Prognosis and treatment of cardiovascular disease in diabetes mellitus

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Primary prevention of coronary heart disease in diabetes mellitus

It has been estimated that coronary artery disease is present in every second unselected diabetic patient. Several studies from all over the world show that patients with insulin-dependent diabetes (Type 1) exhibit a dramatic excess in mortality compared to non-diabetic subjects. While acute, metabolic complications dominate the causes of death in patients with short diabetes duration, long-term excess mortality is restricted almost exclusively to those 30 to 40% of Type 1 diabetic patients who develop diabetic nephropathy during the course of the disease. Borch-Johnsen found a high excess mortality only in those Type 1 patients who developed persistent proteinuria (i.e., clinical diabetic nephropathy), while patients with normal proteinuria had a mortality rate similar to that of the general population (Figure 1) [1]. Nephropathy is, however, not the direct cause for increased mortality rates in these patients. Although the risk of progression to renal failure is high in Type 1 diabetes with macroalbuminuria, in Europe only few Type 1 patients will die a renal death, because renal replacement therapy is, in general, available to all patients with end stage renal failure. Much rather, cardiovascular events represent the main cause of death in patients with diabetic nephropathy. Due to yet unknown factors the incidence of coronary heart disease starts to rise soon after development of overt proteinuria (Figure 2) [2]. This is very different from the situation in non-insulin-dependent diabetes (Type 2); in these patients coronary heart disease and elevated albumin excretion in urine often precede the development of diabetes. Interestingly, the distributions of the causes of death is very similar in Type 1 diabetic patients with nephropathy and in Type 2 diabetes. In two long-term follow-up trials we have described the causes of death in 85 Type 1 patients with overt diabetic nephropathy [3], and in 216 consecutive Type 2 diabetic patients [4]. Cardiac mortality was the leading cause of death in both Type 1 and Type 2 diabetes. The distribution of the different causes of death in both groups is shown in Table 1. Recently, a large prospective finish follow-up study in Type 1 patients described in patients with diabetic nephropathy a 126- and 58-fold relative increase in mortality due to cardiovascular diseases for women and for men respectively, while mortality rates were only modestly elevated in patients with normal renal function [5].

The cumulative incidence of cardiovascular disease by the age of 40 years was 43% in Type 1 diabetic patients with nephropathy and 7% in those with...
out. When compared to patients with normal renal function the presence of nephropathy increased the risk of coronary heart disease and stroke 10-fold.

It has been recognized for decades that the risk of coronary events is increased in Type 2 diabetic patients [6]. Most studies have found that the higher the level of glycaemia, the greater was the risk for cardiovascular disease. In a study summarizing results in different population cohorts this risk ratio for men rose from 0.34 to 6.07 from the lowest to the highest glycaemia percentile [7]. The question remains, however, whether this association is causal [8]. Interestingly, the positive association between cardiovascular risk and glycaemia is not only present in Type 2 diabetes but is also operative in non-diabetic subjects. In the 20-year evaluation of three European cohort studies the cardiovascular mortality risk was increased in the upper 2.5 % of the non-diabetic range of glycaemia [9]. This indicated that even non-diabetic “hyperglycaemia” may represent a marker of an elevated cardiovascular risk.

Most surprisingly, until now, there are only two prospective randomised intervention studies investigating the effect of blood glucose lowering on cardiovascular complications [10, 11]. The first study – the University Group in Diabetes Project (UGDP) – failed to show any positive effect of the anti-hyperglycaemic interventions [10]. Recently, the results of the second study – the United Kingdom Prospective Diabetes Study (UKPDS) – have been published [11]. In this study intensive blood glucose lowering policy aiming at fixing plasma glucose levels below 6 mmol/L did not result in a significant reduction in mortality (relative risk: 0.94, p = 0.44). The risk of myocardial infarction was non-significantly reduced (relative risk: 0.84, p = 0.052).

In summary, the excess risk to develop a coronary heart disease in Type 1 diabetes is almost exclusively due to those patients who develop diabetic nephropathy. As this renal complication can be prevented by good glycaemic control [12], primary prevention of cardiovascular disease should be possible in Type 1 diabetic patients. On the contrary, in elderly Type 2 diabetic patients coronary heart disease develops for unknown reasons before diabetes becomes manifest. Therefore, in these patients effective primary prevention through antidiabetic treatment does not appear possible.

Association between elevated urinary albumin excretion and coronary heart disease

Although excretion of small but abnormally elevated quantities of albumin in the urine may be an early feature of diabetic glomerular disease it is also found in non-diabetic subjects. In an investigation of healthy, normotensive, untreated factory workers with a mean age of 50 years the prevalence of microalbuminuria (albumin excretion > 20 µg min⁻¹) was 2.2 % [13]. In the Islington Diabetes Survey, including random patient selection from general practice, microalbuminuria was found in 9.4 % non-diabetic subjects and in 23 % of newly diagnosed diabetic patients [14]. In this study there was a significant correlation between the albumin excretion rate and both systolic and diastolic blood pressure values. Increased prevalence rates of microalbuminuria in non-diabetic patients with essential hypertension have been described repeatedly. A survey of patients from general practice found a prevalence of microalbuminuria of 10 % in hypertensive patients compared to 4 % in normotensives and 23 % of diabetic patients [15]. Among a hospitalised group of nearly 400 hypertensive non-diabetic patients the prevalence of microalbuminuria was 27 % [16]. In this study, albumin excretion rates were correlated with 24-hour blood pressure readings, and they were increased in patients with hypertensive retinopathy, cardiac ventricular hypertrophy and reduced glomerular filtration rate. In obese subjects elevated urinary albumin excretion is associated with hypertension, body mass index, and body fat distribution [17].

