Drug Class Review

Beta Adrenergic Blockers

Preliminary Scan Report #3

February 2015

Last Report: Update #4, 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)

Dates of Previous Scan Reports

Scan #1: October 2010
Scan #2: October 2013

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

Condition	Measured Outcomes
Hypertension	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
Chronic stable angina (treatment duration ≥ 2 months)	1. Exercise tolerance 2. Attack frequency 3. Nitrate use
Post-coronary artery bypass graft (long-term treatment)	1. All-cause mortality 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 arrhythmia	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 rebleeding

Harms

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

Study designs (from last update report)

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

METHODS FOR SCAN

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from October 2013 through January 2015 using terms for included drugs. We limited results to randomized controlled trials and controlled clinical trials conducted in humans and published in English. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) for identification of new drugs, new populations, and new serious harms. To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials, controlled clinical trials, and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan(s)
None.

New Serious Harms

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan(s)
None.

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan

No new comparative effectiveness reviews were identified that would stand in place of a DERP review in terms of scope.

Identified in previous Preliminary Update Scan(s)

None.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches for this scan resulted in 126 citations. Of those, 3 potentially relevant new trials (Table 2) and 2 companion publications (Table 3) were identified; all of which were head-to-head in design. The 3 newly identified trials and 1 of the companion publications involved the use of carvedilol in populations with heart failure. The second companion publication involved the use of carvedilol in populations with permanent atrial fibrillation.

Together with the trials identified in previous scans, we have identified a total of 20 trials of beta adrenergic blockers (in 22 publications): 11 head-to-head trials (in 13 publications) and 9 placebo-controlled trials. The majority of the head-to-head evidence pertains to the use of carvedilol in populations with heart failure. Among the publications of placebo-controlled trials, all involved patients with heart failure and 7 of 9 provide results from subanalyses of previously included head-to-head trials (Table 2).

Study and population characteristics of primary head-to-head trials (Table 2) and companion head-to-head trials (Table 3) are provided below. Abstracts of head-to-head trials are provided in Appendix A. Abstracts of placebo-controlled trials are available upon request.

Table 2. Characteristics of primary head-to-head trials (N=11)

Author, Year Study Name	Beta Blockers	Population
Hypertension		
Espinola-Klein, 2011	Nebivolol vs metoprolol	Hypertension with intermittent claudication
Coronary Artery Bypass Grafting		
Iliuta, 2009	Betaxolol vs metoprolol	Coronary artery bypass grafting
Shahzamani, 2011	Carvedilol vs metoprolol	Coronary artery bypass grafting
Heart Failure		
Hori, 2014 MAIN-CHF II	Bisoprolol fumarate vs. carvedilol	Japanese patients with chronic heart failure
Lainscak, 2013 CIBIS-ELD	Bisoprolol vs. carvedilol	Elderly patients with heart failure
Jabbour, 2010	Carvedilol vs. metoprolol succinate vs. bisoprolol	Heart failure and chronic obstructive pulmonary disease
Udelson, 2009	Carvedilol vs. carvedilol phosphate	Heart failure
Marazzi, 2011	Carvedilol vs. nebivolol	Hypertensive heart failure
Contini, 2013 CARNEBI	Carvedilol vs. nebivolol vs. bisoprolol	Heart failure
Other Conditions		
Ulimoen, 2013	Carvedilol vs metoprolol	Permanent atrial fibrillation
Sen, 2009	Nebivolol vs metoprolol	Cardiac syndrome X

*Shading indicates trials or publications identified in the present scan

Table 3. Characteristics of companion head-to-head trials (N=2)

Author, Year Study Name	Beta Blockers	Population
Heart Failure		
Scherer, 2013 Sub-analysis of CIBIS-ELD	Bisoprolol vs. carvedilol	Elderly patients with heart failure
Other Conditions		
Ulimoen, 2014	Carvedilol vs. metoprolol	Permanent atrial fibrillation

*Shading indicates trials or publications identified in the present scan

Placebo-controlled trials (N=9)

Bisoprolol

- Hawkins, 2009 (heart failure and moderate to severe chronic obstructive pulmonary disease)
- Castagno, 2010 (companion to CIBIS-II; heart failure and renal impairment)

