

# Timing of referral of chronic kidney disease patients to nephrology services (adult)

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## GUIDELINES

No recommendations possible based on Level I or II evidence

## SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Patients with an estimated glomerular filtration rate (eGFR)  $<30$  mL/min per  $1.73$  m<sup>2</sup> should generally be referred to a nephrology service for assessment and multidisciplinary management of chronic kidney disease (CKD). This is to provide adequate time (at least 3–6 months) for predialysis education, creation of permanent dialysis access and planned initiation of dialysis/pre-emptive transplantation or alternatively, supportive management and palliation for those who do not wish to or are not deemed suitable for chronic dialysis (Level III evidence).

## IMPLEMENTATION AND AUDIT

1. Data on the time at which patients were referred relative to the commencement of dialysis should continue to be obtained through the ANZDATA Registry.
2. All patients with known CKD should be referred early, in accordance with the above and should receive appropriate multidisciplinary CKD management and education under the supervision of a nephrologist.

## BACKGROUND

Late referral (defined as initiation of dialysis  $<1$ – $6$  months – usually  $<3$  months – after initial referral to a nephrologist) of patients with CKD is associated with:

- increased patient morbidity and mortality
- increased use of temporary venous catheters at initiation of haemodialysis
- less use of peritoneal dialysis
- reduced likelihood of listing on a transplant waiting list and of transplantation
- increased need for and duration of hospital admission, and
- increased initial costs of care following the commencement of dialysis.

These outcomes can be improved by referring patients to a multidisciplinary CKD clinic service for appropriate treatment well in advance of the need for dialysis. An eGFR of 30 mL/min per  $1.73$  m<sup>2</sup> or less suggests a high likelihood of progression and need for consideration of renal replacement therapy and thus, can be considered a prospective surrogate marker for a retrospective condition (late referral).

## SEARCH STRATEGY

**Databases searched:** MeSH terms and text words for CKD, predialysis and dialysis were combined with MeSH terms and text words for referral and combined with MeSH terms and text words for prognosis, survival, morbidity, access and quality of life. The search was carried out in Medline (1950–January, Week 4, 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline. **Date of search:** 6 February 2008.

## WHAT IS THE EVIDENCE?

There are no randomized controlled trials addressing the timing of referral, nor are these likely to occur for logistic and ethical reasons. There is a meta-analysis which analyses non-randomized prospective and retrospective cohort studies.<sup>1</sup>

## Meta-analysis

Chan *et al.* performed a meta-analysis of the English language literature from 1980 to 2005. Twenty-two studies yielded a total of 12 749 patients.<sup>1</sup> The duration of follow up was from 0.8 to 4.9 years. Late referral was associated with increased overall mortality (RR 1.99, 95% CI: 1.66–2.39). At 1 year, mortality was 29% in the late referral group and 13% in the early referral group (RR 2.08, 95% CI: 1.31–3.31). The duration of hospitalization at the initiation of dialysis was increased by 12 days (95% CI: 8.0–16.1). There was considerable heterogeneity due to differences in the definition of late referral (regarded as ‘management that

could have been improved by earlier contact') ranging from <1/1 month to 1/1 year. The authors recommend concordance with the Kidney Disease Outcomes Quality Initiative guideline of referral at CKD stage IV (GFR <30 mL/min per 1.73 m<sup>2</sup>).

### Prospective studies

Abderrahim *et al.* studied 299 Tunisian diabetic patients.<sup>2</sup> One-third initiated dialysis as an emergency and 91% of all patients commenced with temporary venous access. Survival at 1 year was 68.4%, at 2 years 59.6%, and at 4 years it was 45.3%. Nearly 27% of patients died in the first 3 months, mainly from infection or cardiovascular disease. Age, comorbidity (hypertension and Type I diabetes) and urgent initiation of dialysis were independent risk factors for death.