Elevated albumin excretion rates predict cardiovascular mortality risk also in non-diabetic populations. In the Framingham study a cohort aged 50–62 years at entry was followed up for 16 years [18]; proteinuria above 200 mg/l was associated with a threefold increase in mortality. In a 4 year follow-up study of non-diabetic subjects albuminuria independently of other cardiovascular risk markers strongly predicted death, coronary heart disease and peripheral vascular disease [14]. Different mechanisms could be involved in an elevated urinary albumin excretion. Such mechanisms include renal haemodynamic changes, secondary to the direct transmission of raised systemic pressure to the glomerular arteriolar network [19]. Also, direct effects of endothelial damage and/or perselectivity changes of the glomerular filtering barrier and/or altered tubular albumin reabsorption and structural damage to the glomerula and arterioles are likely to play a role in the amount of albumin found in the urine [20].

Several reports have shown that microalbuminuria is already present before or very early in the course of Type 2 diabetes. Non-diabetic subjects with impaired glucose tolerance or a parental history of diabetes already have an increased prevalence of microalbuminuria [21]. Elevated albumin excretion is associated with insulin resistance [22, 23] and hence, microalbuminuria may preclude the development of Type 2 diabetes [24]. This comes as no surprise, since in non-diabetic subjects microalbuminuria is associated with high blood pressure, high insulin concentrations, low high-density lipoprotein cholesterol concentrations and high triglyceride concentration, a cluster of risk markers typical for prediabetic subjects. In the Kuopio study, including more than 1000 participants (aged 65–74 years) as many as 30 % of normoglycaemic subjects had microalbuminuria [24]. During the 3.5 years follow-up 69 subjects newly developed diabetes and 70 % of those already had an elevated albumin excretion at the entry into the study.

The nature of albuminuria in Type 2 diabetic patients is heterogeneous. This is different from patients with Type 1 diabetes in whom microalbuminuria hallmark the presence of glomerular lesions typical for diabetic nephropathy in most cases. While microalbuminuria predicts overt proteinuria in 80 % of Type 1 diabetic patients, only 20 % of microalbuminuric Type 2 diabetic patients will progress to overt nephropathy [25]. In biopsy studies of unselected microalbuminuric Type 2 diabetic patients only about 30 % have glomerular changes typical for diabetic nephropathy, while 30 % have non-specific histological kidney lesions and the rest has a normal.

<table>
<thead>
<tr>
<th>Causes of death follow-up</th>
<th>IDDM patients with diabetic nephropathy</th>
<th>NIDDM patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>52 %</td>
<td>46 %</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>18 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Septicemia</td>
<td>9 %</td>
<td>11 %</td>
</tr>
<tr>
<td>Malignoma</td>
<td>0 %</td>
<td>8 %</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>6 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Other</td>
<td>15 %</td>
<td>20 %</td>
</tr>
</tbody>
</table>
renal structure [26]. Hence, despite the presence of microalbuminuria, a large proportion of Type 2 diabetic patients does not have any renal disease. In addition, in those with renal histopathology microalbuminuria is associated with elevated markers of endothelial dysfunction, such as von Willebrand factor [27]. Suggesting that some of the renal structure abnormalities in microalbuminuric Type 2 diabetic patients are related to endothelial dysfunction rather than being a sign of typical diabetic renal disease.

Since albuminuria is associated with several risk markers and predictors of cardiovascular disease, it should therefore predict itself in mortality and cardiovascular morbidity in univariate analyses. However, several studies in Type 2 diabetic patients have unanimously suggested that microalbuminuria independently of other known cardiovascular risk markers predicts all-cause mortality mainly by increasing the risk for cardiovascular events. In a 3.4-years follow-up study microalbuminuric Type 2 diabetic patients showed a highly significant excess mortality, chiefly from cardiovascular causes, being 28 % compared to those without microalbuminuria of 4 % only; in this study 50 % of deaths were caused by cardiovascular events [28]. The higher the albumin excretion rate the higher the risk of death: In a three year follow-up study Type 2 diabetic patients with normoalbuminuria had a 5 % risk of death compared to 10 % in those with microalbuminuria and 26 % in macroalbuminuric patients [29]. Similar results were obtained in a 8-year follow-up trial where mortality was 32 % in initially normoalbuminuric Type 2 diabetic patients and 56 % in those with elevated albuminuria [30]. Deaths due to cardiovascular disease occurred in 7 % of patients with normoalbuminuria and in 26 % of patients with micro- or macroalbuminuria. Only two patients died due to renal causes. Microalbuminuria nearly doubles the risk of dying of a cardiovascular cause, with a mortality risk due to a large vessel disease of about 70 % [31]. Interestingly, Stehouwer found that microalbuminuria in Type 2 diabetic patients was associated with an increased risk of new cardiovascular events only in the presence of endothelial dysfunction as indicated by elevated von Willebrand factor [32]. In conclusion, elevated urinary albumin excretion represents a powerful predictor of cardiovascular mortality in Type 2 diabetic patients, apparently unaffected by microalbuminuria. The mechanisms of the pathophysiological link between albuminuria and cardiovascular disease remain to be elucidated.

**Silent myocardial ischaemia**

Numerous studies have suggested that silent myocardial ischaemia is 2–5 times more common in diabetic patients than in others [33]. Hence, using symptoms of angina in patients with diabetes has a poor sensitivity for the diagnosis of coronary heart disease. In prospective studies 32 to 42 % of diabetic patients lack angina on infarction, compared with only 6–15 % of non-diabetic patients [33]. The lack of anginal pain accompanying critical ischaemia represents a clinical phenomenon, which is not fully understood. Langer et al. showed that silent myocardial ischaemia was more prevalent in diabetic patients with autonomic neuropathic dysfunction, 38 vs. 5 % [34]. An autopsy study has shown that in diabetic patients with painless infarction, the autonomic nerve fibers of the heart display typical lesions of autonomic neuropathy that may affect sensory impulse transmission [35]. In Type 1 diabetic patients the risk for silent myocardial ischaemia may already be more prevalent at the stage of incipient diabetic nephropathy. Myocardial ischaemia (as detected by stress echocardiography) without any symptoms of angina was found in 25 % Type 1 diabetic patients with microalbuminuria but in only in 6 % of normoalbuminuric Type 1 diabetic patients [36]. In about 30–70 % of asymptomatic Type 2 diabetic patients 24-hour ambulatory electrocardiography shows ST-segment depression characteristic of myocardial ischaemia without symptoms of angina [37, 38]. However, in diabetic patients non-invasive tests may not be sufficiently reliable for the diagnosis of coronary heart disease. Valensi et al. found a high prevalence of left ventricular hypertrophy among those with a false positive ECG stress test, thallium 201 myocardial scintigraphy and ambulatory 48 hour ECG recordings [39]. At least one of these tests was positive in 30 % of asymptomatic Type 1 (n = 17) and Type 2 (n = 75) diabetic patients. But, only 10 % had significant coronary stenosis on coronary angiography. In a study in 136 asymptomatic Type 1 and Type 2 diabetic patients the results of a non-invasive test battery for signs of coronary heart disease were compared with the diagnosis made by coronary angiography [40]. 40 % patients (30 %) had at least one pathological non-invasive test result, but only 12 (9 %) had significant coronary narrowing on coronary angiography. False positive results occurred in 56 % on thallium scintigraphy, but only in 7 % on exercise electrocardiography.

