Trend from cardiovascular to non-cardiovascular late mortality in patients with renal replacement therapy since childhood

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INTRODUCTION

Few data exist on the very long-term outcome of patients with chronic kidney disease (CKD). Between 1998 and 2000, we conducted a comprehensive study to evaluate the Late Effects of Renal Insufficiency (LERIC) in all Dutch children who had started chronic renal replacement therapy (RRT) at <15 years of age between 1972 and 1992. Previous analyses of this cohort including data up to the year 2000 showed that, in this age category, patients with CKD had a 31-fold increased risk of mortality when compared with the general population [1], and that cardiovascular disease was by far the most important cause of death among both the dialysis patients and transplant recipients, accounting for 41% of all deaths [1, 2].

Our findings were confirmed by McDonald and Craig [3], who found a similar mortality risk in patients from Australia and New Zealand who started RRT before the age of 20 years between 1962 and 2000. They found the equally high percentage of 45% of all deaths being contributed to cardiovascular disease [3]. Among the survivors in the LERIC cohort in 1999, we also found a high prevalence of cardiovascular disease, which was reflected by an overall increased mean arterial wall stiffness, left ventricular hypertrophy in 40% and aortic calcifications on ultrasound in 19% of patients [2]. In 2002, Oh et al.
showed similar cardiovascular abnormalities in young adults with chronic renal failure since childhood and treated with RRT, including a high prevalence of calcifying arteriopathy. Coronary calcifications were observed in 92% of patients, and carotid intima-media thickness was significantly increased compared with matched controls [4].

Given this high prevalence of cardiovascular disease among the survivors of RRT since childhood and a possible further increase due to advancing age, we expected cardiovascular death to become an even more pronounced problem after 2000. We conducted an extended follow-up study of this cohort to investigate the actual trend in long-term mortality and causes of death after 2000.

**RESULTS**

**Study population**

The total cohort consisted of 249 patients (Table 1). Only 3 of the 249 patients (1.2%) were lost to follow-up. The median age at the start of RRT was 11.2 (range 1.9–15.0 years) and 54.6% were males (Table 1). The median age of survivors was 28.9 (range 21.0–40.9 years) in 1999 and 40.0 (range 31.6–50.8 years) in 2010. The median total follow-up time was 25.5 (range 0.3–39.9 years), time on haemodialysis 2.3 (range 0.03–36.5 years), time on peritoneal dialysis 2.4 (range 0.01–18.6 years) and time living with a renal graft 19.7 (range 0.0.1–39.3 years; Table 1). Among the 231 (93%) transplant recipients, 71 (31%) lived with a single transplant—not necessarily their first—for more than 20 consecutive years and up to 37.2 years (Table 1).

Ninety-two patients received only a single renal allograft (39.8%). Transplantation was performed twice in 84 (36.4%) patients, three times in 43 (18.6%), four times in 8 (3.5%), five times in 1 (0.4%) and six times in 3 (1.3%). Patients changed treatment modality between 1 and 11 times during the study period. Of the 249 patients, only 2 (0.8%) patients lived on a functioning graft during their entire follow-up (median survival 25.3 years) and 18 (7.2%) only received dialysis (median survival 3.7 years).

Of the 186 patients who were still alive in 2000, 79% had a functioning renal graft, similar to the proportion of the 152 patients who were still alive in 2010 (80%).

**Mortality and causes of death**

Of all 249 patients, 42 died between 1972 and 1989, 21 between 1990 and 1999 and 34 between 2000 and 2010. The overall (1972–2010) MR was 1.69/100 patient-years. The median age at the time of death was 22.8 (range 4.2–46.24 years). In the last decade, 12 of the patients died from cardiovascular disease, 44 from infections, 20.5 from malignancies, 20.5 from other causes and 3% (1 case) from unknown cause. Most patients died while on dialysis (53%; Supplementary material, Appendix 1). Of those who died of cardiovascular disease, 75% received dialysis at the time of death; of those who died of infections, this was 60%. Of those who died of infections in the last decade, one-third died of PD-related peritonitis.
A Cox-regression analysis adjusted for background mortality confirmed this change in the pattern. We found a 50% reduction in the risk of overall mortality for 1990–99 when compared with 1972–89 [hazard ratio (HR): 0.50, 95% CI: 0.29–0.86, P = 0.01], but no reduction in overall mortality risk for 2000–10 when compared with 1972–89 (HR: 0.75, 95% CI: 0.47–1.20, P = 0.2; Table 3). After adjustment for expected cardiovascular background mortality, the risk of cardiovascular mortality was 74% lower in 1990–99 than in 1972–89 (HR: 0.26, 95% CI: 0.10–0.66, P = 0.005) and in 2000–10, and it was 91% lower than in 1972–89 (HR: 0.09, 95% CI: 0.02–0.45, P = 0.003; Table 3).