Astor *et al.* in the CHOICE study examined a cohort of 356 patients.<sup>3</sup> Those that had been seen by a nephrologist at least 1 month prior to initiation of dialysis were more likely to start dialysis with an arteriovenous (AV) fistula or graft than those referred later (39% vs 10%). Late referrals had a more prolonged period of catheter use. Furthermore, patients referred earlier than 4 months were more likely to use an AV fistula rather than an AV graft as their first AV access than those referred later (45% vs 31%).

Bhan *et al.* studied 93 consecutive patients commencing dialysis over a 1-year period.<sup>4</sup> Patients referred late (<90 days) were more likely not to have a functioning fistula (48%). However, most of the late referrals were due to acute disease, rather than true late referrals of chronic disease. On multivariate analysis, peripheral vascular disease and rapid deterioration of GFR were negative predictive factors for a fistula.

Caskey *et al.* examined the quality of life of patients by a visual analogue scale (262 patients) and the SF-36 (226 patients) and showed that a planned first dialysis rather than early referral per se was associated with better quality of life at 8 weeks following initiation of dialysis.<sup>5</sup>

Two interesting studies using data from the ANZDATA Registry database have been published by Cass *et al.*<sup>6</sup> All patients with end-stage kidney disease (ESKD) commencing dialysis over a period of 45 months from 1 April 1995 to 31 December 1998 were studied. Patients who either died or were transplanted in the first year were excluded from the analysis. Of the 4243 patients (26.9%), 1141 were referred late – defined as commencing dialysis within 3 months of referral to a nephrologist. The late referral group had more comorbidity. These patients not only were less likely to receive a transplant (adjusted RR 0.78, 95% CI: 0.64–0.95), but were more likely to die after the first year on dialysis (adjusted HR 1.19, 95% CI: 1.04–1.35). Dialysis modality and creatinine clearance at the time of dialysis initiation did not affect these results. Cass suggests that the worse outcome in the late referral group may suggest suboptimal predialysis care.

Cass and colleagues also looked at the association between social disadvantage and late referral in 3334 patients from the ANZDATA Registry.<sup>7</sup> The patient's post-

code at the start of treatment was used as an indicator of place of residence. The analysis was restricted to capital cities to exclude remote area patients who would have moved home to more easily access dialysis. Australian Bureau of Statistics data allowed correlation between the postcode and an index of socioeconomic disadvantage. A total of 889 patients (26.7%) were referred late with a range from 13.6% to 43.7% between geographical areas. The areas with the higher percentage of late referrals were those of relative disadvantage – the highest being Darwin, with a large indigenous community. Disadvantaged areas also had a higher burden of ESKD.

Curtis *et al.* studied 288 patients who commenced dialysis following more than 3 months' exposure to nephrology care.<sup>8</sup> Patients seen in multidisciplinary clinics had significantly increased survival at 14 months compared with standard nephrological care, with the hazard ratio for mortality for standard versus multidisciplinary care being 2.17 (95% CI: 1.11–4.28).

Frimat *et al.* reviewed 148 patients with type 2 diabetes who commenced dialysis in the EPIREL study.<sup>9</sup> Mortality within 3 months of renal replacement therapy was associated with physical impairment in ambulation and commencing dialysis in life-threatening circumstances. Commencement of dialysis in an emergency was associated with late referral (<3 months), worse biochemistry and increased hospitalization. After 3 months, survival at 1 year was 16.4% better in those with regular nephrological care versus late referral.

Fujimaki and Kasuya studied 119 patients older than 60 years of age (mean age = 74 years) and showed increased need for urgent initiation of dialysis in late referred patients.<sup>10</sup> Urgent dialysis was associated with increased mortality.

In a study of 101 Brazilian patients commencing haemodialysis, Gonçalves *et al.* showed increased mortality and hospitalization in late referred patients (<3 months prior to initiation of dialysis) and in patients with temporary venous access.<sup>11</sup> By univariate analysis, late referral (HR 10.77, 95% CI: 1.41–82.45) and albumin (HR 0.23, 95% CI: 0.11–0.47) were associated with reduced survival. By multivariate analysis, only late referral was associated with increased hospitalization (HR 3.51). Late referral was associated with increased mortality and hospitalization, independently of temporary venous access.