**Prognosis after myocardial infarction**

It is well established that the presence of diabetes increases the mortality rate after acute myocardial infarction (AMI) 1.5 to 3-fold [41, 42]. Mortality from AMI before hospital admission is about 20–30 % and does not differ between diabetic and non-diabetic patients [43]. Of those diabetic patients who reach the hospital 60–80 % are still alive one year later, compared to 80–90 % of non-diabetic patients [41, 44, 45]. In a recently published part of the prospective MONICA Study 28 % of diabetic patients died during the first month and 44 % during the first year after AMI [43, 46]. The relative increase in mortality risk seems to be higher in diabetic women than in men: In the Rancho Bernardo study the relative risk of death attributed to ischaemic heart disease was increased 2.5 fold for men and 3.4 fold for women compared to non-diabetic control subjects after adjustment for confounding factors [47].

Increased AMI mortality in diabetic patients may have several explanations. First, diabetic patients experience more severe coronary atherosclerosis and more often multivessel disease [42], which doubles their risk for a subsequent re-infraction [48]. Also, some [49] but not all [46] studies reported that diabetic patients have larger and more frequent anterior infarcts, which are associated with a poorer prognosis than inferior myocardial infarctions. Second, congestive heart failure and cardiogenic shock are more common and more severe in diabetic patients than would be predicted from infarct size [42]. Hence, development of severe congestive heart failure after AMI occurs more often in diabetic patients and thereby contributes to the higher case fatality [50]. Third, diabetic patients are more likely than non-diabetics to have fatal ventricular arrhythmias after AMI [46, 51] and AV block III [45]. Fourth, beta-blocker treatment in coronary heart disease is less frequently used in diabetic patients [45, 52, 53]. This occurs despite the fact that all large intervention studies have convincingly shown that betablocker treatment in diabetic patients after AMI is even more effective than in non-diabetic patients [54–60] (Table 2). Hence, withholding betablockers in diabetic patients with coronary heart disease doubles their mortality risk [45, 61]. Fifth, Type 2 diabetic patients are often treated with oral antidiabetic sulphonylurea agents, which
may increase the risk of dying during critical myocardial ischaemia [62]. Sixth, proliferation of smooth muscle cells is involved in the healing of the ulcerated coronary plaque [63, 64] and fosters plaque stabilization through synthesis of macromolecules that strengthen the fibrous cap [65]. Endothelial dysfunction and insulin resistance at the cellular smooth muscle level, which is a frequent feature of Type 2 diabetes [66], may impair the coronary healing processes and plaque stabilization.

**Ventricular arrhythmias**

Diabetic patients have an increased risk of dying from sudden death, presumably due to fatal ventricular arrhythmia [46, 51]. We have looked at the causes of death in 85 Type 1 diabetic patients with hypertension and diabetic nephropathy during a mean follow-up period of 9 years [3]. Total mortality was nearly 40%, over 60% of which was due to cardio- or cerebrovascular causes, there were no renal deaths (Table 1). Sudden and unexpected deaths, which accounted for 30% of mortality, occurred only in patients with a maximum QT interval duration in the ECG of > 450 ms [31]. On life table analysis, the group of patients with the longest maximal QTc durations, which was arbitrary defined as > 470 ms, had a significantly increased mortality risk (Figure 3).

QT prolongation predisposes to ventricular arrhythmias in patients with and without diabetes presumably by increasing the risk of ventricular re-entry tachycardias and ventricular fibrillation. Most patients with diabetic nephropathy exhibit some degree of autonomic neuropathy [67] with a reduced vagal activity which can lead to alteration of the QT interval increasing the risk of sudden death [68]. However, QT prolongation may also be directly caused by myocardial cell defects [69] which lead to a reduced electrical stability predisposing to ventricular arrhythmia. Such cellular defects may be caused by (silent) ischaemia and/or myocardial fibrosis in patients with coronary artery disease. In addition, volume overload and/or hypertension can reduce the threshold for arrhythmia through an increased ventricular wall stress. Also, renal failure, diuretic treatment and treatment with angiotensin converting enzyme inhibitors (ACEI) can induce electrolyte imbalances leading to reduced myocardial stability. Furthermore, patients with diabetic nephropathy have an increased risk of severe hypoglycaemia. Prolongation of the QT interval occurs during very low blood glucose concentrations and may increase the risk of arrhythmic death in predisposed patients [70]. In patients with newly diagnosed Type 2 diabetes the cumulative incidence of sudden death after 4.5 years is about 10% of all fatal events [71] and prolonged QT interval and QT dispersion are important predictors of cardiac death in these patients [4, 72]. Patients with impaired glucose tolerance and Type 2 diabetic patients with long QT intervals have been found to have an increased risk of sudden death [73] caused by torsade-de-points and ventricular fibrillation [74]. We have followed 216 consecutive Type 2 diabetic patients for a period of 15 years to delineate the impact of the QT interval duration on total and cardiac mortality [4]. During the follow-up period 158 patients (73%) died. In the final model, independent predictors of total mortality were the length of QT dispersion corrected for heart rate (QTc dispersion), age, male sex, systolic blood pressure, total cholesterol, HDL cholesterol, presence of diabetic retinopathy and micro- or macroproteinuria. Of the 108 patients with a QTc dispersion above the median of 0.668 s [31] 101 died during the follow-up as compared to 57 of those with a lower/equal length of QTc dispersion (Figure 4). There was a continuous increase in the mortality risk with prolongation of the QTc dispersion.

