Invited Comment

Cardiovascular complications in the diabetic patient with renal disease: an update in 2003

Ralf Dikow and Eberhard Ritz

Department of Internal Medicine, Ruperto Carola University Heidelberg, Germany

Keywords: beta-blockers; coronary arterial bypass grafting; coronary heart disease; diabetes; diabetic nephropathy; myocardial infarction; glycaemic control; PTCA

Epidemiology

Coronary heart disease [defined as myocardial infarction, angina, history of bypass surgery, percutaneous transluminal coronary angiography (PTCA) or pathology on coronary angiography] is frequently found in patients starting dialysis. Stack and Bloembergen [1] examined a national random sample of 4025 patients entering renal replacement programmes in the USA. The prevalence of coronary heart disease was 38% and it was significantly more common in diabetic patients (46.4%) than in non-diabetic patients (32.2%). This difference was highly significant on multivariate analysis.

Much of the cardiac pathology is acquired prior to dialysis. This is documented by the high frequency of coronary lesions, i.e. 30–40%, which is found when diabetic patients undergo coronaryography before they are put on the waiting list for transplantation. The conclusion that much of the cardiac pathology is acquired even before the pre-terminal phase of renal disease is supported by the Canadian multicentre observation cohort where the prevalence of cardiovascular disease was 47%, independent of the severity of renal dysfunction. Progression, i.e. either new events or worsening of existing pathology, was seen in 20% of the patients over 23 months [2]. The odds ratio for a new event in diabetic compared with non-diabetic patients was 5.3 and this difference was highly significant.

A table is presented to compare the cardiac findings in diabetic and non-diabetic patients on dialysis. The table shows a higher prevalence of concentric left ventricular hypertrophy, ischaemic heart disease, and cardiac failure in diabetic patients. The adjusted relative risks for ischaemic heart disease, overall mortality, and cardiovascular mortality are significantly higher in diabetic patients compared to non-diabetic patients.

Table 1. Cardiac findings in diabetic patients on dialysis (after Foley et al. [6])

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Diabetic patients (n=116)</th>
<th>Non-diabetic patients (n=317)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentric left</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Ventricular hypertrophy</td>
<td>50%</td>
<td>38%</td>
<td>0.003</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>32%</td>
<td>18%</td>
<td>0.00001</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>48%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>Adjusted relative risk (diabetic/non-diabetic)</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>3.2</td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>2.3</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>2.6</td>
<td></td>
<td>0.0001</td>
</tr>
</tbody>
</table>

An increased risk of cardiac complications was noted in patients, including diabetic patients, who had only mild to moderate renal failure and had developed myocardial infarction. Acute and post-discharge mortality was significantly elevated [3,4] and the renal patients had more frequent atrial and ventricular arrhythmia, heart block, asystole, pulmonary congestion and cardiogenic shock [5]. This adverse outcome was only in part explained by the less frequent use of thrombolysis, active intervention and cardioprotective medication.

Once the diabetic patient is on dialysis the prevalence of cardiac morbidity and the risk to develop ischaemic heart disease de novo is high, as documented by several studies. The most impressive information is provided by an inception cohort of 433 Canadian patients, 116 of whom were diabetics [5,6]. At baseline (Table 1), diabetics had more left ventricular hypertrophy (LVH), more ischaemic heart disease and more congestive heart failure. No difference between diabetic and non-diabetic patients was found with respect to the de novo appearance or progression of LVH and congestive heart failure. In contrast, the relative risks of de novo ischaemic heart disease as well as overall and cardiovascular mortality were significantly higher in the diabetic patients. This observation is consistent.
with the idea that atherogenesis is accelerated in diabetes over and above what is found in non-diabetic renal patients [7]. This hypothesis is supported by an observation from Osaka, Japan, which documented a linear relation between creatinine clearance and intima-media thickness of the carotid and femoral arteries. Diabetes was an independent factor by multivariate analysis [8].

The frequency of cardiac arrest and sudden death in the dialysis unit is much higher for diabetic compared with non-diabetic patients [9]. This complication was more frequent during sessions on Monday (long interval between dialysis sessions and dietary transgressions on weekends); further predictors were dialysis against low potassium dialysate and age, but also diabetes.

It deserves comment that even renal transplantation does not completely abrogate the risk. The National Institute of Health reported that in diabetic patients the incidence of acute coronary syndromes was less after renal transplantation (hazard ratio 0.38). The rate of new events was 0.79% per patient year compared with 1.67 prior to transplantation, but this is still substantially higher than what is found in the matched background population [10].

