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## Beta-Blockers and Diabetes Mellitus

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Beta-blockers have been convincingly shown to reduce total and cardiovascular morbidity and mortality in hypertensive diabetic patients. After myocardial infarction these agents confer a twice as high protective effect when compared to non-diabetic patients. However, most paradoxically, beta-blocking agents are used less frequently in diabetes. A thorough analysis of the literature does not reveal adverse metabolic effects, a higher risk of hypoglycaemia or less nephroprotective effects of beta<sub>1</sub>-selective beta-blocking agents, which could justify the reticence in prescribing these antihypertensive agents to diabetic patients. The unnecessary less frequent prescription of beta<sub>1</sub>-selective beta-blockers in diabetes mellitus contributes to the higher cardiovascular mortality in these patients. *J Clin Basic Cardiol 2001; 4: 17–20.*

**Key words:** beta-blockers, hypertension, diabetes mellitus, nephropathy

Cardiovascular disease and stroke are major causes of mortality both in insulin-dependent (type 1) and non-insulin-dependent (type 2) diabetic patients. Effective blood pressure control reduces this severely increased mortality and represents one of the main aims of treatment in diabetic patients. Several studies from all over the world have shown that patients with type 2 diabetes mellitus exhibit a dramatic 2- to 3-fold excess in cardiovascular mortality compared to non-diabetic subjects. The major still unresolved problem in the treatment of diabetes is that about 70 % of these patients prematurely die from cardio- and cerebrovascular causes. In two long-term follow up trials we have described the causes of death in 85 IDDM patients with overt diabetic nephropathy [1] and in 216 consecutive NIDDM patients [2], and cardiac mortality was the leading cause of death in both IDDM and NIDDM patients. The distribution of different causes of death in both groups is shown in Table 1. Recently, risk of mortality associated with hypertension in diabetes was assessed in 3648 newly diagnosed type 2 diabetic patients [3], hypertension was present in 35 % of women and 46 % of men. When compared to normotensive diabetic patients the mortality risk associated with hypertension was doubled over a median follow-up period of 4.6 years. Cardiac events including sudden death accounted for 58 % and stroke for 13 % of all causes of death.

Most patients with Type 2 diabetes mellitus have or will develop essential hypertension. At the beginning of the last decade large intervention trials performed in older patients with essential hypertension included about 10 % type 2 diabetic patients [4–6]. These trials have impressively shown

that antihypertensive treatment with conventional antihypertensive agents including cardioselective β-blockers reduce morbidity and mortality both in patients with systolic and diastolic hypertension. These trials provided no hints that these beneficial effects would be different in diabetic patients.

After new antihypertensive agents had emerged, soon their superior effects in the antihypertensive treatment of diabetic patients were postulated. However, there have only been few studies aiming at valid clinical end-points and comparing different antihypertensive strategies including β-blockers. The CAPP study compared the ACE-inhibitor captopril with conventional antihypertensive treatment based on beta-blockers and diuretics [7]. The prospective evaluation of this study demonstrated that conventional therapy is significantly superior to captopril in preventing strokes. The *post-hoc* retrospective evaluation postulated a superior effect of captopril in the diabetes subgroup. However, this result was not confirmed by data from a prospective comparison of the conventional antihypertensive treatment with ACE-inhibitors, and was possibly due to the open study design and the way the data were analysed. The United Kingdom Prospective Diabetes Study (UKPDS) did not only demonstrate that tight blood pressure control reduces the risk of fatal and non-fatal macro- and microvascular diabetic complications [8]. It also prospectively investigated the effect of the ACE-inhibitor captopril and the cardioselective β-blocker atenolol within the tight-control group [9]. The effect of both drugs was not significantly different. However, with regard to diabetes related mortality there was a trend to a better effectivity of atenolol [9].

**Table 1.** Causes of death over a period of 9 years in 85 patients with type 1 diabetes mellitus and overt diabetic nephropathy [1], and over a study period of 15 years in 216 patients with Type 2 diabetes mellitus [2]

Causes of death during follow-up	Type 1 diabetic patients with diabetic nephropathy	Type 2 diabetic patients
Cardiovascular	52 %	46 %
Cerebrovascular	18 %	15 %
Septicaemia	9 %	11 %
Malignoma	0 %	8 %
Hypoglycaemia	6 %	0 %
Others	15 %	20 %

### Beta-Blocker Treatment is Often Withheld in Diabetic Patients

β-blocker treatment in coronary heart disease is less frequently used in diabetic patients [10, 11]. Only 40–50 % of diabetic patients receive β-blockers after myocardial infarction, a considerably lower number than non-diabetic patients [12]. Even in a large recently published intervention study in high risk diabetic patients aiming at reduction of cardiovascular mortality, only 28 % received β-blockers [13]. This occurs paradoxically despite the fact that all large intervention studies have convincingly shown that β-blockers in diabetic patients after AMI are more effective than in non-diabetic pa-

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tients [14–20] (Table 2). Withholding  $\beta$ -blockers in diabetic patients with coronary heart disease doubles their mortality risk [20–22]. In recent years a decline of heart disease mortality was noticed in the general population and attributed to the improvement of cardiovascular treatment including  $\beta$ -blockers. This decline in cardiovascular mortality did not occur in diabetic patients, and the less frequent prescription of  $\beta$ -blockers in these patients may have contributed to this phenomenon [23].

