



The Bulletin of Medicaid Drug Utilization Review in Iowa

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* * *

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REVIEW OF BETA-BLOCKER USE POST-MYOCARDIAL INFARCTION

By: Amy Van Meter, PharmD Candidate, Drake University 2007

The benefits of β -blocker use following a myocardial infarction (MI) have been well established. Numerous studies have shown a significant reduction in mortality and reinfarction rate associated with the use of these medications.¹ They have also been found to provide additional reduction in cardiovascular mortality independent of the use of ACE inhibitors.² According to ACC/AHA Practice Guidelines, β -blocker therapy should be initiated within a few days of the event in all patients with ST-Elevation Myocardial Infarction (STEMI) without a contraindication and should be continued indefinitely.¹ It is also recommended that therapy be started in non-STEMI patients, as an improvement in survival rate has been shown.² Despite the overwhelming evidence of reduction of mortality, β -blocker therapy following myocardial infarction continues to be underused. Less than half of MI patients are prescribed β -blocker use chronically.¹ Relative contraindications, including heart failure (HF), chronic obstructive pulmonary disease (COPD), and diabetes mellitus, were once thought to preclude the use of β -blockers in some patients. However, research now suggests that the benefits of therapy outweigh the risks in these patients. Additional monitoring is required following initiation of therapy to ensure adverse events do not occur.¹

β -blockers have traditionally been considered contraindicated in HF because of their negative inotropic effects. However, conclusive evidence shows that long-term use of a β -blocker, such as propranolol or carvedilol, reduces mortality and morbidity in post-MI patients with left ventricular dysfunction, with or without signs of HF. In patients with systolic HF, practice guidelines advise the use of an ACE inhibitor first, then titrating a β -blocker such as carvedilol or metoprolol XL.²

COPD is not a contraindication to β -blocker use unless there is significant reactive airway disease. Research has shown a major reduction in mortality post-MI in these patients with β -blocker use.² However, β_2 -blockade may cause bronchoconstriction, so cardioselective β -blockers, such as atenolol or metoprolol, may be safer in COPD patients. Evidence suggests that cardioselective β -blockers do not produce significant short-term reduction in airway function or increases in the incidence of COPD exacerbations. Nevertheless, these medications should be administered with careful monitoring in COPD patients.³

Diabetes is a significant risk factor for early and late mortality following MI⁴. β -blocker use in diabetes patients has been questioned in the past, due to the risk of masking symptoms of hypoglycemia and potential interference with insulin release. However, it has been shown that β -blocker use in these patients significantly lowers the one-year mortality rate, compared to those not receiving β -blocker therapy, regardless of type and severity of diabetes mellitus. Therapy was not associated with an increase in diabetes complications.⁴

β -blocker therapy is not widely utilized in the elderly, African-Americans, and those with peripheral vascular disease. Less than 51% of elderly patients (>age 65) were started on a β -blocker acutely following an MI. However, those who did receive this therapy had a significantly lower rate of in-hospital mortality compared to those not receiving therapy. A 40% decrease in the relative risk of death was reported for African-American patients who received therapy at hospital discharge, despite the belief that these patients may not respond as well to these medications. In patients with peripheral vascular disease, β -blocker therapy is well tolerated. Clinical studies do not support the concept that β -blockers increase claudication.²

There is strong evidence to support the use of β -blockers post-MI in all patients that do not have a contraindication. The benefits of this therapy to patients with relative contraindications, including HF, diabetes mellitus, and COPD, have been shown to outweigh the risks. It is advised that therapy be initiated immediately following MI and continued indefinitely.

(Endnotes)

¹ Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Practice Guidelines: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: 2004 update. A report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2004; 110: 82-292.

² Gheorghiade M and Goldstein S. Beta-blockers in the post-myocardial infarction patient. *Circulation*. 2002; 106: 394-398.

³ Salpeter SR, Ormiston TM, Salpeter EE, et al. Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis. *Respiratory Medicine*. 2003; 97(10): 1094-1101.

⁴ Chen J, Marciniak TA, Radford MJ, et al. Beta-blocker therapy for secondary prevention of myocardial infarction in elderly diabetic patients. *J Am Coll Cardiol*. 1999; 34: 1388-1394.

