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Month/Year of Review: January 2012
PDL Class: Oral Beta Blockers

Date of Last Review: July 2009
Source Document: DERP Report

Current Preferred Agents:
Acebutolol HCL
Atenolol
Carvedilol
Labetalol HCL
Metoprolol Tartrate
Nadolol
Propranolol HCL

Current Non-Preferred Agents:
Betaxolol
Bisoprolol
Metoprolol Succinate
Nebivolol, (Bystolic®)
Penbutolol, (Levabutol®)
Pindolol
Timolol

Previous Recommendations:

1. In patients with mild-moderate HF, bisoprolol, carvedilol or metoprolol succinate (ER) reduce mortality.
2. In patients with severe HF, carvedilol or metoprolol succinate (ER) reduce mortality.
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.

PA Criteria/QL: Patient must have a covered ICD9 diagnosis.

Methods:

Search Strategy
A MEDLINE OVID search was conducted using the following search terms:
Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Nadolol, Nebivolol, Penbutolol, Pindolol, Propranolol, Timolol, heart failure, myocardial infarction, MI, atrial fibrillation, atrial arrhythmias, atrial flutter, esophageal and gastric varices, angina pectoris, chronic stable angina, migraines, migraine disorders, hypertension, portal hypertension, left ventricular dysfunction

The following limitations were used for the search:
All clinical trials, or clinical trial, or comparative study, or controlled clinical trial, or evaluation studies, or meta analysis, or multicenter study, or randomized controlled trial
English language
Humans
2009-present

Results:
The MEDLINE search retrieved 328 full citations. After a review of citations and abstracts, 48 studies were identified for assessment. Of those, four trials are included below, one placebo and three head-to head trials. A sub-analysis of the SENOIRS trial is a placebo controlled trial that looks at prevention of CV events in CAD patients over 70 on nebivolol. Three head-to-head trails with various beta blockers looked at the following outcomes: reversal of left ventricular dysfunction, prevention of AF in HF patients after post-op CABG, and improvement in symptoms in HF patients with non-selective beta-blockers. Although all of these studies had an outcome for the intervention group over the comparator group, none of these studies should impact current clinical practice. Citations and abstracts for the four included trails are listed in Appendix A.

The search of the Cochrane, AHRQ, DERP, and VA/DoD websites did not identify any relevant new systematic reviews. Search of the FDA website found no new FDA-approved drugs, indications, or relevant safety alerts.

New FDA-approved drugs:
None identified.

New FDA Indications:
None identified.

New FDA safety alerts:
None identified.

New Systematic Reviews:
None identified.

Appendix A:

1 Ambrosio G, Flather M.D, Böhm M, Cohen-Solal A, Murrone A, et al. β-blockade with nebivolol for prevention of acute ischaemic events in elderly patients with heart failure. Heart 2011;97 (3): 209-214.

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 β-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 β-blockade in HF patients with underlying CAD

2 Vinereanu D, Gherghinescu C, Ciobanu AO, Magda S, Niculescu N, et al. Reversal of subclinical left ventricular dysfunction by antihypertensive treatment: A prospective trial of nebivolol against metoprolol. J Hypertens 2011;29(4):809-17.

Objectives: To assess the effects of antihypertensive treatment on subclinical left ventricular dysfunction and to compare the effects of nebivolol with metoprolol.
Methods: This is a prospective, randomized, parallel, active-controlled, PROBE design study (ClinicalTrials.org: NCT00942487) in 60 patients (53 ± 9 years, 67% men) with arterial hypertension, left ventricular hypertrophy, normal ejection fraction, and no coronary heart disease, randomized to either a nebivolol-based or a metoprolol-based treatment, who had conventional and tissue Doppler echocardiography, at rest and during dobutamine stress, at baseline and after 6 months.
Results: SBP and DBP, and resting heart rate decreased by 13, 13, and 12%, respectively, on nebivolol, and by 11, 13, and 7%, respectively, on metoprolol (all, $P < 0.01$). Mean longitudinal early diastolic velocity increased by 16% ($P < 0.05$) on nebivolol compared with 9% (P = not significant) on metoprolol (P = not significant for intergroup differences), whereas flow propagation velocity increased by 34% on nebivolol ($P < 0.05$) and did not change on metoprolol ($P < 0.01$ for intergroup differences). Mean longitudinal displacement increased by 10% on nebivolol ($P < 0.05$) and did not change on metoprolol ($P < 0.05$ for intergroup differences), whereas ejection time increased by 5% on nebivolol ($P < 0.05$) and did not change on metoprolol. All the other parameters of left ventricular function were not different between the two treatment arms.

