol had increased levels of plasma NOx, plasma L-arginine, the L-arginine/ADMA ratio and decreased levels of plasma ADMA compared to those of the patients taking metoprolol (p<0.001). In addition, exercise duration to 1-mm ST depression and total exercise duration significantly increased after treatment in the nebivolol group compared to the metoprolol group (p<0.01). In the nebivolol group,
Canadian Cardiovascular Society (CCS) angina classification improved by one or more categories in 12 (70%) patients, whereas it deteriorated or remained in the same category in 5 (30%) patients. Meanwhile, in the metoprolol group, the CCS angina classification improved by one or more categories in 7 (41%), whereas it deteriorated or remained in the same category in 10 (59%) patients. CONCLUSION: Circulating endothelial function parameters (plasma ADMA, L-arginine, NOx levels) were impaired in patients with CSX. Nebivolol treatment was associated with better improvements in both circulating endothelial function and exercise stress test parameters than metoprolol. We believe that further studies are needed to evaluate the effects of nebivolol treatment on long-term clinical outcomes in patients with CSX.


BACKGROUND: Suboptimal compliance in taking guideline-based pharmacotherapy in patients with chronic heart failure (HF) potentially increases the burden of hospitalizations and diminishes quality of life. By simplifying the medical regimen, once-daily dosing can potentially improve compliance. The Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial was designed to measure differential compliance, satisfaction, and quality of life in chronic HF patients taking carvedilol immediate release (IR) twice daily versus the bioequivalent carvedilol controlled-release (CR) once daily. METHODS AND RESULTS: CASPER was a prospective multicenter, 3-arm, parallel-group, randomized clinical trial for a 5-month period. The primary objective of the study was to evaluate and compare compliance with carvedilol IR twice daily (BID) and carvedilol phosphate CR once daily (QD) in patients with chronic HF who were taking carvedilol IR. Secondary objectives included comparisons of quality of life (Kansas City Cardiomyopathy Questionnaire), satisfaction with medication, and brain natriuretic peptide levels between subjects taking the two formulations. A total of 405 patients with chronic HF and left ventricular dysfunction were randomized to: (A) carvedilol IR twice daily, given double blind; (B) carvedilol CR taken in the morning and placebo in the afternoon, given double blind; or (C) carvedilol CR once daily, open label. Compliance was measured using the medication event monitoring system that captures time of bottle opening. The primary end point was a comparison of taking compliance (doses taken divided by total number of prescribed doses over the actual duration of the study) between the double-blind carvedilol IR BID versus the open-label carvedilol CR QD groups. Sample size estimates were based on assumptions of 75% compliance with BID dosing and 90% compliance with QD dosing. Mean compliance with carvedilol IR BID was 89.3% compared with 88.2% for carvedilol CR QD, and differential mean compliance was 1.1% (95% CI -4.4%, 6.6%; ie, not significant). There were no statistically significant differences in compliance between any of the 3 groups, nor differences in quality of life, treatment satisfaction, or physiologic measures among the 3 study arms. There were also no significant differences in adverse events or side effects among patients switching from carvedilol IR to carvedilol CR in arms B or C over the 5-month study duration compared with patients remaining on
carvedilol IR. CONCLUSIONS: Compliance among chronic HF patients in the CASPER trial was high at baseline and unaffected by QD versus BID dosing. Over the 5-month follow-up period, there were no differences in adverse events among patients switching from carvedilol IR to CR.
Placebo-controlled trials


AIMS: Information on the effectiveness of beta-blockade in patients with heart failure (HF) and concomitant renal impairment is scarce and beta-blockers are underutilized in these patients. METHODS AND RESULTS: The Cockcroft-Gault formula normalized for body surface-area was used to estimate renal function (eGFR(BSA)) in 2622 patients with HF, left ventricular ejection fraction < or =35%, New York Heart Association class III/IV and serum creatinine <300 micromol/L (3.4 mg/dL) in the second Cardiac Insufficiency Bisoprolol Study II. Patients were divided into four sub-groups according to baseline eGFR(BSA) (<45, 45-60, 60-75 and > or =75 mL/min per 1.73 m(2)). Cox proportional-hazards models adjusted for pre-specified confounders were used to assess the effect of bisoprolol and potential heterogeneity of effect across the eGFR(BSA) sub-groups. Older age, female-sex, diabetes and ischaemic-aetiology were more common in those with reduced eGFR(BSA). The hazard associated with bisoprolol use for all-cause mortality, the composite of all-cause mortality or HF-hospitalization and HF-hospitalization alone was consistently <1.0 across eGFR(BSA) categories with no treatment by renal-function interaction (P = 0.81, P = 0.66, P = 0.71, respectively). The rate of bisoprolol discontinuation was higher in patients with eGFR(BSA) < 45 mL/min per 1.73 m(2). Nevertheless the absolute benefit of bisoprolol was greater for patients with chronic kidney disease compared with those without. CONCLUSION: The beneficial effects of bisoprolol on mortality and hospitalization for worsening heart-failure were not modified by baseline eGFR(BSA). Renal impairment should not prevent the use of bisoprolol in patients with HF.


