

Drug Class Review on Beta Blockers



Update #3: Preliminary Scan Report

December 2006

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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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 only to assist with Participating Organizations’ consideration of allocating resources toward a full update of this topic. 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 FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Update #2 Final Report was completed in May of 2005.

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, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, penbutolol, pindolol, propranolol, propranolol LA, timolol)

Effectiveness outcomes

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

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events

Study designs

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

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (January 2005 to December 2006). We used terms for included drugs and limits for humans, English and controlled clinical trials.

We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

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

RESULTS

Overview

We identified 145 potentially relevant citations. Of those, there are 17 new potentially relevant controlled clinical trials (Appendix A).

New Drugs

A controlled release form of carvedilol was approved by the US FDA in October 2006. Approval appears to be based on pharmacokinetic and pharmacologic studies only.

New Indications

None

New Safety Alerts

Atenolol

2/05: new info under warnings and precautions about risk of hypoglycemia/bradycardia for neonates

Carvedilol

8/05: Post-marketing reports of Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme, Urinary Incontinence in Women, interstitial Pneumonitis

8/06: New info under warnings and precautions about adverse effects of beta-blockers on glycemic control

Metroprolol tartrate

9/06: Asked to submit Dear Health Care Professional letter to Medwatch about new info about AE's in patients comorbid w/HTN+angina - Gangrene in patients with pre-existing severe peripheral circulatory disorders has also been reported very rarely; rhinitis; vomiting; photosensitivity and worsening of psoriasis; weight gain, arthritis, and retroperitoneal fibrosis

9/06: Also, new info about contraindications: previous hypersensitivity; sick-sinus syndrome; severe peripheral arterial circulatory disorders; pheochromocytoma

Metroprolol succinate

4/05: post-marketing reports of urticaria

APPENDIX A

Brady, A. R., J. S. R. Gibbs, et al. (2005). "Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial.[see comment]." *Journal of Vascular Surgery* **41**(4): 602-9.

OBJECTIVE: To assess whether a pragmatic policy of perioperative beta-blockade, with metoprolol, reduced the 30-day cardiovascular morbidity and mortality and reduced the length of hospital stay in average patients undergoing infrarenal vascular surgery. **METHODS:** This was a double-blind randomized placebo-controlled trial that occurred in vascular surgical units in four UK hospitals. Participants were 103 patients without previous myocardial infarction who had infrarenal vascular surgery between July 2001 and March 2004. Interventions were oral metoprolol (50 mg twice daily, supplemented by intravenous doses when necessary) or placebo from admission until 7 days after surgery. Holter monitors were kept in place for 72 hours after surgery. **RESULTS:** Eighty men and 23 women (median age, 73 years) were randomized, 55 to metoprolol and 48 to placebo, and 97 (94%) underwent surgery during the trial. The most common operations were aortic aneurysm repair (38%) and distal bypass (29%). Intraoperative inotropic support was required in 64% and 92% of patients in the placebo and metoprolol groups, respectively. Within 30 days, cardiovascular events occurred in 32 patients, including myocardial infarction (8%), unstable angina (9%), ventricular tachycardia (19%), and stroke (1%). Four (4%) deaths were reported. Cardiovascular events occurred in 15 (34%) and 17 (32%) patients in the placebo and metoprolol groups, respectively (unadjusted relative risk, 0.94; 95% confidence interval, 0.53-1.66; adjusted [for age, sex, statin use, and aortic cross-clamping] relative risk, 0.87; 95% confidence interval, 0.48-1.55). Time from operation to discharge was reduced from a median of 12 days (95% confidence interval, 9-19 days) in the placebo group to 10 days (95% confidence interval, 8-12 days) in the metoprolol group (adjusted hazard ratio, 1.71; 95% confidence interval, 1.09-2.66; $P < .02$). **CONCLUSIONS:** Myocardial ischemia was evident in a high proportion (one third) of the patients after surgery. A pragmatic regimen of perioperative beta-blockade with metoprolol did not seem to reduce 30-day cardiovascular events, but it did decrease the time from surgery to discharge.