In non-diabetic patients a prolonged QTc interval and/or QTc dispersion were described as markers for excess mortal-

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**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

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-diabetic patients</th>
<th>Diabetic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers and acute reduction of mortality after AMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Göteborg Metoprolol Trial [54]</td>
<td>36 %</td>
<td>58 %</td>
</tr>
<tr>
<td>MIAMI Trial [55]</td>
<td>12 %</td>
<td>50 %</td>
</tr>
<tr>
<td>ISIS 1 [56]</td>
<td>15 %</td>
<td>22 %</td>
</tr>
<tr>
<td>Malmberg et al. [57]</td>
<td>29 %</td>
<td>69 %</td>
</tr>
<tr>
<td><strong>Beta-blockers and long-term reduction of mortality after AMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BHAT [58]</td>
<td>25 %</td>
<td>35 %</td>
</tr>
<tr>
<td>Gundersen et al. [59]</td>
<td>34 %</td>
<td>63 %</td>
</tr>
<tr>
<td>Kjekshus et al. [60]</td>
<td>49 %</td>
<td>56 %</td>
</tr>
</tbody>
</table>

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**Figure 3.** Kaplan-Meier curves of survival over the study period of 5–13 years of 85 patients with insulin dependent diabetes mellitus (IDDM) and overt diabetic nephropathy and maximal QTc intervals > 470 ms [31] and ≤ 470 ms [31] at baseline p = 0.0004 (log rank test) [3]

**Figure 4.** Kaplan-Meier curves of survival over the study period of 15–16 years of 216 patients with non insulin dependent diabetes mellitus and a QTc dispersion at baseline below and above the median of 0.668 s [31]; p = 0.0001 (log rank test) [4]
ity in chronic heart failure, hypertrophic cardiomyopathy, coronary heart disease, peripheral artery disease and after myocardial infarction [4]. Such co-morbidity is particularly frequent in Type 2 diabetic patients and is expected to contribute to the increased mortality risk. Disturbed glucose metabolism of the heart may directly contribute to an impaired myocardial electrical stability. In a recent report of the Zutphen Elderly Study QTc duration was associated with circulat ing levels of insulin and glucose intolerance [75]. Hence, reduced myocardial glucose uptake may be involved in impaired cardiac repolarisation as indicated by a prolongation of the QT interval. As shown in Type 1 and Type 2 diabetes, a QT dispersion prolongation may also result from cardiac adrenergic dysinnervation with altered balance of sympathetic and parasympathetic cardiac nerve activity leading to a reduced electrical stability [68, 76, 77]. Regional myocardial hypoxia and dysinnervations may lead to focal QT prolongation increasing the QT dispersion [78]. Such prolonged QTc dispersion indicates the presence of electrical myocardial in-homogeneity, which can be expected to create a potential difference during repolarisation and generate an excitatory current of a sufficient magnitude to reexcite the fibers with the shorter action potential duration and consecutively lead to re-entry arrhythmias [79]. Likewise, blockade of adenosine tri-phosphate-dependent potassium channels by sulphonylurea drugs is known to lengthen repolarisation and produce early afterdepolarisations which may cause triggered activity in the hypoxic myocardium and may even lead to fatal ventricular tachyarrhythmias [80–82].

Revascularization treatment

Percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft surgery (CABG) have both been proven effective in coronary revascularization. However, in nephropathic diabetic patients the risks of postoperative renal failure, stroke and low output syndrome associated with CABG, and the risk of radiocontrast-induced acute renal failure and coronary restenosis after PTCA represent major limitations to both methods of coronary revascularization [83, 84]. In a prospective follow-up study in 268 diabetic patients, one month after CABG mortality was 6.7 % in diabetic patients versus 3.0 % in non diabetic patients [85]. Mortality after the first month during the 2 year follow-up was 7.8 % vs. 3.6 % respectively. In a randomised intervention study performed in diabetic patients after myocardial infarction and thrombolytic therapy, invasive strategy including PTCA and CABG resulted in a 3-fold increase in mortality (14.8 % versus 4.2 %, p < 0.001) as compared to a conservative strategy [86]. Regrettfully, to date there are no other randomized prospective trials after myocardial infarction comparing invasive revascularization strategy with conservative therapy in diabetic patients.

PTCA has been reported to have a lower rate of acute mortality when compared to CABG. However, the increased risk of restenosis after PTCA in diabetic patients limits the value of PTCA. The frequent restenosis after PTCA in diabetic patients has been attributed to an exaggerated intimal hyperplasia caused by endothelial dysfunction, which is a frequent feature of diabetic nephropathy even during the early course of the disease [87, 88]. Hence, theoretically, PTCA would result in poorer long-term outcomes in these patients when compared to CABG. One retrospective 6-year cohort study [89] reported increased total mortality after PTCA when compared to CABG (37 % vs. 30 %); but these results were not confirmed by another retrospective investigation, which showed a non-significantly lower 5-year mortality of 11 % after CABG as compared to 14 % after PTCA [90]. Clearly, non-randomized retrospective studies are only of limited value for comparing the effects of these two revascularization strategies. Also, one randomized prospective study had not sufficient power to find differences between PTCA and CABG in the diabetic subgroup of the study patients [91]. The only prospective randomized follow-up study comparing PTCA and CABG in a sufficiently large group of diabetic patients reported a five-year survival of 81 % for CABG and 66 % for PTCA [92]. In this study in-hospital mortality in diabetic patients was higher for CABG (1.2 %) versus PTCA (0.6 %) [92]. The worse long-term outcome after PTCA was caused by a higher long-term cardiac mortality being 21 % in the PTCA group and 6 % in the CABG group. These results were attributed to a beneficial effect of CABG with internal mammary artery grafting in diabetic patients, because in the CABG group cardiac mortality was 3 % in patients who received an internal mammary artery grafting compared to 18 % in those with a saphenous vein graft [92].