John *et al.* identified 3822 patients with CKD (median calculated GFR 28 mL/min per 1.73 m<sup>2</sup>) from biochemical samples processed at two laboratories in Kent, UK, who were unknown to the renal service.<sup>12</sup> At 31.3 months, 8.1% of these patients had been referred. Unreferred patients had a median survival of 28.1 months. The majority had stable renal function but 27.5% were anaemic (Hb <11 g/dL). It was suggested that patients without complications and stable disease could be monitored in community or at general medical clinics as referral of all CKD patients would be inappropriate and would overwhelm renal services.

Joly *et al.* studied a cohort of 146 consecutive octogenarians referred over a 12-year period.<sup>13</sup> Of these, 37 patients were not offered dialysis: these had an increased incidence

of social isolation, late referral, poor Karnofsky score and diabetes. Six patients refused dialysis and 101 patients commenced dialysis. Median survival was 28.9 months in those dialysed *versus* 8.9 months in those treated conservatively. Two-year survival was 60% in the dialysis group *versus* 15% in the conservative care group. Predictors of death at 1 year on dialysis were poor nutrition, late referral and functional dependence. Beyond 1 year, the sole predictor of death was peripheral vascular disease.

Jungers *et al.* studied 1057 consecutive patients starting dialysis at the Necker Hospital in Paris over a 10-year period (excluding acute renal failure and advanced malignancy).<sup>14</sup> Predialysis nephrological care (PNCD) was associated with better outcome: 5-year survival was 59% in those with less than 6 months PNCD, 65.3% for 6–35 months care, 77.1% for 36–71 months care and 73.3% for more than 72 months of care. Less than 6 months PNCD was an independent predictor of mortality along with age, diabetes and prior cardiovascular disease.

Jungers *et al.* also published a study in 2006 of 1391 consecutive patients who commenced dialysis at their institution from January 1989 to December 2000.<sup>15</sup> Late referral was defined as <6 months before initiation of dialysis and accounted for 30% of patients throughout this period. Major cardiovascular events were twice as high in late referrals and even in those followed up for up to 35 months, before initiation of dialysis. Duration of predialysis care was a significant risk factor for mortality.

Kazmi *et al.* used data from the Dialysis Morbidity and Mortality Study and studied a cohort of 2195 prospective incident patients.<sup>16</sup> Using propensity score analysis, late referral (<4 months) was found to be associated with a higher risk of death at 1 year after initiation of dialysis compared with early referral (HR 1.42; 95% CI: 1.12–1.80).

Kee *et al.* retrieved all serum creatinines and HbA1Cs over a 2-year period for 345 441 adults in Northern Ireland.<sup>17</sup> A total of 16 856 were determined to have a creatinine greater than 150 not due to acute renal failure. Review by a renal specialist over the following 12 months occurred in only 19% of diabetic CKD patients and 6% of non-diabetic CKD patients, although disadvantaged patients did not seem to be under-investigated compared with more affluent patients. Elderly patients and those remote from a renal unit were referred significantly less often. The authors discuss the resource implications of changed referral criteria for CKD.

Kessler *et al.* in a prospective study of 502 patients demonstrated a strong correlation between late referral and early death with OR 2.7 for <12 but >4 months, 2.8 for <4 but >1 month and 4.9 for <1 month.<sup>18</sup> This was mainly attributable to cardiovascular disease at initiation of dialysis. However, referral pattern had little impact on survival beyond the first 90 days. Emergency first dialysis was also an independent risk factor for not being placed on the transplant waiting list.