Metoprolol CR

- Ghali, 2009 (companion to MERIT-HF; heart failure and decreased renal function)

Nebivolol

- Ambrosio, 2011 (ischemic events)
- Cohen-Solal, 2009 (influence of renal dysfunction)
- de Boer, 2010 (influence of diabetes)
- Mulder, 2012 (influence of atrial fibrillation)
- van Veldhuisen, 2009 (influence of impaired and preserved left ventricular ejection fraction)

Propranolol

- Silberstein, 2012 (migraine)

SUMMARY

Since the last update report, we have identified no new drugs, no new serious harms, and no new comparative effectiveness reviews of beta adrenergic blockers. We have identified a total of 20 trials of beta adrenergic blockers (in 22 publications): 11 head-to-head trials (in 13 publications) and 9 placebo-controlled trials. The majority of the head-to-head evidence pertains to the use of carvedilol in populations with heart failure.

APPENDIX A. ABSTRACTS OF POTENTIALLY RELEVANT NEW HEAD-TO-HEAD TRIALS OF BETA ADRENERGIC BLOCKERS*

*Shading indicates studies identified in the current scan

Primary Studies (N=11)

Contini, M., et al. (2013). "Multiparametric comparison of CARvedilol, vs. NEbivolol, vs. BIsoprolol in moderate heart failure: the CARNEBI trial." International Journal of Cardiology **168**(3): 2134-2140.

BACKGROUND: Several beta-blockers, with different pharmacological characteristics, are available for heart failure (HF) treatment. We compared Carvedilol (beta1-beta2-alpha-blocker), Bisoprolol (beta1-blocker), and Nebivolol (beta1-blocker, NO-releasing activity).

METHODS: Sixty-one moderate HF patients completed a cross-over randomized trial, receiving, for 2 months each, Carvedilol, Nebivolol, Bisoprolol (25.6 +/- 12.6, 5.0 +/- 2.4 and 5.0 +/- 2.4 mg daily, respectively). At the end of each period, patients underwent: clinical evaluation, laboratory testing, echocardiography, spirometry (including total DLCO and membrane diffusion), O2/CO2 chemoreceptor sensitivity, constant workload, in normoxia and hypoxia (FiO2=16%), and maximal cardiopulmonary exercise test.

RESULTS: No significant differences were observed for clinical evaluation (NYHA classification, Minnesota questionnaire), laboratory findings (including kidney function and BNP), echocardiography, and lung mechanics. DLCO was lower on Carvedilol (18.3 +/- 4.8*mL/min/mmHg) compared to Nebivolol (19.9 +/- 5.1) and Bisoprolol (20.0 +/- 5.0) due to membrane diffusion 20% reduction (*=p<0.0001). Constant workload exercise showed in hypoxia a faster VO2 kinetic and a lower ventilation with Carvedilol. Peripheral and central sensitivity to CO2 was lower in Carvedilol while response to hypoxia was higher in Bisoprolol. Ventilation efficiency (VE/VCO2 slope) was 26.9 +/- 4.1* (Carvedilol), 28.8 +/- 4.0 (Nebivolol), and 29.0 +/- 4.4 (Bisoprolol). Peak VO2 was 15.8 +/- 3.6*mL/kg/min (Carvedilol), 16.9 +/- 4.1 (Nebivolol), and 16.9 +/- 3.6 (Bisoprolol).

CONCLUSIONS: beta-Blockers differently affect several cardiopulmonary functions. Lung diffusion and exercise performance, the former likely due to lower interference with beta2-mediated alveolar fluid clearance, were higher in Nebivolol and Bisoprolol. On the other hand, Carvedilol allowed a better ventilation efficiency during exercise, likely via a different chemoreceptor modulation. Results from this study represent the basis for identifying the best match between a specific beta-blocker and a specific HF patient.

Espinola-Klein, C., G. Weisser, et al. (2011). "-Blockers in patients with intermittent claudication and arterial hypertension: results from the nebivolol or metoprolol in arterial occlusive disease trial." Hypertension **58**(2): 148-154.

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 nebivolol 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.