AIM: To determine the safety and efficacy of nebivolol in elderly heart failure (HF) patients with renal dysfunction. METHODS AND RESULTS: SENIORS recruited patients aged 70 years or older with symptomatic HF, irrespective of ejection fraction, and randomized them to nebivolol or placebo. Patients (n = 2112) were divided by tertile of estimated glomerular filtration rate (eGFR). Mean age of patients was 76.1 years, 35% of patients had an ejection fraction of >35%, and 37% were women resulting in a unique cohort, far more representative of clinical practice than previous trials. eGFR was strongly associated with outcomes and nebivolol was similarly efficacious across eGFR tertiles. The primary outcome rate (all-cause mortality or cardiovascular hospital admission) and adjusted hazard ratio for nebivolol use in those with low eGFR was 40% and 0.84 (95% CI 0.67-1.07), 31% and 0.79 (0.60-1.04) in the middle tertile, and 29% and 0.86 (0.65-1.14) in the highest eGFR tertile. There was no interaction noted between renal function and the treatment effect (P = 0.442). Nebivolol use in patients with moderate renal impairment (eGFR <60) was not associated with major safety concerns, apart from higher rates of drug-discontinuation due to bradycardia. CONCLUSION:
Nebivolol is safe and has a similar effect in elderly HF patients with mild or moderate renal impairment.


The beneficial effects of beta blockers in younger patients with heart failure (HF) due to systolic dysfunction are well established. However, data from patients > or =70 years old with diabetes mellitus and HF are lacking. The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure [SENIORS] tested the efficacy of the vasodilator beta blocker nebivolol in patients > or =70 years old with HF and impaired or preserved left ventricular ejection fraction. In the present analysis, we evaluated the association between diabetes mellitus and baseline glucose levels on the primary outcome (all-cause mortality and cardiovascular hospitalization) and secondary end points, including all-cause mortality, cardiovascular hospitalizations, and cardiovascular mortality. Of 2,128 patients, 555 (26.1%) had diabetes mellitus. Of the 555 patients with diabetes mellitus, 223 (40.2%) experienced the primary end point compared to 484 (30.8%) of the 1,573 nondiabetic patients (p <0.001). For the nondiabetic patients, the rate of the primary outcome for placebo compared to nebivolol was 33.7% for the placebo group and 27.8% for the nebivolol group (hazard ratio 0.78, 95% confidence interval 0.65 to 0.93; p = 0.006). In the diabetic subset, the rate was 40.3% for the placebo group and 40.1% for the nebivolol group (hazard ratio 1.04, 95% confidence interval 0.80 to 1.35, p = 0.773). The subgroup interaction p value was 0.073. The baseline glucose levels in the nondiabetic patients did not significantly affect the outcomes. The effect of diabetes mellitus on outcome was independent of the left ventricular ejection fraction and was most pronounced in those with HF due to a nonischemic etiology. In conclusion, in patients > or =70 years old with HF, diabetes mellitus was associated with a worse prognosis. Nebivolol was less effective in the patients with diabetes and HF than in those with HF but without diabetes who were > or =70 years old. Copyright (c) 2010 Elsevier Inc. All rights reserved.