After adjustment for the expected infectious background mortality, there was a borderline significant trend suggesting an increased risk of death by infections in the last decade 2000–10 when compared with 1972–89 (HR: 2.12, 95% CI: 0.88–5.11, P = 0.09; Table 3). The trend was, however, statistically significant when we compared infectious mortality in 2000–10 with that in 1990–99: the risk of death from infections in the last decade was more than thrice the risk in 1990–99 (HR: 3.22, 95% CI: 1.16–8.99, P = 0.03).

### Discussion

In contrast to our expectations, we found a substantial shift from cardiovascular disease to non-cardiovascular disease as the cause of death over the last 10 years in a long-term nationwide follow-up study of patients with paediatric CKD. This occurred while the overall mortality had stabilized over time.

This study is unique in its length of follow-up of patients who started RRT in childhood. Our specific interest in the long-term follow-up of young patients unfortunately hampers the comparison with registry data that are usually presented.
for overall groups or older age categories with a relatively short follow-up. In addition, time may have affected mortality and causes of death in our cohort in three different fashions. First, there may be an effect of calendar time, as both mortality and causes of death may have changed over time among RRT patients as well as within the general population. Time has also led to a selection of survivors in our cohort and finally, our patients have grown older. We will discuss our results with respect to cardiovascular and infectious death in comparison with other studies, taking these three time dimensions into consideration.

Cardiovascular mortality
Trends over calendar time. As cardiovascular disease turned out to be the most important cause of death in young end stage renal disease (ESRD) patients during the 1990s, several authors have highlighted the huge impact of ESRD and RRT on cardiovascular integrity and function [1, 6–10]. Yet, there are more recent data that confirm a trend of infections gradually replacing cardiovascular disease as the most important cause of death over the last decade. The United States Renal Data System (USRDS) data show a decreasing burden of cardiovascular mortality among the dialysis patients of all ages over the last years (MR 120/1000 per py) in 2001 to (MR 83/1000 py in 2008) [11] without changes in other causes of death over time (MR 100/1000 py in 1998, 2001 and 2008) [12]. This trend was similar in patients, aged 20–44 years, with a cardiovascular MR declining from 40.5/1000 py in 2001 to 31.3/1000 py in 2008 [11]. Australian and New Zealand Dialysis and Transplantation Registry (ANZDATA) also showed decreasing cardiovascular MRs for all dialysis patients (MR 9.0/100 py in 1992 to 6.4/100 py in 2005), but not among the younger patients aged 35–54 years [13]. In our study, among patients who started RRT at very young age, the decline in cardiovascular deaths over time was far more pronounced than in both the USRDS and ANZDATA studies. This difference may partially be explained by the lack of patients with diabetes mellitus in our cohort, whereas the prevalence of this disease in the RRT population with adult onset of RRT has significantly increased according to both the USRDS and ANZDATA over time. According to the USRDS data, the prevalence of diabetes mellitus as primary disease in the specific age group of our patients increased from 32.5 in 1996 to 42% in 2005, whereas the percentage of diabetes patients aged <55 years in the ANZDATA database even doubled over time from 21.9 in 1992 to 43.3% in 2005 [13, 14]. The absence of increase in cardiovascular deaths in ANZDATA cohort over time with such a concomitant substantial increase in the proportion of diabetic patients with a related severe cardiovascular burden also indicates a change in cardiovascular outcome in dialysis patients.

A possible explanation for the trend of decreased cardiovascular mortality over the last decade could be an increased awareness of the burden of cardiovascular disease in renal patients among physicians and those that may have resulted in better treatment and consequently better survival. If this would be true for our patients, it would also mean that a more aggressive treatment of cardiovascular disease and the prevention of risk factors may be beneficial even in patients who are already on dialysis or living with a functioning graft for a long time. Previous studies have shown that optimized treatment for cardiovascular comorbidity, for example, with Angiotensin-converting-enzyme inhibitors, β-blockers and angiotensin receptor blockers in patients receiving haemodialysis may indeed induce a reduction in both left ventricular hypertrophy and hypertension [15, 16].

The decline in cardiovascular death in our population partly reflects the trend in the western general population. However, according to the MRR, the decline in our RRT patients was much more pronounced than in the general population.