It has been speculated that the benefit of conventional antihypertensive treatment with  $\beta$ -blockers will be offset in diabetic patients, because some negative effects on metabolic parameters such as insulin sensitivity and blood glucose have been reported for these agents in some studies. Also, in review articles,  $\beta$ -blocking agents are often referred to as less nephroprotective when compared to other antihypertensive agents like ACE-inhibitors. In addition, there is still a fear of an increased risk of severe hypoglycaemia in diabetic patients treated with  $\beta$ -blockers. In the following we will analyse the literature looking for the evidence for adverse metabolic effects or less nephroprotective effects of  $\beta$ -blocking agents in diabetic patients, which could explain the reticence in prescribing these antihypertensive agents to diabetic patients.

**Do beta-blockers have adverse effects on blood glucose metabolism?**

Beta<sub>2</sub>-receptors appear to play an important role in the stimulated hepatic glucose production in humans [24]. Adverse effects of blockade of  $\beta_2$ -receptors on glucose metabolism have been recognised and repeatedly described [25, 26]. In contrast to unselective  $\beta$ -blockers, beta<sub>1</sub>-selective blockers appear to be without relevant influence on glucose metabolism [26–29]. However, in some studies adverse effects of  $\beta_1$ -selective  $\beta$ -blockers have been described as well [30]. A validity of this conclusion is brought into question by significant weight gain in the  $\beta$ -blocker-treated groups during the study period. In such circumstances, it is impossible to demonstrate any specific metabolic effect of an antihypertensive drug, as even small changes in body weight may markedly affect glucose tolerance and insulin sensitivity [31, 32]. A small weight gain was often described in patients receiving beta-blockers without appropriate dietary advice [33]. It is of note that the impressive benefits of  $\beta$ -blocker therapy in patients with [9] and without diabetes [33] were observed despite simultaneous gain in body weight. However, when care is taken to educate patients on how to maintain their body weight, the often observed increases in weight during beta-blocker therapy can be avoided. In a 4-weeks study on the

effects of a  $\beta_1$ -selective  $\beta$ -blocker as compared to an ACE-inhibitor on insulin sensitivity body weight increased only 0.4 kg during  $\beta$ -blocker treatment [34]. Both drugs had no influence on insulin sensitivity in this study. Hence, when body weight is maintained beta<sub>1</sub>-selective  $\beta$ -blockers do not have adverse effects on blood glucose and/or insulin sensitivity.

**Do beta-blockers mask symptoms of hypoglycaemia?**

Severe hypoglycaemia represents a major risk in diabetic patients treated with insulin or sulfonylureas – a dangerous iatrogenic complication that is frequently present in type 1 diabetic patients with advanced diabetic nephropathy [35]. Undisturbed awareness of hypoglycaemic symptoms enables patients to recognise early low plasma glucose concentrations and prevent any further decrease of blood glucose. Theoretically,  $\beta$ -blockers could diminish the adrenergic counterreaction to low blood glucose concentrations. The impact of  $\beta$ -blockade on hypoglycaemia has been addressed in several experimental investigations [36–42]. Some of these studies described a diminished occurrence of tremor and heart pounding under  $\beta$ -blockade [37–39], but in most of them sweating was increased [36, 37, 42], as did the total occurrence of symptoms [42]. Until present, no study reported a clinically relevant hypoglycaemia unawareness associated with  $\beta$ -blocker treatment. In addition, four recent epidemiological studies have independently confirmed previous findings that cardioselective  $\beta$ -blocking agents are not associated with an increased risk of severe hypoglycaemia. However, most interestingly, these studies have shown that treatment with ACE-inhibitors is associated with an increased risk of severe hypoglycaemia in NIDDM patients using insulin or sulfonylureas [43–46].

Hence,  $\beta$ -blockers do not mask hypoglycaemia but may change the pattern of symptoms by increasing the occurrence of sweating. No study has ever reported an increased risk of severe hypoglycaemia associated with  $\beta$ -blocker treatment in diabetic patients. Even in patients prone to hypoglycaemia [35, 47] and in individuals with low levels of glycosylated haemoglobin [36,48]  $\beta$ -blockers do not increase the hypoglycaemic risk.

**Do beta-blockers prolong hypoglycaemia?**

Glycogenolysis and gluconeogenesis in liver are stimulated through  $\beta_2$ -receptors [49]. Blockade of these receptors could prolong recovery time from hypoglycaemia. Under unselective  $\beta$ -blocker treatment, such prolongation of hypoglycaemia has been described [39, 50]. Under  $\beta_1$ -selective  $\beta$ -blocker treatment, however, the recovery from hypoglycaemia was not impaired in patients with insulin [37–39, 51] or oral hypoglycaemic agents [38].