In summary, both PTCA and CABG result in poorer morbidity and mortality results in diabetic patients compared to those without diabetes; patients with diabetic nephropathy are at a particular risk of an adverse outcome. Any superiority of both invasive revascularization treatment strategies over conservative drug therapy has not as yet been demonstrated. If revascularization is needed because of severe angina, preliminary studies advocate that CABG with internal mammary artery grafting is probably superior to PTCA.

Glycaemic control, oral anti-diabetic agents and insulin

Several studies suggest an increasing gradient of cardiovascular risk with decreasing glucose tolerance, increasing glycaemia and glycosylated haemoglobin [94, 95]. In contrast, a review of several epidemiological studies found only a small and inconsistent effect of mild hyperglycaemia on cardiovascular disease risk, especially after adjustment for other known cardiovascular risk markers [8, 96].

In IDDM patients' maintenance of near normoglycaemic control has been shown to prevent the development of microangiopathic complications, i.e., diabetic nephropathy, retinopathy and neuropathy [12]. This may also apply to younger Type 2 diabetic patients [11, 97]. Since the reduction of life expectancy in Type 1 diabetic patients is restricted to those patients who develop diabetic nephropathy [1] (Figure 1), it can be assumed that prevention of diabetic nephropathy by near-normoglycaemia will near-normalise the incidence of cardiovascular complications in Type 1 diabetic patients. In fact, such a trend has already been described in large intervention trials in Type 1 and Type 2 diabetic patients [11, 12].

On the other hand, beneficial effects of hypoglycaemic treatment on microvascular complications have not been demonstrated in a representative group of Type 2 diabetic patients, who are, in Europe, on average older than 65 years. In fact, there is no evidence that blood glucose lowering will have a beneficial effect on morbidity or mortality from macrovascular disease in an average patient with Type 2 diabetes [8]. In the UGDP in patients who were treated with oral antidiabetic agents (the sulphonylurea tolbutamide or the biguanide phenformin) cardiovascular mortality was significantly increased when compared to insulin or placebo [10]. In contrast to these findings and without any further evidence as to safety or benefit in diabetic patients with coronary artery disease, sulphonylurea derivatives have represented the main treatment strategy in Type 2 diabetic patients for decades. Recently, a patho-
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physiological explanation has been proposed for the increase of cardiovascular mortality in Type 2 diabetic patients treated with these agents. Sulphonylurea derivatives exert their primary effect by closing so-called adenosine-5'-triphosphate-depend

cent potassium (K$_{ATP}$) channels in the beta cell of the pancreas, which promotes an influx of calcium and subsequent stimulation of insulin release. However, the same channels play an important role in the protection of the myocardial tissue against ischaemia and their closure leads to amplified ischaemic damage [62]. Blocking the K$_{ATP}$-channels by sulphonylureas during acute myocardial ischaemia abolishes the protective effect of preconditioning, increases calcium influx and thereby the ischaemic and reperfusion injury, decreases coronary blood flow, deteriorates myocardial function, and may increase the risk of re-entry arrhythmias. Besides previously conducted animal experiments, recent findings in humans have provided the pathophysiological plausibility for the hypothesis, as sulphonylureas appear to aggravate the hypoxaemic damage to the myocardium in the case of coronary occlusion or stenosis [98–101]. In fact, this hypothesis fits well the observation that the alleged cardiotoxic effect of sulphonylureas appears to exert itself in an increased lethality of myocardial infarctions or cardiac death rates, rather than by increasing the incidence of cardiovascular morbidity [10].

As a result of the UGDP Study the biguanide agent phenformin has been removed from the U.S. market for "imminent hazard". Surprisingly, without any further data on endpoint effectiveness and safety of biguanides, we now have to face a "renaissance" of the biguanide and sulphonylurea therapy in Type 2 diabetic patients. Recently, doubts about the safety of this combination therapy with regard to mortality have been published [102]. In an evaluation of 1136 patient-years in two U.S. open and controlled studies all seven deaths occurred in the patients originally assigned to metformin treatment, of whom six patients received a combination of metformin and sulfonylurea, while no deaths occurred in the control groups, p < 0.01. As a consequence of this report, FDA representatives admitted that "...more information is needed about the safety of metformin..." and "...a large study is now underway in the United States, which is designed to compare total mortality and from cardiovascular causes..." for patients with Type 2 diabetes receiving sulfonylurea therapy in Type 2 diabetic patients. Recently, the results of the UKPDS study have been published [103]. In this trial, treatment with metformin reduced mortality in overweight diabetic patients, but the combination of sulfonylurea and metformin increased mortality. Regrettfully, the UKPDS study was not designed to rule out the effect of treatment with sulfonylureas in Type 2 diabetic patients with cardiovascular complications [104]. Patients with clinically relevant coronary artery disease were excluded during the recruitment process: the entire cohort included but 3 % of patients with a history of angina pectoris (excluding those with present angina), 2 % with a history of myocardial infarction, and patients with heart failure were also excluded [105].

These results were confirmed by the data from the UKPDS [103]. In this trial, treatment with metformin reduced mortality in overweight diabetic patients, but the combination of sulfonylurea and metformin increased mortality. Regrettfully, the UKPDS study was not designed to rule out the effect of treatment with sulfonylureas in Type 2 diabetic patients with cardiovascular complications [104]. Patients with clinically relevant coronary artery disease were excluded during the recruitment process: the entire cohort included but 3 % of patients with a history of angina pectoris (excluding those with present angina), 2 % with a history of myocardial infarction, and patients with heart failure were also excluded [105]. The evaluation of the effect of sulfonylureas on the risk of mortality in diabetes is also impossible because the main aim of the study was to investigate the effect of glycaemic control on diabetes complications, and therefore in patients with unsatisfactory control sulfonylurea treatment was changed. After 6 years about 50 % of the patients originally assigned to sulfonylurea therapy were switched to other medication [106]. If 50 % of a study population does not remain in the original treatment group, an intention-to-treat-analysis is not reliable.