Contreras, G., T. Greene, et al. (2005). "Blood pressure control, drug therapy, and kidney disease." *Hypertension* **46**(1): 44-50.

The African American Study of Kidney Disease and Hypertension examined the effect on renal function decline of 2 blood pressure (BP) goals (low mean arterial pressure [MAP] $< \text{or} = 92$ versus usual MAP 102 to 107 mm Hg) and 3 antihypertensives (ramipril versus amlodipine versus metoprolol). We previously reported that in all drug groups combined the BP intervention had similar effects on the primary outcome of glomerular filtration rate (GFR) slope or the main secondary clinical composite outcome of end-stage renal disease (ESRD), death, or GFR decline by 50% or 25 mL/min per 1.73 m². This report examines the effect of the BP intervention separately in the 3 drug groups. The BP effect was similar among the drug groups for either GFR slope or the main clinical composite. However, the BP effect differed significantly among the drug groups for the composite of ESRD or death ($P=0.035$) and ESRD alone ($P=0.021$). Higher event rates for amlodipine patients assigned to the usual BP goal (0.087 per patient-year for ESRD or death and 0.064 per patient-year for ESRD) were seen compared with the remaining groups of the factorial design (range, 0.041 to 0.050 for ESRD or death; and range, 0.027 to 0.036 for ESRD). The low BP goal was associated with reduced risk of ESRD or death (risk reduction 51%; 95% confidence interval, 13% to 73%) and ESRD (54%; 8% to 77%) for amlodipine patients, but not for patients assigned to the other drug groups. These secondary analyses suggest a benefit of the low BP goal among patients assigned to amlodipine, but they must be interpreted cautiously.

de la Pena, J., E. Brullet, et al. (2005). "Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial." Hepatology **41**(3): 572-8.

beta-Blockers and endoscopic variceal ligation (EVL) have proven to be valuable methods in the prevention of variceal rebleeding. The aim of this study was to compare the efficacy of EVL combined with nadolol versus EVL alone as secondary prophylaxis for variceal bleeding. Patients admitted for acute variceal bleeding were treated during emergency endoscopy with EVL or sclerotherapy and received somatostatin for 5 days. At that point, patients were randomized to receive EVL plus nadolol or EVL alone. EVL sessions were repeated every 10 to 12 days until the varices were eradicated. Eighty patients with cirrhosis (alcoholic origin in 66%) were included (Child-Turcotte-Pugh A, 15%; B, 56%; C, 29%). The median follow-up period was 16 months (range, 1-24 months). The variceal bleeding recurrence rate was 14% in the EVL plus nadolol group and 38% in the EVL group (P = .006). Mortality was similar in both groups: five patients (11.6%) died in the combined therapy group and four patients (10.8%) died in the EVL group. There were no significant differences in the number of EVL sessions to eradicate varices: 3.2 +/- 1.3 in the combined therapy group versus 3.5 +/- 1.3 in the EVL alone group. The actuarial probability of variceal recurrence at 1 year was lower in the EVL plus nadolol group (54%) than in the EVL group (77%; P = .06). Adverse effects resulting from nadolol were observed in 11% of the patients. In conclusion, nadolol plus EVL reduces the incidence of variceal rebleeding compared with EVL alone. A combined treatment could lower the probability of variceal recurrence after eradication.

de Simone, G., K. Wachtell, et al. (2005). "Body build and risk of cardiovascular events in hypertension and left ventricular hypertrophy: the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study." Circulation **111**(15): 1924-31.