Long-term follow-up and ageing. Long-term outcome data on patients with ESRD are sparse. Most studies exist on transplanted patients. Previous studies in transplanted patients showed a decrease in cardiovascular death at longer follow-up [17, 18]. The USRDS data have been analysed for all-cause, cardiovascular and infectious mortality in patients who received their first transplant at <21 years of age, between 1983 and 2006, and with a follow-up until 2006 [17]. This study showed a significant decrease in cardiovascular mortality in young transplant recipients over time [17, 18]. The risk of all-cause death decreased yearly by 1% after the end of the first year of the first transplant. This decrease in risk was most pronounced for cardiovascular death (16% per year) after the end of the first year of the first transplant [17]. Using the same data, Meier-Kriesche et al. showed a progressive decrease in cardiovascular death rates in transplant recipients >18 years by renal transplant vintage. The MR decreased from 20.8/1000 py 0–3 months after transplantation to 2.8/1000 py 60+ months after transplantation [18]. These findings suggest that transplantation may halt or even reverse the progression of cardiovascular disease. Most of our patients were transplanted, so this certainly will have contributed to a decrease in cardiovascular death in our study. However, we found the same trend in reduction of cardiovascular death among dialysis patients and therefore transplantation cannot be solely responsible for the reduction of cardiovascular death. Moreover, the prevalence of risk factors for cardiovascular death, such as increased vascular stiffness, left ventricular hypertrophy and aortic valve calcification, was high among our patients in 1999, despite the fact that most of them had a long-time lasting functioning graft at that time.

In 2010, all our patients were between 30 and 50 years old. In line with what can be expected in ageing patients, the overall mortality increased over the last decade. However in contrast to that, the cardiovascular disease induced MR decreased with advancing age over the last decade. This could of course have been the result of a selection process and hence of a survivor bias; the sickest patients with cardiovascular comorbidity may have died already before 2000 of cardiovascular disease, leaving the strongest patients for the observation period after 1999. However, as mentioned before, among these survivors, there was a high prevalence of risk factors for cardiac death in 1999 [2]. Furthermore, this trend was only
Table 2: MRs (deaths/100 pys) and MRR (MR in patients/MR in age- and gender-related general population) over three time periods

<table>
<thead>
<tr>
<th></th>
<th>1972–89 (95% CI)</th>
<th>1990–99 (95% CI)</th>
<th>2000–10 (95% CI)</th>
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<tbody>
<tr>
<td>Mortality rate</td>
<td></td>
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<tr>
<td>All causes</td>
<td>2.14/100 py (1.54–2.89)</td>
<td>1.11/100 py (0.69–1.70)</td>
<td>1.86/100 py (1.29–2.60)</td>
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<tr>
<td>Cardiovascular</td>
<td>0.97/100 py (0.58–1.51)</td>
<td>0.37/100 py (0.15–0.76)</td>
<td>0.22/100 py (0.06–0.56)*</td>
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<tr>
<td>Infection</td>
<td>0.51/100 py (0.24–0.94)</td>
<td>0.32/100 py (0.12–0.70)</td>
<td>0.82/100 py (0.46–1.35)</td>
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<tr>
<td>Malignancy</td>
<td>0.20/100 py (0.05–0.51)</td>
<td>0.11/100 py (0.01–0.40)</td>
<td>0.38/100 py (0.15–0.78)</td>
</tr>
<tr>
<td>Other</td>
<td>0.41/100 py (0.18–0.81)</td>
<td>0.32/100 py (0.12–0.70)</td>
<td>0.38/100 py (0.15–0.78)</td>
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<td>0.05/100 py (0.00–0.28)</td>
<td>0/100 py (0.00–0.00)</td>
<td>0.05/100 py (0.00–0.28)</td>
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<thead>
<tr>
<th>Mortality rate ratio</th>
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<tbody>
<tr>
<td>All causes</td>
<td>53.0 (36.9–69.1)</td>
<td>19.7 (10.8–28.6)</td>
<td>26.8 (17.8–35.8)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>660.3 (368.1–952.5)</td>
<td>70.0 (14.0–126.0)</td>
<td>19.6 (0.5–38.7)</td>
</tr>
<tr>
<td>Infections</td>
<td>502.5 (177.5–827.5)</td>
<td>101.8 (14.1–189.5)</td>
<td>352.6 (174.0–531.2)</td>
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<tr>
<td>Malignancies</td>
<td>29.2 (12.3–46.1)</td>
<td>18.8 (8.0–29.6)</td>
<td>18.5 (11.5–25.5)</td>
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<tr>
<td>Other</td>
<td>17.1 (5.9–28.2)</td>
<td>8.6 (1.0–16.2)</td>
<td>12.8 (3.4–22.2)</td>
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<td>Unknown</td>
<td>19.9 (0.9–38.9)</td>
<td>0 (0.0–0.0)</td>
<td>10.5 (0.3–20.7)</td>
</tr>
</tbody>
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*P < 0.05 compared with 1972–89.

**Figure 1:** (a) MR/100 person years per age category per ERA. (b) MR/100 person years per era in age category 10–20 years. (c) MR/100 person years per era in age category 20–30 years. (d) MR/100 person years per era in age category 30–40 years.
Infectious mortality

Trends over calendar time. We found a trend in infectious mortality in three different time periods that suggests an increased risk of death by infections in 2000–10 when compared with 1972–89 and 1990–99.