Conclusion: Patients with mild-to-moderate hypertension have a beneficial effect from 6-month antihypertensive treatment on diastolic longitudinal left ventricular function; effects are significant with nebivolol, but not with Metoprolol

3 Marazzi G, Iellamo F, Volterrani M, Caminiti G, Madonna M, et al. Comparison of effectiveness of carvedilol versus bisoprolol for prevention of postdischarge atrial fibrillation after coronary artery bypass grafting in patients with heart failure. Am J Cardiol 2011;107(2):215-9.

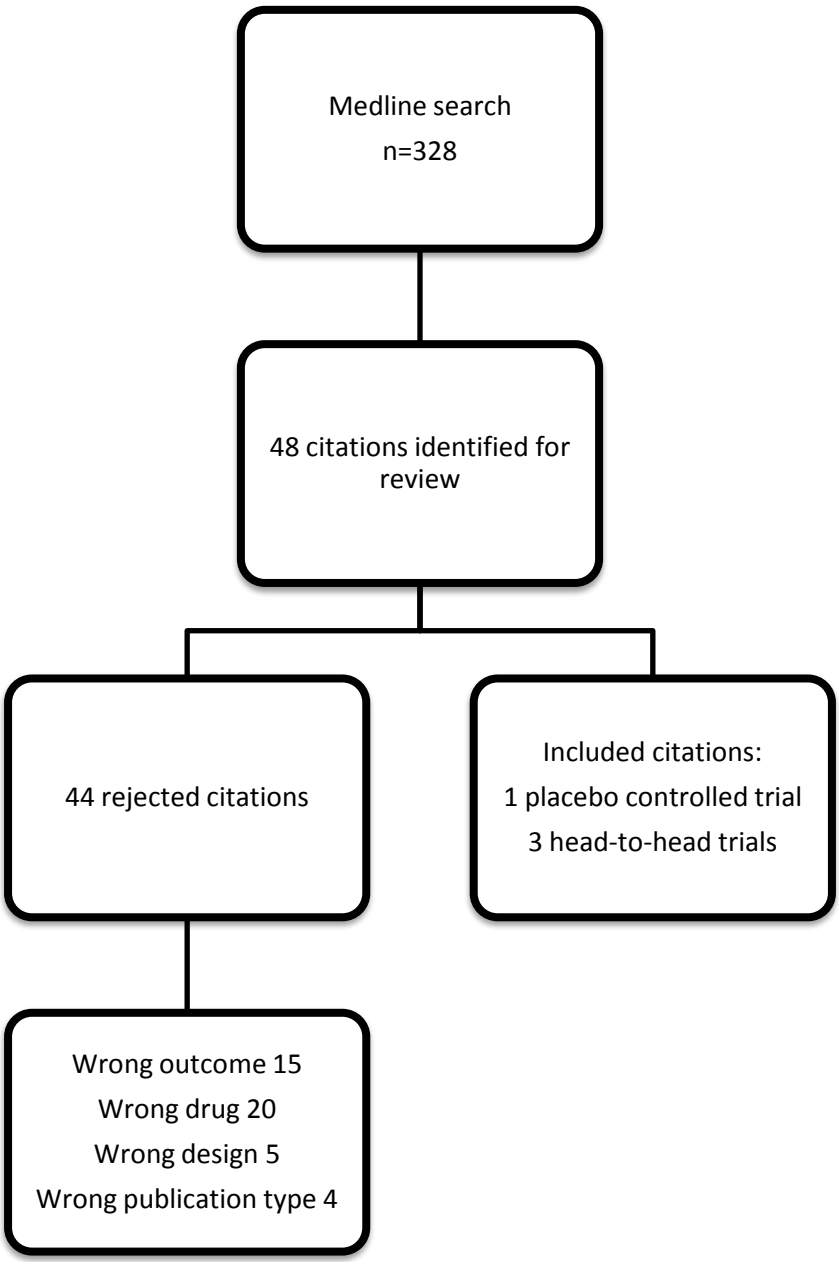
Atrial fibrillation (AF) occurs frequently soon after coronary artery bypass grafting (CABG) and often results in increased mortality and morbidity, particularly in patients with heart failure. New-onset AF is also a common event in the early period after discharge from a cardiac surgery clinic. Current guidelines recommend β blockers as first-line medication for the prevention of AF after CABG. In this prospective study, we investigated the effectiveness of the highly selective β1 receptor antagonist bisoprolol compared to the less selective β blocker carvedilol in preventing postdischarge AF after CABG in patients with decreased left ventricular function. Three hundred twenty patients (231 men, 89 women, mean age 66 ± 10 years) with ejection fraction <40% who underwent CABG and were then referred to an in-hospital cardiac rehabilitation program were randomized to receive bisoprolol (n = 160) or carvedilol (n = 160) starting 4 to 5 days after surgery. Bisoprolol was started at 1.25 mg 1 time/day and carvedilol was started 3.125 mg 2 times/day. All patients underwent continuous telemetric electrocardiographic monitoring for 5 days after entry in the study and thereafter 2 times/day routinely up to hospital discharge. During follow-up, 23 patients (14.6%) in the bisoprolol group and 37 patients (23%) in the carvedilol group developed AF (relative risk 0.6, confidence interval 0.4 to 0.9, p = 0.032). Twenty-six percent of all AF episodes were asymptomatic. At the 4-week outpatient visit, those in the bisoprolol group showed a significantly greater decrease in heart rate, being in sinus rhythm or AF (-15.6 ± 3 vs -9.4 ± 3 beats/min, p = 0.021), whereas changes in systolic and diastolic blood pressures did not differ significantly. In conclusion, bisoprolol is more effective than carvedilol in decreasing the incidence of postdischarge AF after CABG in patients with decreased left ventricular function.