In a prospective cohort study of 828 patients, Kinchen *et al.* defined early referral as >12 months, intermediate referral as 4–12 months and late referral as <4 months.<sup>19</sup> Mortality at 2.2 years from initiation of dialysis was

increased in both intermediate and late referral groups compared with the early referral group (OR 1.2 and 1.8, respectively) adjusted for comorbidity. Late referral was associated with an increased burden and severity of comorbid disease.

Lee *et al.* reported on 157 consecutive incident haemodialysis patients. Only 35% had permanent access at initiation.<sup>20</sup> Patients with diabetes were more likely to have PNCD, to have predialysis access surgery and to initiate dialysis with permanent vascular access.

Lorenzo *et al.* published a study of a 5-year prospective cohort of 538 incident patients.<sup>21</sup> Patients who were seen >3 months prior to initiation of dialysis were regarded as 'planned', compared with 'unplanned' patients who were seen within 3 months. Follow up was for a mean of  $24 \pm 16$  months. Unplanned patients had an increased risk of mortality (HR 1.73, 95% CI: 1.23–2.44) and of hospitalization (HR 1.56, 95% CI: 1.36–1.79). Commencing dialysis with temporary venous access also increased mortality (HR 1.75, 95% CI: 1.25–2.46) and there was an additive effect of unplanned presentation and initiation with temporary access on mortality with HR 2.89 (95% CI: 1.97–4.22). Both late presentation and temporary dialysis access are independent and additive risks for mortality.

Nakamura *et al.* studied 366 patients with cardiovascular disease and CKD. A total of 194 patients were seen early (>6 months prior to first dialysis) and 172 were seen late.<sup>22</sup> Clinical data and initial renal function did not differ between the two groups. Patients were observed for 41 months. Late referred patients had a more rapid deterioration in renal function ( $P < 0.005$ ), reduced survival ( $P < 0.0001$ ) and commenced dialysis more frequently with temporary access (72% *vs* 30%,  $P < 0.001$ ). By multivariate analysis, age and early referral were significant variables predicting mortality.

Ortega *et al.* conducted a study of 96 patients, which showed an RR of death of 0.39 for initiation of dialysis with an AV fistula compared with a central venous catheter (CVC).<sup>23</sup> This was regardless of diabetic status, early referral or planned *versus* unplanned dialysis.

Ravani *et al.* in a prospective study of 229 patients showed increased survival with HR 0.48 for patients who participated in a predialysis educational programme compared with unstructured specialist care (controlling for comorbidities, demographics, duration of predialysis follow up and dialysis modality).<sup>24</sup> Median follow up was for 37.8 months. This survival advantage persisted when late referral and observation for <1 year were excluded.

Riegel *et al.*, in a prospective study of 551 patients from Germany, showed that only 38.7% of patients with CKD stage 4 were under nephrological care.<sup>25</sup> These patients had a higher incidence of planned initiation of dialysis (81.0% compared with 48.0%), less hospitalization (54.5% *vs* 83.7%) and a shorter duration of hospital stay (11.4 *vs* 17.4 days).

Roderick *et al.* studied 250 patients referred for renal replacement therapy over a 12-month period.<sup>26</sup> Ninety-six patients (38%) were referred late (<4 months), which were further defined as avoidable and unavoidable late referrals. These patients were less likely to receive standard CKD

therapies, were in a poorer clinical state and more frequently commenced dialysis emergently. Mortality at 6 months was 16% in the early referral group compared with 28% in the avoidable late referral group and 35% in the unavoidable late referral group, respectively.

Starck in 2001 studied a prospective cohort of 2264 patients in the Dialysis Morbidity and Mortality (DMM) Study Wave 2.<sup>27</sup> Late referral (within 4 months of initiation of dialysis) was associated with higher mortality at 1 and 2 years with RR 1.68 (95% CI: 1.31–2.15) and 1.23 (95% CI: 1.02–1.47), respectively. Patients who were seen by a nephrologist at least twice in the year before dialysis commencement had a lower risk of death with RR 0.8 (95% CI: 0.62–1.03). Late referral patients were less likely to have a fistula, to be on erythropoietin and to have had two or more predialysis nephrologist visits.