BACKGROUND: Obesity may independently increase the risk of adverse events in hypertension with target-organ damage. We investigated whether body build was independently associated with higher cardiovascular risk and whether treatment with losartan relative to atenolol influenced the impact of body build on the primary composite end point of cardiovascular death, stroke, and myocardial infarction and on cardiovascular death in patients with hypertension and left ventricular hypertrophy in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. **METHODS AND RESULTS:** The population of 9079 patients was divided as follows: thin (body mass index [BMI] <20 kg/m², 2%), normal weight (BMI 20 to 24.9, 24%), overweight (BMI 25 to 29.9, 45%), and obese (class I: BMI 30 to 34.9, 21%; class II: BMI 35 to 39.9, 6%; class III: BMI > or =40, 2%). Incident diabetes increased progressively with BMI and was somewhat higher in the atenolol arm. Differences in gender and race were detected among the body build groups. Rates (Cox proportional hazard analysis) of the primary composite end point did not differ among body build groups after adjustment for age, gender, race, smoking habit, prevalent cardiovascular disease, and left ventricular hypertrophy. Cardiovascular death was more frequent among thin (P<0.05) and pooled class II-III obesity (both P<0.04) than normal-weight groups. Risk was not attenuated significantly by losartan treatment, nor did it interfere with the greater benefit of losartan- as opposed to atenolol-based treatment. **CONCLUSIONS:** In the LIFE study, stratification for classes of body build identified increased risk of cardiovascular mortality in both thin and moderately-to-severely obese individuals. This risk was not attenuated significantly by losartan treatment, nor did it interfere with the greater benefit of losartan-based treatment as opposed to atenolol-based treatment.

Deedwania, P. C., T. D. Giles, et al. (2005). "Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF." American Heart Journal **149**(1): 159-67.

BACKGROUND: The objective of the current study was to examine the efficacy and tolerability of the beta-blocker metoprolol succinate controlled release/extended release (CR/XL) in patients

with diabetes in the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). METHODS: The Cox proportional hazards model was used to calculate hazard ratios (HR) for convenience expressed as relative risks (risk reduction = 1-HR), and 95% confidence intervals (CI). RESULTS: The risk of hospitalization for heart failure was 76% higher in diabetics compared to non-diabetics (95% CI 38% to 123%). Metoprolol CR/XL was well tolerated and reduced the risk of hospitalization for heart failure by 37% in the diabetic group (95% CI 53% to 15%), and by 35% in the non-diabetic group (95% CI 48% to 19%). Pooling of mortality data from the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), MERIT-HF, and the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) showed similar survival benefits in patients with diabetes (25%; 95% CI 40% to 4%) and without diabetes (36%; 95% CI 44% to 27%); test of diabetes by treatment interaction was non-significant. Adverse events were reported more often on placebo than on metoprolol CR/XL. CONCLUSIONS: Patients with heart failure and diabetes have a much higher risk of hospitalization than patients without diabetes. Regardless of diabetic status, a highly significant reduction in hospitalizations for heart failure was observed with metoprolol CR/XL therapy, which was very well tolerated also by patients with diabetes. Furthermore, the pooled data showed a statistically significant survival benefit in patients with diabetes.

Fossum, E., A. Moan, et al. (2005). "The effect of losartan versus atenolol on cardiovascular morbidity and mortality in patients with hypertension taking aspirin: the Losartan Intervention for Endpoint Reduction in hypertension (LIFE) study." *Journal of the American College of Cardiology* **46**(5): 770-5.

OBJECTIVES: We conducted a subgroup analysis in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study to determine whether aspirin interacted with the properties of losartan, an angiotensin-II receptor antagonist. BACKGROUND: Negative interactions between angiotensin-converting enzyme inhibitors and aspirin have been reported. There are no data reported from clinical trials about possible interactions between angiotensin-II receptor antagonists and aspirin. METHODS: The LIFE study assigned 9,193 patients with hypertension and left ventricular hypertrophy (LVH) to losartan- or atenolol-based therapy for a mean of 4.7 years, with 1,970 (21.4%) taking aspirin at baseline. The primary composite end point (CEP) included cardiovascular death, stroke, and myocardial infarction (MI). The present cohort was stratified by aspirin use at baseline. RESULTS: Blood pressures were reduced similarly in the losartan with aspirin (n = 1,004) and atenolol with aspirin (n = 966) groups. The CEP was reduced by 32% (95% confidence interval 0.55 to 0.86, p = 0.001) with losartan with aspirin compared to atenolol with aspirin, adjusted for Framingham risk score and LVH. The test for treatment versus aspirin interaction, excluding other covariates, was significant for the CEP (p = 0.016) and MI (p = 0.037). CONCLUSIONS: There was a statistical interaction between treatment and aspirin in the LIFE study, with significantly greater reductions for the CEP and MI with losartan in patients using aspirin than in patients not using aspirin at baseline. Further studies are needed to clarify whether this represents a pharmacologic interaction or a selection by aspirin use of patients more likely to respond to losartan treatment.