**Manifestations of heart disease**

It is the unfortunate experience of most nephrologists that diffuse and complex three vessel disease with very distal involvement is the rule rather than the exception in the diabetic patient on dialysis, rendering intervention difficult. This has been documented by Varghese et al. [11], who noted this constellation in 27% of diabetic compared with 12% of non-diabetic patients on dialysis. This pattern resembles what is also characteristically found in peripheral artery disease of the diabetic patient. With the new technique of electron beam CT, Raggi et al. [12] found more intense coronary calcification in the diabetic patients on dialysis. It is currently still uncertain whether this finding represents calcification of plaques or calcification of the media. In the diabetic patient calcification of the media is common.

**Acute coronary syndrome**

If the diabetic patient with renal failure develops an acute coronary syndrome, what are his chances compared with the non-diabetic patient? Herzog et al. [13] reported that the long-term mortality was abysmal in non-diabetic and even more so in diabetic patients who had survived an acute myocardial infarction, i.e. 59.3 ± 0.3% in non-diabetic vs 62.3 ± 0.5% in diabetic patients at 1 year and 81.4 ± 0.2% vs 86.1 ± 0.4% at 3 years, respectively. Recently, it has also been documented that modern interventions including thrombolysis, PTCA or coronary arterial bypass grafting were not widely used in this high-risk population [3–5,13]. Although the impressive DIGAMI study of Malmberg et al. [14] documented the benefit of intensified insulin and glucose treatment, this therapeutic strategy is not widely adopted in dialysed diabetic patients.

Why is the cardiac prognosis so poor in the diabetic patient on renal replacement therapy? It would be naive to believe that it is completely explained by the severity of coronary atherosclerosis. Undoubtedly, further cardiac abnormalities aggravate the risk, e.g. congestive heart failure [15] and LVH, both of which are much more prevalent in diabetic patients [5,6]; disturbed sympathetic innervation [16]; microvessel disease with arteriolar thickening and deficient capillarization [17]; diminished coronary reserve, secondary to diminished availability of nitric oxide and deranged cardiomyocyte metabolism.

In the isolated Langendorf heart preparation, insulin-mediated glucose uptake was significantly less in uraemic animals compared with controls [18]. Such insulin resistance resembles what is seen in diabetic animals. In uraemic animals, this was accompanied by diminished expression of the Glut-4-transporter in the plasma membrane of cardiomyocytes. This finding is important because under ischaemic conditions the cardiomyocyte must use glucose to produce energy-rich nucleotides, particularly ATP. This necessitates the delivery of sufficient glucose, as to generate a given amount of ATP by glycolysis requires more glucose than generation by mitochondrial oxidation. In uraemia, however, glucose delivery is impaired, as it is in diabetes. The alternative fuel for the heart, i.e. free fatty acids, further depletes oxygen, decreases inotropy and increases arrhythmogenicity. This constellation is one further argument in favour of the DIGAMI protocol, i.e. co-administration of glucose and insulin to achieve strict normoglycaemia, which dramatically reduces mortality in acute myocardial infarction [14] and even in critically ill patients with acute renal failure [19].

**Predictors of cardiac risk**

A number of factors have been shown to predict cardiac death of which we shall mention a few. Shemin et al. [20] showed that residual renal function is very important. The adjusted odds ratio for patients with residual renal function was 0.44 compared with patients without residual renal function. One can discuss whether it is less hypervolaemia or some metabolic consequence of renal function conservation, or the role of residual renal function as a surrogate for duration of disease which is responsible for this finding, but it is sensible that every effort is made not to endanger residual renal function, for instance by administration of radio contrast media.

Plasma norepinephrine concentrations predict cardiac death [21]. This finding is not surprising, as
neurohumoral activation is generally a predictor of cardiac death in patients with coronary heart disease and cardiac failure. The uptake of labelled norepinephrine analogues is diminished in the posterior wall of the left ventricle even of patients with diabetes of recent onset [16] and, possibly as a compensatory mechanism, uptake is increased at the basis. Regional inhomogeneity of sympathetic innervation and denervation suprasensitivity in patches of denervated cardiac tissue are of course highly undesirable in patients at high cardiac risk such as the diabetic patients. It is against this background that Zuanetti et al. [22] had strongly advocated more liberal use of beta-blockers in patients with diabetes, based upon an analysis of all secondary prevention trials where diabetic patients derived greater benefit, i.e. per cent reduction of cardiac death, compared with non-diabetic patients. Many nephrologists hesitate to use beta-blockers in diabetic patients on dialysis, because they are concerned about their adverse metabolic effect. This caution is not justified. In a prospective trial Koch et al. [23] had found that only 3% of dialysed type 2 diabetic patients who died from cardiac causes were on beta-blockers, but no <13% of those who survived. Interestingly, only 18% of the patients with a history of myocardial infarction were on beta-blockers. This observation illustrates: (i) that many diabetic dialysis patients are denied the administration of a beta-blocker, even when the drug is clearly indicated and (ii) that the findings are strongly suggestive of a beneficial effect of beta-blockers, even though this was not a controlled interventional study. A benefit has meanwhile also been suggested by the observational DOPPS study [24]: mortality was 17% less in dialysed patients on beta-blockers than in those who did not receive beta-blockers. In an interventional trial a benefit was also seen in dialysis patients with cardiac failure [25].