Stehnan-Breen *et al.* also used data from the DMM Study.<sup>28</sup> Only 34.4% of patients had permanent access at the initiation of dialysis; 67% of patients had an AV graft rather than a fistula. Early referral was an important predictor of permanent access with OR 0.33, along with serum albumin (OR 1.55), erythropoietin use (OR 1.79) and fewer predialysis nephrologist visits (OR 0.1) – all surrogate markers of timely referral.

Wauters *et al.*, in a prospective study of 279 patients in three countries (France, Italy and Switzerland), found 71.6% were referred early (>6 months), 15.1% intermediate (1–6 months) and 13.3% late (<1 month).<sup>29</sup> Late referral was associated with an active cancer, rapid progression of CKD, the structure of the dialysis centre (city worse than private or regional centres) and the nature of the referring physician (nephrologists and general practitioners better).

### Retrospective studies

Sesso and Belasco in 1996 reported the outcomes of 205 consecutive patients with non-diabetic nephropathy who were commenced on dialysis between October 1992 and March 1995 in the Nephrology Division of Hospital São Paulo, Brazil.<sup>30</sup> Patients were divided into a 'late diagnosis group' of 106 patients who were diagnosed <1 month before dialysis was commenced and an 'early diagnosis' group who had been diagnosed >3 months prior to the initiation of dialysis. Twenty-one patients whose diagnosis had been made between 1 and 3 months before the commencement of dialysis was excluded from the analysis. The main clinical features of the late diagnosis group at presentation were dyspnoea/pulmonary oedema (41%), severe hypertension (26%), severe asthenia (22%) and apathy/mental changes (8%). The rate of pulmonary infections (17.9% vs 5.1%,  $P < 0.01$ ) and mean systolic blood pressure ( $172 \pm 4$  mmHg vs  $161 \pm 4$  mmHg) were significantly higher in the late diagnosis group. All patients in the late diagnosis group required a CVC for initiation of dialysis. In the early diagnosis group, 33% of patients had a vascular access created electively. Creatinine clearance at the time of initiation of dialysis was significantly lower in the late dialysis group ( $4.4 \pm 0.5$  mL/min vs  $6.4 \pm 0.5$  mL/min,

$P < 0.01$ ). Survival at 6 months was significantly decreased (69% vs 87%,  $P < 0.01$ ) and the risk of death was 2.77 times higher in the late dialysis group. In multivariate analysis, the most significant predictors of poor outcome were age, intercurrent pulmonary infection and low serum albumin at the commencement of dialysis.

In Ratcliffe *et al.*'s retrospective review of characteristics of all patients accepted for dialysis in the Oxford Unit in 1981, criteria for commencement of dialysis were uraemic symptoms associated with a creatinine clearance less than 6 mL/min.<sup>31</sup> Thirty-two patients were referred >1 month (early diagnosis group) and 23 patients were referred <1 month (late diagnosis group) before the commencement of dialysis. In the early referral group, 91% of patients commenced dialysis electively, 72% had a functioning fistula at the time of initiation of dialysis and 22% were commenced on continuous ambulatory peritoneal dialysis. Only two patients required initiation of dialysis via a CVC. In the late referral group, 39% of patients commenced haemodialysis via a CVC. 'Serious complications', which significantly prolonged the length of stay in hospital, were significantly more frequent in the late diagnosis group (70% vs 9%,  $P < 0.001$ ).