4 Marques F, De Castro RBP, Nobre F, Pintya AO, Gallo Jr. L, et al. Replacement of carvedilol for propranolol in patients with heart failure. Arq Bras Cardiol 2010;95(1):107-14.

Background: Large clinical trials using the beta-blockers carvedilol, metoprolol, bisoprolol and nebivolol have demonstrated improvement of survival and symptoms in patients with heart failure. Despite the lack of scientific evidence, it is plausible that their beneficial effects are extensible to other beta-blockers.
Objective: To evaluate the impact of the replacement of carvedilol for propranolol on left ventricular function, functional capacity, quality of life, pressure levels, and cardiac autonomic control in patients with heart failure.
Methods: Twenty nine patients receiving optimized drug therapy including maximum tolerated doses of carvedilol were divided into two groups: replacement of carvedilol for propranolol (n = 15) and continued carvedilol (n = 14). At baseline and 6 months later, clinical and laboratorial assessments were carried out with radionuclide ventriculography, echocardiography, Minnesota questionnaire, walk test, APBM and Holter monitoring.
Results: The clinical and demographic characteristics were similar in the two groups at baseline. Individualized propranolol dose adjustment ensured a similar degree of beta-blockade, as assessed by resting heart rate and chronotropic reserve. The mean propranolol dose used was 109 ± 43 mg/day. Only one patient presented with intolerance to propranolol, thus carvedilol was reintroduced. One death was recorded in group propranolol.

Ejection fraction significantly increased in the propranolol group. No significant change was observed in the other cardiovascular variables after beta-blocker replacement.
Conclusion: Our results indicate that replacement of carvedilol for propranolol in patients with heart failure is not associated with deterioration of the ejection fraction, functional capacity, quality of life, and other cardiovascular variables related to autonomic and blood pressure control.

Appendix B


Medline search
n=328
48 citations identified for review
44 rejected citations
Included citations:
1 placebo controlled trial
3 head-to-head trials
Wrong outcome 15
Wrong drug 20
Wrong design 5
Wrong publication type 4