Recently, the results of the Diabetes mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study (DIGAMI) have been presented in a series of original publications [107–109]. In this prospective randomised trial a total of 620 diabetic patients with acute myocardial infarction were randomized either to an acute treatment with glucose-insulin infusion followed by multidose subcutaneous insulin for more than 3 months, or to a control group, which was treated in most cases with diet and oral hypoglycaemic medication. After a follow-up of 12 months 18.6 % of insulin treated patients and 26.1 % of the control patients have died resulting in a reduction of relative mortality by 29 %. During the first year of treatment the number of fatal reinfarctions was significantly reduced from 45 % in the control group to 28 % in the insulin group. After a mean follow-up of 3.4 years there were 33 % of deaths in the insulin group compared to 44 % in the control group. This substantial difference in mortality can hardly be due to long-term differences in the degree of metabolic control: HbA1C-levels at 3 months were 7.1 % compared to 7.5 % and at 1 year 7.3 % compared to 7.6 %. This insignificant difference is most unlikely to result in a clinically apparent change of the prognosis of the diabetic patients following myocardial infarction [110].

Pending further evidence, the oral antidiabetic agents sulfonylureas and biguanides should not be used in diabetic patients with cardiovascular heart disease because of suspected cardiac toxicity. To date, insulin is the only hypoglycaemic agent, which has been proven as both safe and effective in Type 2 diabetic patients with coronary heart disease.

Antihypertensive treatment

Recently, the risk of mortality associated with hypertension in diabetes was assessed in 3648 newly diagnosed Type 2 diabetic patients [71], 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. In proteinuric diabetic patients the prevalence of hypertension rises to 80–90 %, and there is no doubt that it adds considerably to the already increased morbidity and mortality risk in Type 2 diabetic patients and is the major determinant of the prognosis in nephropathic Type 1 diabetic patients.

Conventional antihypertensive treatment

Most patients with Type 2 diabetes have or will develop essential hypertension. At the beginning of this decade, large intervention trials performed in older patients with essential hypertension included about 10 % Type 2 diabetic patients [112–115]. These trials have impressively shown that antihypertensive treatment with low-dose thiazide diuretic agents often combined with potassium sparing-diuretics and cardio-selective beta-blockers reduce morbidity and mortality both in patients with systolic and/or diastolic hypertension. These trials provided no hints that these beneficial effects would not be operative in diabetic patients.

Nevertheless, it has been speculated that such benefit of conventional antihypertensive treatment with low-dose thiazide diuretics and beta-blockers will be offset in diabetic patients, because some negative effects on metabolic parameters such as serum lipids, insulin sensitivity and blood glucose have been reported for these agents in some studies. To resolve this issue, a subgroup analysis of a large prospective randomized
controlled study has focused on the effect of conventional antihypertensive treatment with a low-dose diuretic and a cardioselective betablocker in Type 2 diabetes [115]. 583 Type 2 diabetic patients and 4149 non-diabetic patients with systolic hypertension had been randomized to receive low dose chlorthalidone alone with atenolol. Outcome rates included cardiac events, stroke and mortality. Not only was the conventional antihypertensive treatment effective in reducing the study events in diabetic patients, but the benefit was twice as great as in non-diabetic patients, resulting in an absolute risk reduction of 101 per 1000 study participants with diabetes and 51 per 1000 study participants without diabetes. Moreover, this study provided information that conventional antihypertensive treatment does not have clinically important influence on blood glucose levels and serum lipids [116]. Because they are proven to reduce cardio- and cerebrovascular morbidity and mortality low dose diuretic agents and cardioselective betablockers should be preferentially used in the pharmacological treatment of hypertensive patients both with and without diabetes.

Recently, we have investigated the effects of intensified antihypertensive treatment strategies in a high risk group of Type 2 diabetic patients, all of whom were hypertensive and micro- or macroproteinuric and nearly all of them insulin treated [117]. All patients were on antihypertensive medication and half of them participated, in addition, in an ambulatory hypertension treatment and teaching programme (intervention group) aimed at improving patients' compliance to pharmacological and non-pharmacological therapy. Antihypertensive therapy in the intervention group was based upon conventional treatment with diuretics and betablockers, while the kind of treatment in the control group was left to the decision of the patient's family practitioner. Participation in this programme resulted in a persistent improvement in the quality of blood pressure control. After a mean follow-up of four years the combined incidence of cardio- and cerebrovascular events was reduced from 26 % in the control group to 14 % in the intervention group (Figure 5).

Angiotensin converting enzyme inhibitors (ACEIs) Despite the indisputable benefits of diuretic/betablocker-based antihypertensive treatment the use of these agents has decreased steadily over the past decade especially in hypertensive diabetic patients. This development was associated with exceptionally heavy promotion of more expensive antihypertensive medication [118, 119]; it took place despite the complete lack of evidence that the use of these newer agents, like ACE-inhibitors and calcium channel blockers, would decrease cerebral- and cardiovascular morbidity and mortality outcomes in hypertensive patients with and without diabetes. In fact, the only published randomized placebo-controlled study which has – up to 1998 – investigated the effect of ACE-inhibitors on clinical endpoints merely showed a non-significant reduction of cardiovascular events and no influence on cerebrovascular events as compared to placebo [120]. This study investigated a subgroup of 2652 high risk hypertensive patients with left ventricular dysfunction as a part of the SOLVD study. In this study enalapril significantly reduced chronic heart failure morbidity, while the number of strokes was exactly the same as in patients receiving placebo. In addition, in a preliminary report of the Captopril Prevention Project (CAPPP), which compared the ACE-inhibitor captopril with conventional antihypertensive treatment using diuretics and/or betablockers in 11,000 hypertensive patients the incidence of cardiovascular events was comparable between the groups, but stroke occurred significantly more often in the captopril group [121].