Jungers *et al.* retrospectively reviewed records of 250 patients who commenced dialysis at the Necker Hospital between January 1988 and December 1990.<sup>32</sup> The records of patients who required emergency dialysis and who had been referred within 4 weeks of commencing dialysis were identified. Of the total cohort, 25% were in this late referral category. From these patients, 20 records were randomly selected and compared with a control group of 20 age- and sex-matched patients who had been regularly followed up at the renal clinics for at least 6 months prior to the commencement of dialysis. In the early referral group, all patients had elective placement of vascular access and had completed hepatitis B vaccination several months in advance of commencing dialysis. In the late referral group, 15 patients required commencement of dialysis via a temporary central venous access, pulmonary oedema was present in 13 patients and malignant hypertension was present in three patients. The later referral group was characterized by more severe biochemical and haematological markers of uraemia such as higher serum creatinine and phosphate concentrations and lower creatinine clearance, serum bicarbonate, calcium and haemoglobin. Systolic and diastolic blood pressures were also significantly higher in the late referral group. The duration of hospitalization ( $33.2 \pm 13.1$  days vs  $5.7 \pm 1.1$  days,  $P < 0.001$ ) and the cost of hospitalization were significantly higher in the late referral group.

Ellis *et al.* in 1998 reported a retrospective review of all patients who developed ESKD and who were accepted for renal replacement therapy (RRT) at Kings College, London over a 2-year period from 1 January 1996 to 31 December 1997.<sup>33</sup> Sixty-four patients were regarded as late referral (<12 weeks prior to commencing RRT) and 134 patients were classified as early referral (>12 weeks prior to starting RRT). In the late referral group, there was objective evidence of renal disease for at least 8 weeks in 50% of patients and 22% of patients had evidence of renal disease for at least

1 year prior to the time of referral. Suboptimal management of CKD prior to referral to the nephrology service was common. Only 33% of diabetic patients were treated with an angiotensin-converting enzyme inhibitor and 49% of patients with CKD and hypertension had inadequate control of blood pressure at the time of referral to the nephrology service. The length of hospitalization was significantly longer in the late referral group (25 vs 9.7 days,  $P < 0.001$ ). However, there was no difference in mortality between the early and late referral groups (12-month survival: 60.5% vs 72.5%).

Khan *et al.* in 1995 reported factors associated with early mortality on dialysis in a retrospective, case-control study of patients being dialysed at a single centre in Aberdeen (UK) between 1 January 1971 and 6 January 1993.<sup>34</sup> Forty-two patients who died within 90 days of the commencement of haemodialysis were compared with age- and sex-matched patients who survived longer than 90 days. In the early mortality group, there were a higher proportion of patients who required urgent dialysis (79% vs 21%,  $P < 0.05$ ) and there was a shorter period of predialysis management (1.1 vs 10.6 months,  $P < 0.0001$ ). A greater prevalence of arteriosclerosis, comorbid illness and smoking and a lower mean serum albumin (31.4 vs 37.1 g/L,  $P < 0.006$ ) were also identified in the early mortality group.

A similar experience was reported by Innes *et al.* in a retrospective analysis of 44 patients who died within 1 year of starting dialysis compared to 44 age- and sex-matched patients who survived more than 1 year. Patients in the early mortality group were characterized by later referral to a nephrologist (median 36 days prior to dialysis) compared with the good prognosis group (median 30 months prior to dialysis).<sup>35</sup>

In a retrospective review of patients commencing dialysis in a metropolitan New York hospital, Ifudu *et al.* in 1996 reviewed the outcomes of 139 patients who had been commenced on dialysis between January 1990 and December 1994. Patients were stratified according to whether they had received predialysis care from a nephrologist (43% of cohort) or a non-nephrologist physician (45%) or had received no predialysis medical care (12%).<sup>36</sup> Patients who had a period of predialysis care by a nephrologist had a significantly reduced need for emergency central venous access (36% vs 69% vs 100%, nephrologist vs non-nephrologist vs no care,  $P = 0.0001$ ) and reduced length of hospital stay for the initiation of dialysis ( $12 \pm 23$  days vs  $25 \pm 21$  vs  $29 \pm 23$  days, respectively,  $P = 0.002$ ). Patients who had received predialysis care from a nephrologist were characterized by a lower mean serum creatinine and less severe acidosis than the other two groups at the time of commencement of dialysis.