Should ACE-I/ARB therapy be used in patients with diabetes who are normotensive?

By: Jana Voss, PharmD Candidate, Drake University 2007

The answer to this question is not definitive. It must be broken down into different subgroups of patients, depending on whether the patient has normoalbuminuria (albumin level <20 mcg/min) or microalbuminuria (albumin level 20 – 299 mcg/min) and whether the patient has type 1 diabetes or type 2 diabetes.

Diabetic nephropathy has been shown to occur in 20-40% of patients diagnosed with diabetes and is the leading cause of end-stage renal disease¹. In type 1 diabetes, microalbuminuria is the first stage of nephropathy and in type 2 diabetes, microalbuminuria is a marker for the development of nephropathy. Microalbuminuria also increases the risk of cardiovascular morbidity and mortality¹. The American Diabetes Association updated the Standards of Medical Care in Diabetes in January 2007. For type 1 diabetes, the recommendations state that patients with hypertension and albuminuria, to any degree, should be treated with ACE inhibitors because they are shown to delay the progression of nephropathy¹. For type 2 diabetes, the recommendations state that patients with 1) hypertension and microalbuminuria, and 2) hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl) ACE inhibitors and ARBs are shown to delay progression to macroalbuminuria¹. These recommendations are all for diabetic patients who have hypertension, but no current recommendations exist for the use of ACE inhibitors or ARBs for diabetic patients who are normotensive.

The trials that look at patients with type 1 diabetes are the EUCLID study, the ATLANTIS study, and the Cost Effectiveness of Treating Type 1 Diabetes Patients with ACE Inhibitors. In the EUCLID (EURODIAB Controlled trial of Lisinopril in Insulin Dependent diabetes) study, lisinopril was used in patients with both normoalbuminuria and microalbuminuria to see if early intervention in patients without hypertension would limit progression of renal disease, and if this effect was different based on various degrees of albuminuria². After the 2 year conclusion of the study, the urinary albumin excretion rate (AER), was 18.8% lower with treatment of lisinopril than with placebo, with an absolute difference of 2.2 mcg/min (these included both normoalbuminuria and albuminuria patients)². Breaking these results down between normoalbuminuria and albuminuria, there was little benefit in those patients who started the trial with an AER of 5 mcg/min or less; but those who started with microalbuminuria had more benefit from treatment with lisinopril than those with normoalbuminuria².

The ATLANTIS (ACE-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects) study measured the effect of AER in normotensive type 1 diabetic patients with microalbuminuria after 2 years of treatment with ramipril 1.25 mg, ramipril 5 mg, or placebo³. The results of this study showed that AER was significantly lower after 2 years of treatment with either ramipril dose versus placebo; there were more patients treated with ramipril that regressed to normoalbuminuria – 11% for 1.25 mg ramipril, 20% for 5 mg ramipril, and 4% for placebo³. These results show that the magnitude with 5 mg of ramipril was greater than 1.25 mg of ramipril, but there was no significant difference between the responses; meaning that both treatment groups had a significant impact on AER.

In the cost effectiveness trial, the study looked at the economic benefits of earlier treatment with captopril for patients diagnosed with type1 diabetes as being more cost effective than waiting to initiate treatment until the development of

microalbuminuria⁴. The relative risk reductions due to treatment with captopril are 50% between macroalbuminuria and ESRD, 65% between microalbuminuria and macroalbuminuria, and 24% between normoalbuminuria and microalbuminuria⁴. The results showed that the use of captopril immediately after the diagnosis of type 1 diabetes for the average adult had a cost of \$27,143 per QALY (quality adjusted life year) – this amount varies considerably when age and HbA1c are taken into account⁴. When age of onset of diabetes is 20 years, with an HbA1c of 9%, the cost effectiveness is \$13,814 per QALY; at age 25 years and HbA1c level of 7%, the cost effectiveness is \$39,530 per QALY⁴. This means that early treatment of type 1 diabetic patients with captopril may have moderate benefit at reasonable amount of money in order to prevent end-stage renal disease⁴. These results show that the higher the level of HbA1c, the greater the benefits of initiating ACE inhibitor treatment, which means that patients with better glycemic control get less benefit from early ACE inhibitor treatment⁴. The study concluded that patients at the age of 20 years of diagnosis of type 1 diabetes may be started on an ACE inhibitor to delay the onset of microalbuminuria, but treatment should be considered based on the patients' age and HbA1c level⁴.