Fossum, E., M. H. Olsen, et al. (2006). "Long-term effects of a losartan- compared with an atenolol-based treatment regimen on carotid artery plaque development in hypertensive patients with left ventricular hypertrophy: ICARUS, a LIFE substudy." *Journal of Clinical Hypertension* **8**(3): 169-73.

In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, there was a 25% risk reduction for stroke with angiotensin receptor blocker-based therapy (losartan) as compared with beta-blocker-based therapy (atenolol) despite comparable blood pressure reductions. This substudy examines treatment effects on the amount and density of atherosclerotic lesions in the common carotid arteries and the carotid bulb in 81 patients during 3 years of treatment. There were no statistically significant changes in the amount of carotid plaque in patients treated with losartan compared with an atenolol-based treatment program. A statistically

nonsignificant increase in plaque density and index (average of plaque amount and density) was seen in the atenolol group compared with those treated with losartan. The small number of patients evaluated may have limited the power to detect a difference in outcome. The difference in carotid plaque index increase between the treatment groups during 3 years of treatment could not be statistically linked to specific treatments in the present substudy.

Jonsson, G., M. Abdelnoor, et al. (2005). "A comparison of the two beta-blockers carvedilol and atenolol on left ventricular ejection fraction and clinical endpoints after myocardial infarction. a single-centre, randomized study of 232 patients." Cardiology **103**(3): 148-55.

BACKGROUND: beta-Blockers have been found to reduce mortality and morbidity in postmyocardial infarction patients. However, it is not fully understood whether all beta-blockers have similar favourable cardiovascular effects. The aim of this study was to compare the effects of carvedilol and atenolol on global and regional left ventricular ejection fraction (LVEF) and on predefined cardiovascular endpoints. **METHODS:** In a single-centre, randomized, open, endpoint-blinded, parallel group study, 232 patients with acute myocardial infarction were randomized to treatment with carvedilol or atenolol. LVEF was measured by gated blood pool scintigraphy during the first week and after 12 months. The treatment was given orally within 24 h. The mean dose was 36.2 and 72.1 mg in the carvedilol and atenolol groups, respectively. **RESULTS:** No significant difference was found between the two study groups in the mean global and regional LVEF. There tended to be fewer first serious cardiovascular events in the carvedilol compared with the atenolol group (RR = 0.83, 95% CI 0.56-1.23, p = 0.39). Cold hands and feet were observed less frequently in the carvedilol group (20 vs. 33%, p = 0.025). **CONCLUSION:** In patients following an acute myocardial infarction, no difference in either global or regional LVEF was observed between baseline and 12 months when treatment with carvedilol was compared with atenolol. Copyright 2005 S. Karger AG, Basel.

Kaushik, R., R. M. Kaushik, et al. (2005). "Biofeedback assisted diaphragmatic breathing and systematic relaxation versus propranolol in long term prophylaxis of migraine." Complementary Therapies in Medicine **13**(3): 165-74.

OBJECTIVES: To evaluate utility of biofeedback assisted diaphragmatic breathing and systematic relaxation in migraine and to compare their efficacy with propranolol in long term prophylaxis of migraine. **METHODS:** 192 migraine patients were randomly distributed into two groups. Propranolol group received propranolol 80 mg/day while biofeedback group received electromyogram (EMG) and temperature biofeedback assisted diaphragmatic breathing and systematic relaxation training accompanied by home practice for 6 months. **RESULTS:** Significant clinical response was seen with biofeedback in 66.66% and with propranolol in 64.58% of patients. Frequency, severity, duration of attacks and number of vomiting episodes were significantly reduced in both the groups at 6 months but inter-group differences were statistically insignificant. During 1 year post-treatment period, significantly lesser resurgence of migraine was seen in biofeedback group as whole (9.37%) and in biofeedback responders in biofeedback group (9.37%) in comparison to resurgence of migraine in propranolol group as whole (38.54%) and in propranolol responders in propranolol group (53.22%) respectively. **CONCLUSIONS:** Biofeedback assisted diaphragmatic breathing and systematic relaxation were very useful in migraine and had significantly better long-term prophylactic effect than propranolol in migraine.