Despite their use for nearly 20 years, there is still an astonishing lack of any valid data on ACE-inhibitor treatment in patients with diabetes and essential hypertension as compared to conventional antihypertensive treatment based on thiazide diuretics. This is particularly troubling as one small study described an increase in mortality in Type 2 diabetic patients treated with the ACE-inhibitor captopril as compared to conventional antihypertensive treatment [122]. In the UKPDS intensive antihypertensive treatment using the betablocker atenolol or ACE-inhibitor captopril resulted in a reduced risk of micro- and macrovascular complications and death. The study did not have the power to rule out clinically important differences between these two antihypertensive agents. However, a non-significant trend in favour of the betablocker was noticed. Therefore, further studies are needed before ACE-inhibitors can be regarded as equivalently effective to the conventional antihypertensive therapy. Thus, convincing evidence for safety and effectiveness of newer antihypertensive agents with regard to the cardio- and cerebrovascular morbidity and mortality is needed, before these agents can be used as the first line antihypertensive therapy in hypertensive diabetic patients with and without cardiovascular disease. More than ten major studies have shown beyond any doubt that ACEI treatment improves survival in patients with clinical heart failure with and without myocardial infarction. These studies did not indicate that the results would be different in diabetic patients. However, in contrast to non-diabetic patients, diabetic patients with severe heart failure face an increased risk of renal function impairment during treatment with ACEIs [123]. This may occur because of a rather high risk of clinically silent renal artery stenosis in Type 2 diabetic patients [124, 125]. Also, treatment with ACE-inhibitors may lead to an increased risk of severe hypoglycaemia in Type 2 diabetic patients using insulin or sulfonylureas [126–129]. Furthermore, these studies also confirmed that cardioselective beta-blocking agents do not increase the risk of severe hypoglycaemia.

In summary, ACEIs should be given diabetic patients with heart failure. However, special caution should apply with regard to the risk of renal failure and severe hypoglycaemia when using ACE-inhibitors in Type 2 diabetic patients.

Calcium channel blockers

Until recently no mortality endpoint data were available for the treatment with calcium channel blockers in diabetic patients. Nevertheless, these agents have been widely recom-
recommended for antihypertensive treatment in diabetic patients despite the fact that they have repeatedly been shown to increase mortality in patients with coronary heart disease in randomized trials [130–132]. Recently, evidence accumulated from three randomized prospective studies that treatment of diabetic patients with calcium channel blockers results in an increase of cardiovascular morbidity and mortality when compared to other antihypertensive agents. In the MIDAS study the calcium channel blocker isradipin was compared with the diuretic hydrochlorothiazide [133]: isradipine lead to an increased risk of cardio- and cerebrovascular events, especially in patients with raised glycosylated haemoglobin levels [134]. In the ABCD study in hypertensive Type 2 diabetic patients treatment with nisoldipin resulted in a five-fold increased risk for fatal and non-fatal myocardial infarction when compared to enalapril (25/235 vs. 5/235) [135]. In the FACET study amloidipine doubled the risk of cardio- and cerebrovascular events as compared to fosinopril (27/191 vs. 14/189) [136]. In a metaanalysis of intervention studies comparing different antihypertensive agents in patients with coronary heart disease, treatment with betablockers resulted in a 24 % reduction of cardiac morbidity and mortality risk, while calcium channel blockers increased this risk by 63 % [137].

In summary, calcium channel blockers should not be used as first line agents in hypertensive patients with diabetes. And, most importantly, the studies comparing calcium channel blockers with other treatment provided the evidence that despite similar blood pressure reduction, different antihypertensive agents may lead to different results regarding the reduction of cardio- and cerebrovascular events. Hence, recommendations of antihypertensive agents as first-line drugs must not be based on surrogate markers but rather on valid clinical end-points.

Antihypertensive treatment in Type 1 diabetes

The two major aims of antihypertensive treatment in hypertensive Type 1 diabetic patients with diabetic nephropathy are the prevention of dialysis and the reduction of the increased risk of cardiovascular mortality. In nephropathic insulin dependent diabetic patients, treatment with ACE-inhibitors was associated in two studies with a slower loss of kidney function as compared to a placebo [138] or to a betablocker [139]. However, in both studies blood pressure values were significantly lower with the ACE-inhibitor treatments when compared to the respective control groups [140, 141]. It is of note that in other randomized intervention studies, in which blood pressure control was kept comparable between the study groups, there was no difference in the decline on GFR when comparing ACE-inhibitors to placebo [142] or a betablocker [143]. In metaanalyses including controlled and uncontrolled studies ACE-inhibitors have been found to be more effective than other antihypertensive agents with regard to the reduction of albuminuria and proteinuria [144], but equally effective with regard to their influence on the decline of glomerular filtration rate (GFR) in diabetic nephropathy [145]. These results have been attributed to the effect of ACE-inhibitors on the charge of the glomerular basement membrane which influences glomerular albumin leakage; this action is, however, without impact on the progression of glomerular histopathological changes and, hence, on the decline of GFR [20]. In nephropathic Type 1 diabetic patients, the ACE-inhibitor lisinopril was reported to reduce albuminuria, but to result in an accelerated loss of GFR when compared to the calcium channel blocker nisoldipine [146]. Thus, there is still no evidence for a specific, i.e., blood pressure independent, beneficial effect of any antihypertensive agent including ACE-inhibitors on the progression of diabetic nephropathy as measured by the progression to renal replacement therapy or by the decline of GFR.

Recently, we have shown that it is possible to achieve a stabilisation of glomerular filtration rate in nephropathic Type 1 diabetic patients over a period of two years, if in addition to good glycaemic control blood pressure is permanently normalised [147]. The antihypertensive drug therapy was based on a random allocation to an open treatment either with an ACEI, a calcium channel blocker or a cardioselective beta-blocker. As assessed by inulin clearance, we have found no differences between the investigated drugs regarding the percentage of patients with stable renal function and the course of GFR.