Another important predictor of cardiac death is glycaemic control. This finding is surprising in view of the common belief that in the uraemic diabetic patient strict glycaemic control is dangerous because of the risk of hypoglycaemia. A study from Taiwan showed, however, that adequate glycaemic control in the 6 months before starting haemodialysis, was associated with better survival: 5-year-mortality was 75.8% in patients with poor and 21.8% in patients with good glycaemic control [26].

Glycaemic control is not only important before initiation of dialysis treatment, but also when patients are on haemodialysis. This has been shown by Zager et al. [27], who found a 68% higher mortality in diabetic patients on dialysis, when haemoglobin Alc was >7.5%. A recent study from Japan confirms that 5 year actuarial survival is 31.7% in diabetic patients on dialysis whose HbA1c is <7.5% compared with 12.1% in patients with HbA1c >7.5% [28]. Glycaemic control may be particularly important in the patient with myocardial ischaemia [14] as discussed above. Although HbA1c values are to some extent confounded by carbamylation, they are still apparently very useful markers of glycaemic control even in dialysis patients.

Further predictors of high cardiac risk are lack of heart rate variability, as an index of autonomic poly-neuropathy, and possibly QT dispersion, although there are doubts about the validity of this index. Finally, in dialysed patients troponin T [29] is a predictor of cardiac risk. The concern about potential artefacts of troponin T measurements in patients with impaired renal function have recently been dispelled [30].

Prevention

Nephrologists are confronted with two challenges: prevention and intervention.

There is unfortunately little evidence-based information on prevention. What is recommended is mainly based on clinical common sense and uncontrolled observations (also see Table 2).

By far the most important aspect is that intervention should start early before the patient reaches the stage of advanced renal failure. In all European countries, renal physicians have to deal with the fact that most diabetic patients are referred late [31]. Emergency haemodialysis is necessary in ∼30% of diabetic patients referred to renal units. It is an important task of nephrologists to educate our colleagues and to motivate them to incorporate the nephrologist into the team caring for the diabetic patient with renal disease. The nephrologist should become the primary care physician once the GFR of a diabetic patient is ∼30 ml/min.

ACE inhibitors or angiotensin receptor blockers have cardioprotective effects and reduce cardiovascular events, particularly stroke [32], independent of blood pressure control. In our opinion they should be given to all diabetic patients.

There is uncertainty whether the beneficial effect of ACE inhibitors is reduced when combined with aspirin [33]. Studies are necessary to clarify this important point.

The importance of achieving very low target blood pressure values has been amply documented in diabetic patients, both in the HOT study [34] and in the UK-PDS study [35]. In the UK-PDS study, a minute difference of blood pressures of no more than 10 mmHg systolic and 5 mmHg diastolic reduced the incidence of strokes by 44% and death from diabetes-related

<table>
<thead>
<tr>
<th>Table 2. Suggested preventive manoeuvres</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start early</strong></td>
</tr>
<tr>
<td>ACE inhibitors or angiotensin receptor blockers</td>
</tr>
<tr>
<td>Low target blood pressure values</td>
</tr>
<tr>
<td>Aspirin?</td>
</tr>
<tr>
<td>Control of hypervolaemia (low salt intake, diuretics)</td>
</tr>
<tr>
<td>Statins (LDL-cholesterol &lt;100 mg/dl)</td>
</tr>
<tr>
<td>Treatment of anaemia</td>
</tr>
</tbody>
</table>

Cardiovascular complications: an update in 2003
causes by 32%. There is a caveat, however. It is known that pulse pressure is highly predictive of cardiovascular death so that the enthusiasm to lower systolic pressure should be tempered if diastolic pressure values are very low. Further evaluation of the data of the IDNT trial also showed that low standing blood pressure, i.e. orthostatic hypotension, had adverse prognostic implications.