Kjeldsen, S. E., P. A. Lyle, et al. (2005). "The effects of losartan compared to atenolol on stroke in patients with isolated systolic hypertension and left ventricular hypertrophy. The LIFE study." Journal of Clinical Hypertension **7**(3): 152-8.

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study reported that a losartan-based antihypertensive regimen reduced cardiovascular morbidity and mortality

(composite of cardiovascular death, stroke, and myocardial infarction) more than therapy based on atenolol in patients with left ventricular hypertrophy and isolated systolic hypertension (ISH). Patients aged 55-80 years with blood pressures 160-200/<90 mm Hg were followed for a mean of 4.7 years. Blood pressure was similarly reduced in the losartan (n=660) and atenolol (n=666) ISH groups. There were 88 (6.6%) patients who experienced a stroke, 18 of which were fatal. Of patients experiencing strokes, 72.7% had an ischemic stroke. ISH patients in LIFE compared to the non-ISH group had a higher incidence of any stroke and embolic stroke, and similar incidences of fatal, atherosclerotic, and hemorrhagic/other strokes. The incidence of any stroke (40% risk reduction [RR], p=0.02), fatal stroke (70% RR, p=0.035), and atherothrombotic stroke (45% RR, p=0.022) was significantly lower in losartan-treated compared to the atenolol-treated patients. The 36% RR for embolic strokes in the losartan group was not statistically significantly (p=0.33) different from the atenolol group. These data suggest that losartan-based treatment is more effective than an atenolol-based treatment for patients with ISH and a high risk for stroke.

Kostis, J. B., A. C. Wilson, et al. (2005). "Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes.[see comment]." American Journal of Cardiology **95**(1): 29-35.

Diuretic-based antihypertensive therapy is associated with the development of diabetes but with improved clinical outcomes. It has been proposed that the duration of clinical trials has been too short to detect the adverse effects of diabetes. We assessed the long-term mortality rate of subjects in the Systolic Hypertension in the Elderly Program (n = 4,732) who were randomized to stepped-care therapy with 12.5 to 25.0 mg/day of chlorthalidone or matching placebo. If blood pressure remained above the goal, atenolol or matching placebo was added. At a mean follow-up of 14.3 years, cardiovascular (CV) mortality rate was significantly lower in the chlorthalidone group (19%) than in the placebo group (22%; adjusted hazard ratio [HR] 0.854, 95% confidence interval [CI] 0.751 to 0.972). Diabetes at baseline (n = 799) was associated with increased CV mortality rate (adjusted HR 1.659, 95% CI 1.413 to 1.949) and total mortality rate (adjusted HR 1.510, 95% CI 1.347 to 1.693). Diabetes that developed during the trial among subjects on placebo (n = 169) was also associated with increased CV adverse outcome (adjusted HR 1.562, 95% CI 1.117 to 2.184) and total mortality rate (adjusted HR 1.348, 95% CI 1.051 to 1.727). However, diabetes that developed among subjects during diuretic therapy (n = 258) did not have significant associations with CV mortality rate (adjusted HR 1.043, 95% CI 0.745 to 1.459) or total mortality rate (adjusted HR 1.151, 95% CI 0.925 to 1.433). Diuretic treatment in subjects who had diabetes was strongly associated with lower long-term CV mortality rate (adjusted HR 0.688, 95% CI 0.526 to 0.848) and total mortality rate (adjusted HR 0.805, 95% CI 0.680 to 0.952). Thus, chlorthalidone-based treatment improved long-term outcomes, especially among subjects who had diabetes. Subjects who had diabetes associated with chlorthalidone had no significant increase in CV events and had a better prognosis than did those who had preexisting diabetes.

McMurray, J., L. Kober, et al. (2005). "Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial.[see comment]." Journal of the American College of Cardiology **45**(4): 525-30.