In a 5 years prospective intervention study we have demonstrated that an intensification of antihypertensive treatment with first line therapy based upon cardioselective betablockers and diuretics in Type 1 diabetic patients with diabetic nephropathy is associated not only with a reduction of the progression of nephropathy and retinopathy but also with a major improvement in life expectancy (Figure 6) [148]. In this study mortality was 56 per 1000 patient years (py) in the control group as compared to 9 per 1000 py in the intervention group. The leading causes of death were cardiovascular. Also, in studies with historical control groups, antihypertensive treatment based on betablockers and diuretics resulted in a major decrease of mortality in patients with diabetic nephropathy [149, 150]. However, this was not the case in all studies on antihypertensive treatment in patients with diabetic nephropathy: A 3-year study in patients with diabetic nephropathy comparing the effects of captopril with placebo showed that mortality was not significantly decreased, despite blood pressure reduction and slowing of progression of renal failure (mortality: placebo: 23/1000 py; captopril 13/1000 py; n.s.) [138]. Furthermore, in a randomized prospective 3-year study in patients with different causes of renal failure including diabetic nephropathy treatment the ACE-inhibitor benazepril decreased blood pressure, slowed progression of nephropathy, but increased total mortality (benazepril: 11/1000 py; placebo: 1.5/1000 py; p = 0.04) [151].

To date a reduction of mortality in diabetic nephropathy has been adequately documented only for conventional antihypertensive treatment based on diuretics and cardioselective betablockers. It is of note that a lack of any benefit [138] or even a negative effect [122, 151] on total and cardiovascular
mortality during antihypertensive treatment with ACE-inhibitors in patients with diabetic nephropathy can not be excluded. A pooled analysis of an increased cardiovascular mortality risk with ACE-inhibitors may be particularly present when treatment is aimed at very low blood pressure values, as is often the case in patients with nephropathy. Also, in patients with renal failure, ACE-inhibitors confer a considerable risk of hyperkalemia. This risk may be low in patients with normal renal function but becomes increasingly common (5–50 %) in those with renal insufficiency [152, 153]. Life threatening hyperkalemia during treatment with ACEI and particularly in diabetic patients with renal failure has been reported [154–156]. In addition, in diabetic patients and in patients with renal failure, ACE-inhibitors reduce erythropoetin secretion and consecutively circulating haemoglobin concentrations [157–159]. This may have particularly detrimental effects in diabetic patients with kidney failure and coronary heart disease, because any worsening of anaemia may further compromise the oxygen delivery to the ischaemic myocardium.

Available evidence strongly supports antihypertensive treatment in diabetic nephropathy. As a consequence of available mortality endpoint results of intervention studies, the treatment should be based on cardioselective beta-blockers and diuretics as first line agents. Until newer antihypertensive compounds, such as ACE-inhibitors, have been shown in prospective controlled studies to have at least equally beneficial effects on mortality in diabetic nephropathy and/or to be superior with regard to slowing the progression of renal failure, these classes of drugs should only be used as second line or additive treatment.

Nicotine replacement therapy

Several large prospective cohort studies have shown that diabetic patients who smoke have an approximately two-fold increased mortality risk with the main cause of death being cardiovascular [160–164]. Smoking increases blood pressure in patients with diabetic nephropathy [165] and may contribute to the progression of diabetic nephropathy [166]. Patients with end stage renal disease, who smoke, run a particularly high mortality risk [167].

Programmes to help diabetic patients to stop smoking have so far been unsuccessful [168]. Even an extensive behaviour therapy anti-smoking intervention programme’s outcome was as poor as a single unstructured anti-smoking advice given by a physician [169]: Only 11 % agreed to participate in a “stop smoking programme” and 6 months after the intervention non-smoking was confirmed only in 5 % of the behaviour therapy group and 16 % of the physicians advice group. However, since nicotine replacement therapy has been shown to double the success of smoking cessation in non diabetic patients [170], such intervention is worth trying, even though studies showing satisfactory smoking cessation rates in diabetic patients are still lacking.

Cholesterol lowering therapy

Total serum cholesterol has been shown to be a predictor of cardiovascular mortality and morbidity in middle-aged Type 2 diabetic patients. Until recently, evidence about the effects of cholesterol lowering on morbidity and mortality in diabetic patients was lacking. A subgroup analysis of the Helsinki Heart Study [171] using gemfibrozil as lipid-lowering drug described a 5-year incidence of major cardiovascular events in Type 2 diabetic patients of 3.4 % in the intervention and 10.5 % in the placebo group, however, this difference was not statistically significant (p = 0.19). In a double blind five year study in patients with myocardial infarction, which included 3573 non-diabetic and 582 diabetic patients, with plasma total cholesterol levels below 240 mg/dl, treatment with pravastatin, an inhibitor of 3-hydroxy-3-hydroxymethyl co-enzyme A reductase (statin), resulted in a 23 % (p = 0.001) reduction in major coronary events in non-diabetic patients and in a 25 % reduction (p = 0.05) in diabetic patients [172]. Recently, a subgroup analysis of the 4S-Study focused on Type 2 diabetic patients with previous myocardial infarction or angina pectoris has been published [173]. In this study simvastatin significantly reduced major coronary events by 55 % (p = 0.002); a trend towards a reduction in total mortality by 43 % (p = 0.087) was also reported.

Based on the results from intervention studies, it seems reasonable to treat diabetic patients under 65 years of age, who have signs of coronary artery disease, with a statin, when total serum cholesterol concentrations exceed 200 mg/dl, or low density lipoprotein concentrations exceed 130 mg/dl.

Aspirin

In an overview of published intervention studies in nearly 47,000 patients (including 10 % diabetic patients), aspirin given in doses between 100 and 400 mg/day has been shown to reduce the risk of myocardial infarction and stroke in patients with high risk of such events [174]. In this analysis diabetic patients on aspirin had 17 % fewer vascular events whereas relative risk reduction was 22 % in non-diabetic patients. Overall, aspirin treatment resulted in an about 30 % reduction in the risk of myocardial infarction. In the Veterans Administration study including 231 diabetic men with limb gangrene or recent amputation, aspirin and dipyridamole did not reduce the incidence of cardiovascular events [175]. In the early treatment of retinopathy study diabetic patients treated with 650 mg aspirin per day had a 13 % lower risk of cardiovascular death when compared to placebo [176]. Hence, available evidence suggests support for aspirin in diabetic patients with coronary heart disease [177].

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