**Are Beta-Blockers Less Nephroprotective Antihypertensive Agents?**

There is no doubt that blood pressure reduction delays the progression of nephropathy. The interesting question is, however, whether a blood pressure reduction with  $\beta$ -blockers offers similar benefit for the diabetic kidney when compared to ACE-inhibitors, or, in other words, whether ACE-inhibitors have specific kidney-protective properties to slow the progression of diabetic nephropathy, ie, over and above their antihypertensive effect. In metaanalyses including controlled and uncontrolled studies ACEIs have been reported to be more effective than  $\beta$ -blockers with regard to the reduction of albuminuria and proteinuria [52], but equally effective

**Table 2.** Overview of acute (up to 3 months) and long-term (more than 1 year) effects of beta-blocker treatment after acute myocardial infarction (AMI) on relative mortality in patients with and without diabetes

Study	$\beta$ -blockers and acute reduction of mortality after AMI (Relative Risk Reduction, %)	
	Non-diabetic patients	Diabetic patients
Göteborg Metoprolol Trial [14]	-36 %	-58 %
MIAMI Trial [15]	-12 %	-50 %
ISIS 1 [16]	-15 %	-22 %
Malmberg et al. [17]	-29 %	-69 %
<b><math>\beta</math>-blockers and long-term reduction of mortality after AMI (Relative Risk Reduction, %)</b>		
BHAT [18]	-25 %	-35 %
Gundersen et al. [19]	-34 %	-63 %
Kjekshus et al. [20]	-49 %	-56 %

**Table 3.** Overview of controlled, randomised, prospective studies of at least two years duration comparing beta-blockers with ACE-inhibitors in type 1 diabetic patients with diabetic nephropathy, reporting the decline of kidney function measured by the loss of glomerular filtration rate (GFR) per year (ml/min/year)

Study	Decline of GFR in the ACEI group (ml/min/year)	Decline of GFR in the $\beta$ -blocker group (ml/min/year)	Comments
Björck et al. 1992 [57]	Enalapril: -2	Metoprolol: -6	1. Significantly lower blood pressure values in the ACE-inhibitor group 2. No linear course of GFR in the ACE-inhibitor group 3. Exclusion of patients with rise in serum creatinine from the ACE-inhibitor group
Elving et al. 1994 [58]	Captopril: -5	Atenolol: -4	1. Similar blood pressure control between the groups 2. 95 % probability to exclude difference of more than 50 % between the groups
Sawicki et al. 1997 [59]	Ramipril: +1	Metoprolol: $\pm 0$	1. Similar blood pressure control between the groups 2. All patients treated with intensified insulin and intensified antihypertensive therapy

with regard to their influence on the decline of glomerular filtration rate (GFR) in diabetic nephropathy [53]. In this context it must be stressed that the change in urinary albumin excretion is often falsely taken as a measure for progression of renal disease [54]. ACE-inhibitors may decrease albuminuria in diabetic glomerulopathy by modulating the intrinsic glomerular basement membrane properties [55] without necessarily influencing the decline of glomerular filtration rate. Recently, the effect of beta-blockers on renal histology in diabetic nephropathy was compared with the effect of ACE-inhibitors and no treatment in a prospective randomised study [56]. In this study, basement membrane thickness, matrix star volume and the overall histological diabetic glomerulopathy index deteriorated in the group without antihypertensive treatment. However, the  $\beta_1$ -selective  $\beta$ -blocker metoprolol had equal beneficial nephroprotective effects on all histological parameters as compared to the ACE-inhibitor enalapril [56].

The main parameter for the measurement of progression of diabetic nephropathy is the change of GFR in long term studies. Until now only three prospective randomised controlled trials in diabetic nephropathy of at least two years duration compared ACE-inhibitors with  $\beta$ -blockers in diabetic nephropathy. Table 3 shows the results of these studies. It becomes clear that due to methodological problems the first study [57] does not prove a superior effect of ACE-inhibitors over  $\beta$ -blockers. The two remaining studies [58, 59] in which blood pressure was lowered to a similar extent in both groups,  $\beta$ -blockers had a comparable effect to ACE-inhibitors on the decline of GFR.

Thus, there is no evidence for a less pronounced nephroprotective effect of  $\beta$ -blockers on progression of diabetic nephropathy as measured by valid clinical parameters, ie the decline of GFR or renal histology.

### Conclusions

This review of the literature does not indicate that  $\beta_1$ -selective  $\beta$ -blocking agents have adverse effects on glucose metabolism, prolong hypoglycaemia or mask hypoglycaemic symptoms. In diabetic nephropathy  $\beta$ -blockers are as nephroprotective as ACE-inhibitors. Given the proven primary and secondary cardioprotective effect in antihypertensive treatment and after myocardial infarction, there is no evidence-based reason to withhold these agents in diabetic patients.

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