OBJECTIVES: Whether beta-blockers reduce atrial arrhythmias and, when added to an angiotensin-converting enzyme (ACE) inhibitor, ventricular arrhythmia is unknown.

BACKGROUND: Ventricular and atrial arrhythmias are common after acute myocardial infarction (AMI) and are associated with a poor prognosis. Angiotensin-converting enzyme inhibitors reduce the incidence of both types of arrhythmia. METHODS: The antiarrhythmic effect of carvedilol was examined in a placebo-controlled multicenter trial, the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study, which enrolled 1,959 patients with reduced left ventricular systolic function after AMI, 98% of whom were

treated with an ACE inhibitor. RESULTS: The incidence of atrial fibrillation/flutter was 53 to 984 (5.4%) in the placebo group and 22 to 975 (2.3%) in the carvedilol group, giving a carvedilol/placebo hazard ratio (HR) of 0.41 (95% confidence interval [CI] 0.25 to 0.68; $p = 0.0003$). The corresponding rates of ventricular tachycardia/flutter/fibrillation were 38 to 984 (3.9%) and 9 to 975 (0.9%) (HR 0.24, 95% CI 0.11 to 0.49; $p < 0.0001$). CONCLUSIONS: Carvedilol has a powerful antiarrhythmic effect after AMI, even in patients already treated with an ACE inhibitor. Carvedilol suppresses atrial as well as ventricular arrhythmias in these patients.

Rousseau, M. F., H. Pouleur, et al. (2005). "Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris." *American Journal of Cardiology* **95**(3): 311-6.

We investigated whether ranolazine therapy improves exercise-induced angina pectoris and myocardial ischemia compared with placebo or with standard doses of atenolol in patients who had chronic angina and evaluated the effects on hemodynamics at rest and during exercise. In this trial, 158 patients who had symptom-limited exercise discontinued beta-blocker therapy and were randomized into a double-blind, 3-period, crossover study of 400 mg of immediate-release ranolazine 3 times daily, 100 mg/day of atenolol, or placebo, each administered for 1 week. Exercise tests were administered at the end of each treatment period. Therapy with ranolazine or atenolol produced statistically significant improvement in all 3 exercise end points compared with placebo. Compared with atenolol therapy, ranolazine therapy resulted in significantly longer total exercise duration and was statistically indistinguishable from atenolol for time to onset of angina and ST-segment depression. Except for a modest increase in systolic blood pressure at peak exercise during ranolazine therapy, hemodynamic measurements did not differ significantly during ranolazine and placebo therapies. In contrast, atenolol significantly decreased blood pressure, heart rate, and rate-pressure product at rest and during exercise compared with placebo or ranolazine. In conclusion, ranolazine therapy prolonged exercise duration and decreased exercise-induced ischemia and angina with quantitative effects equal to or greater than those with atenolol. Unlike atenolol, the anti-ischemic and antianginal effects of ranolazine occurred without decreases in blood pressure, heart rate, or rate-pressure product.

Sarin, S. K., M. Wadhawan, et al. (2005). "Evaluation of endoscopic variceal ligation (EVL) versus propranolol plus isosorbide mononitrate/nadolol (ISMN) in the prevention of variceal rebleeding: comparison of cirrhotic and noncirrhotic patients." *Digestive Diseases & Sciences* **50**(8): 1538-47.

