Preliminary Report

Comparison between two prospective studies of cardiovascular disease carried out amongst renal replacement patients in UK and Italy

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Abstract The data on 256 non-diabetic patients entering renal replacement therapy (RRT) in Manchester between 1 January 1983 and 31 December 1986 were compared with those on 84 non-diabetic patients entering RRT in Milan between 1 January 1983 and 31 December 1988. In each unit, patients had been studied prospectively and the findings were entered on the same database for this report. At the end of the study, 68% of patients were alive in each centre and in each 16% had died from cardiovascular disease. 11% of Manchester and 18% of the Milan patients developed angina. The data do not support the view that there is a differential risk for cardiovascular disease in the Northern and Southern parts of Europe and it may be advisable to study the matter prospectively in a larger patient cohort.

Introduction

For over 20 years, there has been evidence to suggest a causal association between ischaemic heart disease and renal disease [1,2]. An increased risk of death from cardiovascular disease in patients on renal replacement therapy (RRT) has been confirmed in the past few years [2–7] and it is now recognized as the main cause of mortality and one of the major causes of morbidity in patients both on dialysis and after transplantation.

From data reported to the EDTA–ERA Registry it accounts for 51% of deaths in patients on haemodialysis and 36% of deaths of patients after transplantation [5]. The relative risk of such death is much higher in younger than in older subjects and in those with diabetes [8].

The factors involved have not been defined. The uraemic state affects the heart directly by impairing cardiomyocytic function [9] and less directly by anemia, fluid overload, and hypertension which accompany it [10]. Uraemia is associated with hypertension [11] and with significant hyperlipidaemia [12]. Levels of atherogenic factors such as triglycerides and Lp(a) are high, particularly in patients on haemodialysis [13] and peritoneal dialysis [14].

The genetic predisposition of individual patients and the social and dietary patterns of the community also influence the overall risk for the development of ischaemic heart disease in patients on RRT.

Reportedly, there is a different incidence of cardiovascular disease in the general population of different countries [15]. There has been evidence from the United States, Australia, and from individual European countries that the incidence of cardiovascular disease in patients on RRT also varies from place to place [5–8,16–18].

The recent evidence from Europe has suggested that patients on RRT in Southern Europe, broadly defined as countries on the Mediterranean littoral, have significantly lower rates of mortality from ischaemic heart disease than those in such Northern European countries as the UK [5].

However, it must be remembered that these findings derive from the data of the EDTA–ERA Registry which are reported on an annual basis and it is often difficult to be certain of the exact cause of death. This does not imply criticism of the reporting centres. Without properly documented evidence and especially if the patient has died at home, or in a hospital unfamiliar with the patient, the precise cause of an apparently ‘cardiac’ death cannot be determined.

For these reasons, carefully conducted prospective studies have a special place, since those conducting them take prompt and detailed evidence in each case of death. We have reported such a study in a population of patients who were approaching, or in, terminal renal failure in the Northwest of England [18], an area in which therein is documented that the general population is at high risk of developing cardiovascular disease in [19]. We found that the incidence was indeed higher in patients on RRT than has been reported in the general population [20], but with a decreasing relative risk with increasing age.

We conclude also, that with a well-constructed risk
profile obtained before end-stage renal failure had developed, it should be possible to predict quite accurately the development of cardiovascular disease in many cases.

We then found that both of our units had studied prospectively in this way patients entering their respective programmes. This offered the opportunity to compare the findings in Europe from a British (Northern) and Italian (Southern) centre. We hoped to see if the suggested differences between the patient populations in terms of morbidity and mortality from ischaemic heart disease were present.

In each centre, data had been collected on morbidity and mortality in relation to the state at entry to the renal replacement programme and to the types of RRT each patient had received.

We confirmed that the diagnostic criteria and the definitions employed in studying our patients were compatible and established a common database.

Although both units accepted diabetic patients who were suitable for RRT we have confined this report to non-diabetic patients.

**Subjects and methods**

In each centre, one person (GF in Milan and NPV in Manchester) was responsible for the accuracy and completeness of the data. Any death or event was investigated and the clinical, laboratory and electrocardiographic details checked by personal assessment. Postmortem evidence was included, if available.

There were no exclusions from consideration in either centre and in both, all patients who presented and who were suitable for treatment on medical grounds were placed on the programme. The method of RRT deemed most appropriate was used and was changed as necessary. Changes in the mode of RRT were noted and dated. Patients were transplanted as the occasion arose and follow-up was not interrupted.