**BACKGROUND:** Limited information is available on the risk and impact of renal dysfunction on the response to beta-blockade and mode of death in systolic heart failure (HF). **METHODS AND RESULTS:** Renal function was estimated with glomerular filtration rate (eGFR) using the simplified Modification of Diet in Renal Disease (MDRD) equation. Patients from the Metoprolol CR/XL Controlled Randomized Intervention Trial in Chronic HF (MERIT-HF) were divided into 3 renal function subgroups (MDRD formula): eGFR(MDRD) > 60 (n = 2496), eGFR(MDRD) 45 to 60 (n = 976), and eGFR(MDRD) < 45 mL/min per 1.73 m2 body surface area (n = 493). Hazard ratio (HR) was estimated with Cox proportional hazards models adjusted for prespecified risk factors. Placebo patients with eGFR < 45 had significantly higher risk than those with eGFR > 60: HR for all-cause mortality, 1.90 (95% confidence interval
[CI], 1.28 to 2.81) comparing placebo patients with eGFR < 45 and eGFR > 60, and for the combined end point of all-cause mortality/hospitalization for worsening HF (time to first event): HR, 1.91 (95% CI, 1.44 to 2.53). No significant increase in risk with deceased renal function was observed for those randomized to metoprolol controlled release (CR)/extended release (XL) due to a highly significant decrease in risk on metoprolol CR/XL in those with eGFR < 45. For total mortality, metoprolol CR/XL vs placebo: HR, 0.41 (95% CI, 0.25 to 0.68; P < .001) in those with eGFR < 45 compared with HR, 0.71 (95% CI, 0.54 to 0.95; P < .021) for those with eGFR > 60; corresponding data for the combined end point was HR, 0.44 (95% CI, 0.31 to 0.63; P < .0001) and HR, 0.75 (0.62 to 0.92; P = .005, respectively; P = .095 for interaction by treatment for total mortality; P = .011 for combined end point). Metoprolol CR/XL was well tolerated in all 3 renal function subgroups. CONCLUSIONS: Renal function as estimated by eGFR was a powerful predictor of death and hospitalizations from worsening HF. Metoprolol CR/XL was at least as effective in reducing death and hospitalizations for worsening HF in patients with eGFR < 45 as in those with eGFR > 60.


AIMS: Heart failure (HF) and chronic obstructive pulmonary disease (COPD) frequently coexist. No study has prospectively examined the effects of beta-blockade in those with both conditions. METHODS AND RESULTS: We randomized 27 patients with HF and coexistent moderate or severe COPD to receive bisoprolol or placebo, titrated to maximum tolerated dose over 4 months. The primary outcome was forced expiratory volume in 1 s (FEV(1)). The study is registered with ClinicalTrials.gov, number: NCT00702156. Patients were elderly and predominantly male. Cardiovascular comorbidity, smoking history, and pulmonary function were similar in each group (mean FEV(1) 1.37 vs. 1.26 L, P = 0.52). A reduction in FEV(1) occurred after 4 months following treatment with bisoprolol compared with placebo (-70 vs. +120 mL, P = 0.01). Reversibility following inhaled beta(2)-agonist and static lung volumes were not impaired by bisoprolol. All measures of health status exhibited a consistent non-significant improvement, including the Short Form 36 physical and mental component scores (2.6 vs. 0.5 and 0.8 vs. -0.3, respectively), Minnesota Living with Heart Failure Questionnaire (-2.5 vs. 3.5) and Chronic Respiratory Questionnaire (0.07 vs. -0.24). The mean number of COPD exacerbations was similar in the bisoprolol and placebo groups (0.50 and 0.31, respectively, P = 0.44). CONCLUSION: Initiation of bisoprolol in patients with HF and concomitant moderate or severe COPD resulted in a reduction in FEV(1). However, symptoms and quality of life were not impaired.


OBJECTIVES: In this pre-specified subanalysis of the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) trial, which examined the effects of nebivolol in elderly heart failure (HF)
patients, we explored the effects of left ventricular ejection fraction (EF) on outcomes, including the subgroups impaired EF (≤35%) and preserved EF (>35%).

BACKGROUND: Beta-blockers are established drugs in patients with HF and impaired EF, but their value in preserved EF is unclear. METHODS: We studied 2,111 patients; 1,359 (64%) had impaired (≤35%) EF (mean 28.7%) and 752 (36%) had preserved (>35%) EF (mean 49.2%). The effect of nebivolol was investigated in these 2 groups, and it was compared to explore the interaction of EF with outcome. Follow-up was 21 months; the primary end point was all-cause mortality or cardiovascular hospitalizations.

RESULTS: Patients with preserved EF were more often women (49.9% vs. 29.8%) and had less advanced HF, more hypertension, and fewer prior myocardial infarctions (all p < 0.001). During follow-up, the primary end point occurred in 465 patients (34.2%) with impaired EF and in 235 patients (31.2%) with preserved EF. The effect of nebivolol on the primary end point (hazard ratio [HR] of nebivolol vs. placebo) was 0.86 (95% confidence interval: 0.72 to 1.04) in patients with impaired EF and 0.81 (95% confidence interval: 0.63 to 1.04) in preserved EF (p = 0.720 for subgroup interaction). Effects on all secondary end points were similar between groups (HR for all-cause mortality 0.84 and 0.91, respectively), and no p value for interaction was <0.48. CONCLUSIONS: The effect of beta-blockade with nebivolol in elderly patients with HF in this study was similar in those with preserved and impaired EF.