Both EVL and drug therapy are effective in the prevention of variceal rebleeding. Comparisons between the two modalities are few, and only in cirrhotics. This prospective randomized controlled trial compared EVL with drug therapy (propranolol + ISMN) in the prevention of rebleeds from esophageal varices in cirrhotic and noncirrhotic portal hypertension (NCPH) patients. One hundred thirty-seven variceal bleeders were randomized to EVL (Group I; $n = 71$) or drug therapy (Group II; $n = 66$). In Group I, EVL was done every 2 weeks till obliteration of varices. In Group II, propranolol (dose sufficient to reduce heart rate to 55 bpm/maximum tolerated dose) and ISMN (incremental dose up to 20 mg BD) were administered. Group I and II patients had comparable baseline characteristics, follow-up (12.4 vs. 11.1 months), cirrhotics and noncirrhotics [50(70.4%) and 21(29.6%) vs. 51(77.3%) and 15(22.7%)] and frequency of Child's A (35 vs. 27), B (26 vs. 28), and C (9 vs. 11). The mean daily dose was 109 +/- 46 mg propranolol and 34 +/- 11 mg ISMN and was comparable in cirrhotic and NCPH patients. Upper GI bleeds occurred in 10 patients in Group I (5 from esophageal varices) and in 18 patients in Group II (15 from esophageal varices) ($P = 0.06$). The actuarial probability of rebleeding from esophageal varices at 24 months was 22% in Group I and 37% in Group II ($P = 0.02$). The probability of bleed was significantly higher in Child's C compared to Child's A/B cirrhotics ($P = 0.02$). On subgroup analysis, in NCPH patients, the actuarial probability of bleed at 24 months was significantly lower in Group I compared to Group II (25% vs 37%; $P = 0.01$). In cirrhotics, there was no difference in the probability of rebleeding between patients in Group I and those in

Group II ($P = 0.74$). In Group II, 25.7% patients had adverse effects of drug therapy and 9% patients had to stop propranolol due to serious adverse effects, none required stopping ISMN. There were 10 deaths, 6 in Group I (bleed related, 1) and 4 in Group II (bleed related, 1); the actuarial probability of survival was comparable ($P = 0.39$). EVL and combination therapy are equally effective in the prevention of variceal rebleeding in cirrhotic patients. EVL is more effective than drug therapy in the prevention of rebleeds in patients with NCPH and, hence, recommended. However, in view of the small number of NCPH patients, further studies are needed before this can be stated conclusively.

Tatli, E. and T. Kurum (2005). "A controlled study of the effects of carvedilol on clinical events, left ventricular function and proinflammatory cytokines levels in patients with dilated cardiomyopathy." Canadian Journal of Cardiology **21**(4): 344-8.

BACKGROUND: Carvedilol is known to decrease the severity of ventricular dysfunction, to increase the left ventricular ejection fraction (LVEF), and, consequently, to reduce morbidity and mortality in patients with dilated cardiomyopathy. There is accumulating evidence that inflammatory cytokines have an important role in the pathogenesis of heart failure. **OBJECTIVE:** To establish whether the addition of carvedilol has an additive beneficial effect on cytokines in patients with dilated cardiomyopathy who are already receiving treatment with angiotensin-converting enzyme (ACE) inhibitors, digoxin and diuretics. **METHODS AND RESULTS:** In this single-centre, prospective, randomized study, 60 patients with dilated cardiomyopathy with an LVEF less than 40% and already receiving digoxin, ACE inhibitors and diuretics for six months as the standard therapy were randomly assigned to receive either carvedilol ($n=30$) or placebo ($n=30$). Patients received an initial dosage of 3.125 mg carvedilol or placebo twice daily for two weeks, which was then increased at two-week intervals (if tolerated), first to 6.25 mg, then to 12.5 mg, and, finally, to a target dosage of 25 mg twice daily. Clinical examinations, radionuclide studies, and determinations of plasma levels of tumour necrosis factor-alpha (TNF- α), interleukin (IL)-2 and IL-6 were performed at baseline and repeated four months after random assignment. Primary end points were New York Heart Association functional class, LV function and plasma cytokines levels. Eight patients died (seven in the placebo group, $P=0.05$). Patients treated with carvedilol had a significant improvement in functional class compared with the baseline values ($P=0.001$), with a decrease in the levels of cytokines (IL-6 [$P=0.001$] and TNF- α [$P=0.001$]). LVEF increased from $22.14\pm 7.85\%$ to $27.85\pm 11.80\%$ ($P=0.002$), but diastolic function did not change in the carvedilol group. **CONCLUSIONS:** In patients with dilated cardiomyopathy, the addition of carvedilol to treatment with digoxin, ACE inhibitors and diuretics is associated with a significant improvement in symptoms and in LV function, and suppression of inflammatory cytokines.

Wachtell, K., B. Horneham, et al. (2005). "Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study." Journal of the American College of Cardiology **45**(5): 705-11.