A further frequently neglected aspect is control of hypervolaemia. During the Irbesartan trial in type 2 diabetic patients with renal failure the most significant cause of inadequate blood pressure control was inadequate use of diuretics and failure to reduce dietary sodium intake.

We have already emphasized the importance of glycaemic control [27,28] while the patient is on dialysis. The same is obviously true for the predialytic phase [26].

As recommended by the Cholesterol Education Program [36] and documented by the results of the Heart Protection Study [37], administration of statins is sensible and justified in all diabetic patients irrespective of renal function. Whether statins are also useful in terminal renal failure is currently under investigation. In Germany approximately 1300 type 2 diabetic patients on haemodialysis have been recruited for the 4D study, in which patients are treated with either atorvastatin or placebo [38].

Anaemia appears earlier, i.e. at higher levels of GFR in diabetic rather than non-diabetic patients [39]. Against this background it is relevant that even a relatively minor decrease of haemoglobin has been shown to aggravate LVH. LVH is an important cardiovascular risk factor also in the diabetic patient [7].

**Intervention**

The prospect of the diabetic patient in renal failure who develops an acute coronary syndrome is serious. Dacey et al. [40] reported on a prospective regional cohort study in Northern New England. Between 1992 and 1997, 15 575 patients were observed. 283 had diabetes. Overall, 298 deaths were observed. In patients without renal failure the annual death rate was 3.8%. In patients with renal failure, but no diabetes, it was 7.7%, but if diabetes was combined with renal failure, the rate was a devastating 23%.

Very important new information has recently accumulated concerning intervention in the diabetic patient with nephropathy and symptomatic heart disease. In the past, a small study had suggested that interventional management yields superior results compared with conservative management with beta-blockers [41]. There is no doubt that intervention is indicated, but it has remained controversial whether PTCA or coronary bypass surgery is the preferred mode. Although prospective data are not available, compelling information has recently been obtained in large patient samples [42–44]. In patients with coronary revascularization procedures the most powerful predictors of cardiac death were old age and diabetes, the relative risk being 1.37 for diabetics [42]. As summarized in Table 3, PTCA was associated with a lower in-hospital death rate, but also with lower 2-year survival. In diabetic patients the relative risk after bypass surgery was 0.78 compared with PTCA. In a more recent analysis [43], compared with PTCA alone, the risk of all-cause death was 10% lower for PTCA + stent and 21% lower for bypass surgery in uraemic non-diabetic patients. In contrast, in uraemic diabetic patients there was no significant difference in all-cause mortality for stent [risk ratio (RR) 0.99], but a 19% reduction for bypass surgery (RR 0.81) was found compared with PTCA. Improved survival after bypass surgery compared with PTCA in uraemic diabetic patients is reminiscent of the findings in the BARI study [45], which also showed that the advantage of bypass surgery is greater for diabetic compared with non-diabetic patients. In a most recent analysis [44] the risk of cardiac death in chronic dialysis patients was least with coronary artery bypass using internal mammary grafts. Compared with PTCA, the RR was 0.68. It was less favourable for bypass without internal mammary graft, i.e. using autologous veins and the results of PTCA plus stent were comparable. For diabetic patients the survival advantage for coronary artery bypass with internal mammary grafts was proportionally even more impressive. Data for innovative procedures such as brachytherapy and sirolimus coated stents are not yet available.

The group in Osaka, Japan, reported on a series of 223 consecutive patients with diabetes and nephropathy [46]. The presence of diabetic retinopathy was an independent predictor of overall mortality and of the need to repeat a revascularization procedure. Internal mammary grafts were no better if the patients were high-risk individuals with diabetic retinopathy, but such grafts were superior in patients without retinopathy. It is of course unlikely that this is a direct result of retinopathy. It is more plausible that retinopathy is a surrogate marker, for instance of advanced autonomic polyneuropathy.

**Conclusion**

Recently, important epidemiological information has become available on the frequency of cardiovascular disease, its causes and clinical manifestations as well
as the benefit from interventions in the symptomatic diabetic patient with renal disease.

What is needed is more widespread information about, and particularly more implementation of, prevention. Furthermore, currently accepted procedures must be more consistently implemented in the diabetic patient with renal disease and symptomatic heart disease. There is no doubt that there are huge deficits in this respect and this remains a challenge for clinical nephrology.

Conflict of interest statement. None declared.

References

36. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on