The data from Manchester concern the subset of 256 non-diabetic patients (154 men and 102 women) who began RRT between 1 January 1983 and 31 December 1986 from the larger group of patients reported previously [18]. In Milan, the data concern the 84 non-diabetic patients (50 male, 34 female) who commenced RRT between 1 January 1983 and 31 December 1988. Thus the studies are not precisely contemporaneous.

On entry to the RRT programme a detailed clinical history and examination was obtained from each patient. Features recorded for this study included age, sex, previous history of myocardial infarction, angina pectoris or other cardiovascular disease, and smoking status (smokers included ex-smokers). The findings are shown in Table 1.

All patients were followed to the end of the study (that is, a minimum period of 3.5 years) or until death, data being assessed at 31 December 1990 in Manchester and the 31 May 1992 in Milan.

The cause of death was derived from direct assessment of the data and where available, autopsy records and categorized as cardiovascular (EDTA Registry code 11.13,14,15,16,18) or other vascular (EDTA Registry code 22). Deaths from non-cardiovascular causes were recorded similarly but are not analysed further in this report.

**Clinical definitions**

Angina pectoris was defined as a typical history of chest pain on exertion with or without confirmation by exercise stress testing or coronary angiography. Myocardial infarction (MI) was defined as a typical history with either characteristic ECG findings of acute myocardial infarction or an appropriate rise in serum creatinine phosphokinase levels. Cerebrovascular accident (CVA) was defined as a neurological deficit transient or permanent, characteristic of that due to vascular disease and in the absence of evidence of an alternative aetiology.

**Statistical methods**

Kaplan–Meier survival curves [21] were derived and compared using the logrank test. The following end-points were used:

(i) Cardiovascular death only, all other deaths censored (Figure 1).

(ii) Development of angina or of a first myocardial infarction, or cardiovascular death, if this was the primary event (Figure 2).

All data were calculated from the date of first dialysis or the date of transplantation, if that was the first mode of treatment.

To adjust for age, Cox proportional hazards regression analysis [22] was used to compare the patients groups in Manchester and Milan, incorporating a stratification for age at the start of RRT in five bands: < 35, 35–44, 45–54, 55–64, > 65 years.

| Table 1. Characteristics of the patient groups at entry into the RRT programme |
|---------------------------------|--------|--------|
|                                 | Manchester | Milan |
| Number                          | 256     | 84     |
| Male: female (%)                | 60:40   | 59:41  |
| Age (median, range)             | 46 (16–78) | 53 (19–77) |
| Smokers (%)                     | 34      | 36     |
| Previous MI/angina (%)          | 10      | 11     |
| Previous CVA (%)                | 3       | 4      |

**Fig. 1.** Cardiac deaths only □ = Manchester, ○ = Milan. Time from start of renal replacement therapy. Manchester, initial number 256, 112 at 5 years, 37 at 7 years; Milan, initial number 84, 46 at 5 years, 24 at 7 years; $P = 0.59$. 

Results

Prior to entry to the RRT programme, 11% of Milan and 10% of Manchester patients had developed angina or had sustained a myocardial infarction and 3–4% of each group had sustained a CVA (Table 1).

In Manchester, 154 patients received CAPD as the first form of RRT, 15 switching later to haemodialysis; 79 patients were maintained on HD as the only form of dialysis, 23 patients were transplanted without having received prior dialysis. In all, 154 of the 256 patients were transplanted. In Milan, 64 patients were placed on HD and 20 on CAPD. None were transplanted before dialysis; 22 were transplanted during the study.

The status at the end of the study is given in Table 2.

‘Other vascular’ deaths include cerebrovascular events. ‘Other’ deaths were due to infection in seven cases, cachexia predominantly in patients with advanced vasculopathy or malignancy (6 cases each) and in four cases to dementia in patients with diffuse cerebrovascular disease. One patient suffering from Christmas disease had intractable bleeding and one died after severe haematemesis not otherwise defined. One patient died from chronic airways limitation and one from immediate post-transplant complications. In two patients the cause of death was not known.

During the study, 18% of Milan and 11% of Manchester patients developed angina or sustained a non-fatal myocardial infarction, while 7% of Milan and 12% of Manchester patients died from a first cardiovascular event.