OBJECTIVES: We assessed the impact of antihypertensive treatment in hypertensive patients with electrocardiographic (ECG) left ventricular (LV) hypertrophy and a history of atrial fibrillation (AF). **BACKGROUND:** Optimal treatment of hypertensive patients with AF to reduce the risk of cardiovascular morbidity and mortality remains unclear. **METHODS:** As part of the Losartan Intervention For End point reduction in hypertension (LIFE) study, 342 hypertensive patients with AF and LV hypertrophy were assigned to losartan- or atenolol-based therapy for 1,471 patient-years of follow-up. **RESULTS:** The primary composite end point (cardiovascular mortality, stroke, and myocardial infarction) occurred in 36 patients in the losartan group versus 67 in the atenolol group (hazard ratio [HR] = 0.58, 95% confidence interval [CI] 0.39 to 0.88, $p = 0.009$). Cardiovascular deaths occurred in 20 versus 38 patients in the losartan and atenolol groups, respectively (HR = 0.58, 95% CI 0.33 to 0.99, $p = 0.048$). Stroke occurred in 18 versus

38 patients (HR = 0.55, 95% CI 0.31 to 0.97, $p = 0.039$), and myocardial infarction in 11 versus 8 patients ($p = \text{NS}$). Losartan-based treatment led to trends toward lower all-cause mortality (30 vs. 49, HR = 0.67, 95% CI 0.42 to 1.06, $p = 0.090$) and fewer pacemaker implantations (5 vs. 15, $p = 0.065$), whereas hospitalization for heart failure took place in 15 versus 26 patients and sudden cardiac death in 9 versus 17, respectively (both $p = \text{NS}$). The benefit of losartan was greater in patients with AF than those with sinus rhythm for the primary composite end point ($p = 0.019$) and cardiovascular mortality ($p = 0.039$). CONCLUSIONS: Losartan is more effective than atenolol-based therapy in reducing the risk of the primary composite end point of cardiovascular morbidity and mortality as well as stroke and cardiovascular death in hypertensive patients with ECG LV hypertrophy and AF.

Wachtell, K., M. Lehto, et al. (2005). "Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study.[see comment]." Journal of the American College of Cardiology **45**(5): 712-9.

OBJECTIVES: This study was designed to evaluate whether different antihypertensive treatment regimens with similar blood pressure reduction have different effects on new-onset atrial fibrillation (AF). BACKGROUND: It is unknown whether angiotensin II receptor blockade is better than beta-blockade in preventing new-onset AF. METHODS: In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study 9,193 hypertensive patients and patients with electrocardiogram-documented left ventricular hypertrophy were randomized to once-daily losartan- or atenolol-based antihypertensive therapy. Electrocardiograms were Minnesota coded centrally, and 8,851 patients without AF by electrocardiogram or history, who were thus at risk of developing AF, were followed for 4.8 +/- 1.0 years. RESULTS: New-onset AF occurred in 150 patients randomized to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1,000 person-years; relative risk 0.67, 95% confidence interval [CI] 0.55 to 0.83, $p < 0.001$) despite similar blood pressure reduction. Patients receiving losartan tended to stay in sinus rhythm longer (1,809 +/- 225 vs. 1,709 +/- 254 days from baseline, $p = 0.057$) than those receiving atenolol. Moreover, patients with new-onset AF had two-, three- and fivefold increased rates, respectively, of cardiovascular events, stroke, and hospitalization for heart failure. There were fewer composite end points ($n = 31$ vs. 51, hazard ratio = 0.60, 95% CI 0.38 to 0.94, $p = 0.03$) and strokes ($n = 19$ vs. 38, hazard ratio = 0.49, 95% CI 0.29 to 0.86, $p = 0.01$) in patients who developed new-onset AF in the losartan compared to the atenolol treatment arm of the study. Furthermore, Cox regression analysis showed that losartan (21% risk reduction) and new-onset AF both independently predicted stroke even when adjusting for traditional risk factors. CONCLUSIONS: Our novel finding is that new-onset AF and associated stroke were significantly reduced by losartan- compared to atenolol-based antihypertensive treatment with similar blood pressure reduction.