Infections have for a long time been found to be the second cause of death in patients with ESRD [12]. In line with our data, McDonald and Craig [3] showed a decrease of infectious mortality in patients with paediatric onset of ESRD from 39 between 1963 and 1972 to 16% between 1993 and 2002.

In contrast to our findings, the USRDS data showed a decline of infectious mortality between 1989 and 2010 in ESRD patients, aged 20–44 years. This was accompanied by a similar decline in overall mortality [22]. At the same time, there are data that confirm a more recent tendency towards increase of life-threatening infections in patients with ESRD. The USRDSs showed a significant increase in hospitalization due to infection in dialysis patients from 1993 to 2005 [19], as well as in transplanted patients between 1991 and 1998 [20].

The latter may be caused by a more intensive anti-rejection therapy of the last two decades, leading to a more impaired immunity including defective phagocytic function of granulocytes [21]. According to the UK Renal Registry, the number of deaths caused by infections in all patients on RRT has stabilized around 20% between 2000 and 2010. In contrast, the percentage of cardiac deaths decreased from 34 to 22% in this period [22]. The USRDS MRs by infection have also stabilized between 1998 and 2007 [23, 23]. In both hemodialysis and peritoneal dialysis patients, catheter-related infections are considered to be the main source of life-threatening infections, leading to peritonitis in peritoneal dialysis and to central venous line-induced sepsis in haemodialysis.

Our data could not be explained by the trend in the general population, in which infection plays a minor role, and over time even a decreasing, role in the cause of death, at least in the western world [5, 14].

Long-term follow-up and ageing. The USRDs data showed that infectious MR in patients who received their first transplant <21 years of age, between 1983 and 2006 and with a follow-up until 2006, did not change at follow-up [17], suggesting that the risk was the same in the first year, as in the years thereafter. This implies that the relative contribution of infectious death has increased over time. Recurrent needle sticks of arteriovenous fistulas or grafts have also been associated with an increased risk of infections [21]. Jean et al. [24] found that a high incidence of catheter-related bacteremia, and bacteremic catheters were more often observed in patients with longer catheter survival time.

There are no data that support the becoming of age of our patients as a potential factor for an increased risk of fatal infections. Previously, it had been found that, in transplanted patients, very young as well as very old patients were particularly prone to dying of infections [20]. The oldest patient of our cohort was 50 years old in 2010, and very few children have been transplanted at a very young age. This may explain why we found that the risk of infectious death was constant across all age groups.

Limitations

The establishment of the exact cause of death in patients with a complicated course of disease, as was often the case in our
patients, can be difficult. In order to cope with this problem, three observers independently determined the cause of death based on detailed descriptions of all available chart information covering the period around the patient’s time of death. After assessment of interobserver variability, consensus was achieved by discussion.

CONCLUSION

In conclusion, we show that there is a substantial shift in causes of death after long-term RRT since childhood. Cardiovascular mortality decreased significantly in the last 10 years compared with the period 1972–99, and infectious mortality increased (although not significantly). A possible reason for the significant decreased risk of cardiovascular mortality could be the awareness of the cardiovascular burden in these patients that urged a strict cardiovascular management of these patients. Physicians should on the other hand be aware of the emerging burden of potentially fatal infections in these patients and take precautions for prevention.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared.

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Evaluation of characteristics, associations and clinical course of isolated spontaneous renal artery dissection

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Background. Spontaneous renal artery dissection (SRAD) is a rare entity of unknown etiology. We aimed to study the clinical course and outcomes and compare the characteristics of patients with SRAD with those of the general population.

Methods. All cases of isolated renal artery dissection diagnosed at the University of Michigan Hospitals between January 2000 and July 2012 were identified by the ICD-9 code. Cases were matched by age, gender and race with individuals from the 2009–2010 National Health and Nutrition Examination Survey (NHANES). Characteristics and awareness of comorbid conditions were compared. Information about the clinical course after diagnosis was retrieved from the case group to ascertain their outcomes.

Results. Overall, 17 patients with SRAD with a mean age of 38.6 years (SD = 8.3) were identified. Eleven patients were male and 14 were white. The most common presenting symptom was excruciating sudden-onset flank pain ipsilateral to the site of dissection. Fibromuscular dysplasia, Ehlers–Danlos and polyarteritis nodosa were present in 4, 4 and 1 patients, respectively. After adjusting in a multivariable model, the case group was more likely to report history of hypertension, cancer and connective tissue disorders (P < 0.001), and less likely to have obesity (BMI ≥ 30 kg/m²) compared with the general population. Supportive medical treatment, endovascular intervention and surgery were required in 8, 5 and 4 cases, respectively. After discharge from the hospital, hypertension was adequately controlled in all the patients but one.