Hori, M., et al. (2014). "Efficacy and safety of bisoprolol fumarate compared with carvedilol in Japanese patients with chronic heart failure: results of the randomized, controlled, double-blind, Multistep Administration of bisoprolol IN Chronic Heart Failure II (MAIN-CHF II) study.[Erratum appears in Heart Vessels. 2014 Mar;29(2):248]." Heart & Vessels **29**(2): 238-247.

Bisoprolol fumarate (bisoprolol) is a beta-blocker widely used to treat chronic heart failure (CHF). However, few studies have compared its efficacy and safety with those of the widely used beta-blocker carvedilol in Japanese patients with CHF. We designed a confirmatory trial of bisoprolol using carvedilol as a control drug; however, the trial was discontinued after an off-label use of bisoprolol was approved during the study. Bisoprolol and carvedilol were administered for 32 weeks in 31 and 28 patients, respectively. The mean maintenance doses of bisoprolol and carvedilol were 3.3 and 13.6 mg/day, respectively, and the mean durations of treatment were 188.2 and 172.9 days, respectively. Heart-rate changes were similar in both groups. The mean changes from baseline to Week 32 in left ventricular (LV) ejection fraction (EF) (bisoprolol vs carvedilol groups; 11.7 % +/- 8.6 % vs 10.1 % +/- 10.5 %), LV end-diastolic volume (-37.5 +/- 48.7 vs -24.7 +/- 29.4 ml), and LV end-systolic volume (-41.9 +/- 43.0 vs -29.3 +/- 25.9 ml) revealed a decrease in LV volume and an increase in LVEF in both groups. The cumulative event-free rate for a composite of cardiovascular death or admissions to hospital for worsening of CHF was 92.4 % and 94.7 % in the bisoprolol and carvedilol groups, respectively. Overall, 90.3 % and 85.7 % of patients were titrated up to the maintenance doses of bisoprolol and carvedilol, respectively. Bisoprolol, at half the dose used in other countries, is well tolerated and is as effective as carvedilol for treating Japanese patients with mild to moderate CHF.

Iliuta, L., R. Christodorescu, et al. (2009). "Prevention of perioperative atrial fibrillation with betablockers in coronary surgery: betaxolol versus metoprolol." Interactive Cardiovascular & Thoracic Surgery **9**(1): 89-93.

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 prophylaxy 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.

Jabbour, A., P. S. Macdonald, et al. (2010). "Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial." Journal of the American College of Cardiology **55**(17): 1780-7.

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.

Lainscak, M., et al. (2013). "Self-rated health predicts adverse events during beta-blocker treatment: the CIBIS-ELD randomised trial analysis." International Journal of Cardiology **163**(1): 87-92.

BACKGROUND: Self-rated health (SRH) predicts outcome in patients with heart failure. Beta-blockers are known to improve health-related quality of life and reduce mortality in such patients. We aimed to evaluate the relation between SRH and adverse events during titration of beta-blockers in elderly patients with heart failure.

METHODS: The cardiac insufficiency bisoprolol study in the elderly (CIBIS-ELD) is a multicentre, double-blind trial, in which 883 patients aged > 65 years with chronic heart failure (73 +/- 6 years, 38% women, left ventricular ejection fraction [LVEF] 42% +/- 14%) were randomised to bisoprolol or carvedilol. SRH was assessed at baseline and after 12 weeks, using a 5-grade descriptive scale: excellent, very good, good, fair, and poor.

RESULTS: Median SRH at baseline and follow-up was good, but more patients reported fair/poor SRH at baseline (36% vs. 30%, p = 0.012). Women, beta-blocker-naive patients, patients in NYHA class III/IV and those with PHQ-9 score > 12 were more likely to report fair/poor baseline SRH (p < 0.001 for all). During follow-up, SRH improved in 34% of patients and worsened in 8% (p < 0.001). Adverse events were experienced by 64% patients and 38% experienced > 1 adverse event or serious adverse event, with higher prevalence in lower SRH categories. In a multivariate logistic regression model, SRH, age, distance achieved on the 6-min walk test and LVEF >45% predicted adverse events (p < 0.05 for all).

CONCLUSIONS: SRH is an independent predictor of adverse events during titration of beta-blockers and correlates with the proportion and number of adverse events per patient.