For these non-diabetic patients, actuarial survival is not different in the two populations, for cardiac deaths (as a first or subsequent event) or for the development of a new cardiac event (Figures 1 and 2).

After adjusting for age, the incidence of new cardiac events was not significantly different in the two populations (Hazard Rate ratio 1.5, 95% confidence interval 0.9–2.4, n.s.). The incidence of cardiac death, was higher in Manchester but of borderline significance. (Hazard Rate ratio 1.8, 95% confidence interval 0.9–3.3, \( P = 0.054 \)).

Discussion

In the general population, the incidence of death from ischaemic heart disease appears to vary from country to country. However, it is difficult to attribute these differences to any single factor such as the diet, when there are so many contributory factors to consider.

The evidence from the EDTA Registry to suggest that in patients on RRT the incidence of ischaemic heart disease in different European areas followed a striking North–South gradient deserves close consideration.

It is based on the reports of the cause of death recorded in the returns of individual units to the Registry. These constitute, at best, an approximation. For the reasons given already, determining the precise reason for a death in a patient on RRT is both complex and time-consuming. That it is difficult to obtain validated data, especially in retrospect, is readily understandable.

Interestingly, evidence from the United States highlights the fact that the cause of death reported may be different from that recorded in the death certificate [23].

Furthermore, morbidity as well as mortality should be assessed. This requires informed and prospective study.

It is because our units had carried out such studies that we chose to analyse the data together. These reveal that, in terms of morbidity before RRT commenced, morbidity and mortality while on RRT, and overall survival (which appears acceptable) there is little to choose between the patient groups which presented to the two units.

Neither exercised a selection policy in relation to offering RRT to patients presenting in renal failure, other than that of clinical benefit. In each, the patients were drawn from the local districts.

One feature of our analysis was that the pattern of morbidity from ischaemic heart disease was similar in both cohorts either before or after RRT had commenced. While the two populations were too small to make definitive statements as to the significance of the observation, it demonstrates how important is a careful assessment of existing morbidity in any patient entering the renal replacement programme.

Age has an influence on cardiovascular outcome in ESRF. To account for differences in the age structure of the patients studied in the two cohorts, we used a Cox analysis with age stratification and found that there was no significant difference between the patient population in the two centres after adjustment for age. Confirmation of this finding would require a larger cohort study.

There has been interest recently in the role of even
moderate hypertension as a factor in increasing the rate at which, over a prolonged period of haemodialysis, cardiac death occurs on RRT.

While we had data on the blood pressure at entry to the study and in our analysis this did not affect the outcome, we did not structure the study to examine the influence of this and other factors over time.

The overall survival of the two cohorts was similar and acceptable. It seems unlikely that blood pressure was a dominant differentiating factor between the cohorts since we shared a similar philosophy with regard to the careful management of this and other clinical features which might affect outcome.

If the unexpectedly high incidence of cardiac events in this carefully studied Italian cohort is a valid observation, then, elsewhere, patients dying suddenly must not have had the true cause of death recorded.

This raises the question of why such under-recording should be selectively more frequent in some countries than in others. It may be that this reflects a ‘balance of probabilities’ approach. Faced with the option of deciding whether an otherwise unexplained death was due to ischaemic cardiac disease or, for example, to heart failure, the perceived improbability of it being attributable to the former might influence the result.

We are aware of two cases in which sudden death of a dialysis patient was attributed to unexpected heart failure when at post mortem it became clear that an acute myocardial infarction had occurred.

Thus, despite the suggestion in earlier cross-sectional and retrospective studies that the mortality and by inference the morbidity from ischaemic heart disease is lower in patients on RRT in Italy than it is in the UK, the prospective studies reported here provide no evidence to support that proposition.

A definitive answer to the question requires a large prospective study, in which it would be imperative to assess in detail the morbidity in each patient prior to entry to the RRT programme.

Each event must be detailed promptly and in case of death, postmortem evidence obtained as often as possible.

In summary, we present data, collected prospectively, which suggest strongly to us that previous reports on the differential incidence of ischaemic heart disease in patients on RRT in North and South European countries must be evaluated with caution, since they have been obtained from records in which data are entered by different people, sometimes well after the events.

It should be remembered too, that the arbitrary division of Europe into ‘North’ and ‘South’ can mislead. In the general population, the reported incidence of ischaemic heart disease in Greece, a Mediterranean country, is higher than it is in Italy, while in Northern Europe, it is said to be lower in France than in neighbouring UK [15].

References


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