The trials that look at patients with type 2 diabetes are The Use of Enalapril to Attenuate Decline in Renal Function in Normotensive, Normoalbuminuric Patients with Type 2 Diabetes Mellitus, and The Cost Effectiveness of Treating All Patients with Type 2 Diabetes with ACE Inhibitors. The first trial was conducted with normotensive type 2 diabetic patients without microalbuminuria using enalapril 10 mg/day versus placebo for 6 years to study the effects of AER⁵. This study showed that the group treated with enalapril had a significant slowing in the rise of AER – initial drop in AER from an average of 11.6 mcg/min to 9.7 mcg/min after 2 years, then rose to an average of 15.8 mcg/min after 6 years; the placebo group had an initial AER average of 10.8 mcg/min then rose to 26.5 mcg/min after 6 years⁵. In the studied patients, 19% of the placebo group developed microalbuminuria compared to 6.5% of the treatment group; this study showed statistically significant renal protection when being treated with enalapril⁵.

The Cost Effectiveness Trial looked at the economic impact of treating all patients with type 2 diabetes with the ACE inhibitor, lisinopril in order to avoid or delay end stage renal disease. This study used three different strategies to preserve renal function in newly diagnosed type 2 diabetics: treat all patients with ACE inhibitors, screen patients for microalbuminuria, and screen patients for gross proteinuria (albumin excretion >300 mcg/min)⁶. The groups that were screened first were treated with lisinopril if their result was positive. The results for each group for the treat all group had the lowest likelihood of end stage renal disease (1.2%) or death (14.6%), and the highest likelihood of normoalbuminuria (57%) after 10 years⁶. The screen for proteinuria group was associated with the highest cost (\$19,520) and the lowest benefit (15.39 life-years and 11.59 QALYs)⁶. The screen for microalbuminuria group was associated with the lowest cost (\$14,940), compared to the treat all group (\$15,240) which was associated with the highest life expectancy (15.63 and 15.59 life-years) and quality adjusted life years (11.82 and 11.78 QALYs)⁶. The marginal cost-effectiveness ratio (cost for additional QALY) of the treat all group compared to the screen for microalbuminuria was \$7500 per QALY gained⁶. The results suggest that using ACE inhibitors in all patients diagnosed with type 2 diabetes may slow the progression to end stage renal disease at a relatively low cost, which avoids the complex screening process and provides additional benefit for the patient.

To summarize the results for the studies for type 1 diabetes, they suggest that the patients that benefit the most from ACE inhibitor treatment are those who already have microalbuminuria; those with normoalbuminuria benefit a moderate amount. For type 2 diabetics, there is a benefit to treat all patients with ACE inhibitors regardless of whether or not they have microalbuminuria. More studies are needed to show additional benefit in treating all patients with diabetes with ACE inhibitors since end stage renal disease is increasing in prevalence in diabetic patients and is associated with a high mortality rate, reduced quality of life, and expensive treatment costs.

References:

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Iowa Medicaid Drug Utilization Review

Iowa Medicaid Enterprise
100 Army Post Road
Des Moines, Iowa 50315

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Jantoven®

Since the implementation of the Iowa Medicaid Preferred Drug List (PDL) both Coumadin® and warfarin have maintained a preferred status. Effective April 23, 2007, Coumadin® received a nonpreferred status, while warfarin will remain the preferred agent. Patients currently on Coumadin® will be grandfathered in.

Providers should be aware that the use of Jantoven®, which is a branded generic of warfarin and AB rated with Coumadin®, may increase with this PDL change. A safety concern is that Jantoven® is a look alike, sound alike medication that could be confused with the new antidiabetic medication, Januvia®. Patients on Jantoven® should be educated to tell all health care professionals they come into contact with that they are taking warfarin.