Marazzi, G., M. Volterrani, et al. (2011). "Comparative long term effects of nebivolol and carvedilol in hypertensive heart failure patients." Journal of Cardiac Failure **17**(9): 703-709.

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 4deaths, 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.

Sen, N., Y. Tavil, et al. (2009). "Nebivolol therapy improves endothelial function and increases exercise tolerance in patients with cardiac syndrome X." Anadolu Kardiyoloji Dergisi **9**(5): 371-9.

OBJECTIVE: We sought to determine whether nebivolol 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.

Shahzamani, M., A. Ghanavati, et al. (2011). "Carvedilol compared with metoprolol on left ventricular ejection fraction after coronary artery bypass graft." Journal of PeriAnesthesia Nursing **26**(6): 384-387.

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.

Udelson, J. E., S. J. Pressler, et al. (2009). "Adherence with once daily versus twice daily carvedilol in patients with heart failure: 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." Journal of Cardiac Failure **15**(5): 385-93.

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.

Ulimoen, S. R., S. Enger, et al. (2013). "Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation." American Journal of Cardiology **111**(2): 225-230.

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.

Companion Publications (N=2)

Scherer, M., et al. (2013). "Determinants of change in quality of life in the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD)." European Journal of Internal Medicine **24**(4): 333-338.

OBJECTIVE: Little is known about parameters that lead to improvement in QoL in individual patients. We analysed the data of the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) in order to answer the question of how and to what extent change

in health-related QoL during up-titration with bisoprolol vs. carvedilol is influenced by clinical and psychosocial factors in elderly patients with heart failure.
METHODS: This is a QoL analysis of CIBIS-ELD, an investigator-initiated multi-center randomised phase III trial in elderly patients (65 years or older) with moderate to severe heart failure. Clinical parameters such as New York Heart Association functional class, heart rate, left ventricular ejection fraction (LVEF), 6-min walk distance, as well as the physical and psychosocial component scores on the short-form QoL health survey (SF36) and depression were recorded at baseline and at the final study visit.
RESULTS: Full baseline and follow-up QoL data were available for 589 patients (292 in the bisoprolol and 297 in the carvedilol group). Mean physical and psychosocial QoL improved significantly during treatment. In regression analyses, changes in both SF36 component scores from baseline to follow-up were mainly predicted by baseline QoL and depression as well as change in depression over time. Changes in cardiac severity markers were significantly weaker predictors.
CONCLUSION: Mean QoL increased during up-titration of bisoprolol and carvedilol. Both baseline depression and improvement in depression over time are associated with greater improvement in QoL more strongly than changes in cardiac severity measures.

Ulimoen, S. R., et al. (2014). "Calcium channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide levels compared with beta-blockers in patients with permanent atrial fibrillation." European Heart Journal **35**(8): 517-524.
AIMS: Rate control of atrial fibrillation (AF) has become a main treatment modality, but we need more knowledge regarding the different drugs used for this purpose. In this study, we aimed to compare the effect of four common rate-reducing drugs on exercise capacity and levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with permanent AF.
METHODS AND RESULTS: We included 60 patients (mean age 71 +/- 9 years, 18 women) with permanent AF and normal left ventricular function in a randomized, cross-over, investigator-blind study. Diltiazem 360 mg, verapamil 240 mg, metoprolol 100 mg, and carvedilol 25 mg were administered o.d. for 3 weeks. At baseline and on the last day of each treatment period, the patients underwent a maximal cardiopulmonary exercise test and blood samples were obtained at rest and at peak exercise. The exercise capacity (peak VO2) was significantly lower during treatment with metoprolol and carvedilol compared with baseline (no treatment) or treatment with diltiazem and verapamil ($P < 0.001$ for all). Compared with baseline, treatment with diltiazem and verapamil significantly reduced the NT-proBNP levels both at rest and at peak exercise, whereas treatment with metoprolol and carvedilol increased the levels ($P < 0.05$ for all).
CONCLUSION: Rate-reducing treatment with diltiazem or verapamil preserved exercise capacity and reduced levels of NT-proBNP compared with baseline, whereas treatment with metoprolol or carvedilol reduced the exercise capacity and increased levels of NT-proBNP.