Abdulkader *et al.* looked at risk factors for hospital death of patients with CKD who were first reviewed by a nephrologist as an emergency in-hospital referral.<sup>37</sup> A total of 414 patients were seen in a tertiary hospital in São Paulo in Brazil. Mortality was 13%. Non-survivors were older, required ventilation and inotropic support, had a higher rate of infection and had a lower creatinine (attributed to malnutrition).

Avorn *et al.* identified 3014 patients who started dialysis in a 6-year period and who were known to have renal disease more than 12 months prior to commencement.<sup>38</sup> There was a 37% increased mortality rate at 1 year in those who had not seen a nephrologist until 90 days or less before starting dialysis. Similarly, those who saw a nephrologist 5 times or less in the 12 months preceding dialysis had a 15% higher mortality rate than those seen more than 5 times.

Avorn *et al.*, in a similar cohort of 2398 patients with a diagnosis of renal disease at least 1 year before initiation of dialysis, showed that those who had seen a nephrologist more than 90 days prior to starting dialysis were 38% more likely to have undergone predialysis access surgery (OR 1.38, 95% CI: 1.15–1.64).<sup>39</sup> Late referral patients were more likely to start dialysis with temporary vascular access (OR 1.42, 95% CI: 1.17–1.71).

Cass *et al.*, in an Australian study using ANZDATA, showed that late referral (<3 months) reduces access to transplantation.<sup>40</sup> A total of 3310 patients were studied, of whom 892 were referred late. These patients had more comorbidities and were more likely to have diabetic nephropathy. Adjusting for variables including age and comorbid conditions, they had an OR of listing on the transplant list of 0.49 (95% CI: 0.41–0.59) and were less likely to receive a transplant (HR 0.65, 95% CI: 0.55–0.77). This was most evident in the first 3 months; however, the transplant rate remained lower throughout the course of RRT.

Castellano *et al.* in a retrospective analysis of 117 patients showed that patients with an unplanned initiation of dialysis had a lower incidence of permanent vascular access (3.8% vs 83.1%) and higher rate of hospitalization at initiation of dialysis (90.4% vs 6.1%) as well as longer duration of hospitalization and worse biochemical indices.<sup>41</sup> However, there was no statistically significant difference in mortality at 6 months.

Cooper *et al.* studied a retrospective cohort of 134 patients.<sup>42</sup> Twenty-six started dialysis with a creatinine clearance >10 mL/min and 108 with a creatinine clearance <10 mL/min. The late start group had lower total body nitrogen (a marker of nutritional status) as well as serum albumin. There was a direct correlation between renal function and total body nitrogen.

Devins *et al.* collected follow-up data on 335 patients with CKD who had participated in an RCT of predialysis psychosocial intervention from the 1980s.<sup>43</sup> Mean duration of follow up was 8.5 years. Median survival was increased by 2.25 years in patients who received this intervention (HR 1.32, 95% CI: 1.0–1.74) and survival after initiation of dialysis was increased by 8 months (HR 1.35, 95% CI: 1.02–1.775). Early referral *per se* had no survival benefit.

Gallego *et al.* studied 106 patients who were referred early (>6 months) and 33 referred late.<sup>44</sup> Late referrals had increased early mortality, hospitalization and emergency dialysis. Long-term survival, however, did not differ between the two groups.

The GIMEP group from Italy published a study in 2002 of 1137 patients starting dialysis. This showed that 89% of 616 early referral patients had permanent access at the time of dialysis commencement and 44% started with peritoneal

dialysis.<sup>45</sup> In contrast, only 0.8% of 521 late referrals (<2 months prior to initiation of dialysis) had permanent access and only 9.1% started with peritoneal dialysis. Of interest, units with a structured predialysis education programme had a greater number of patients starting with permanent access and on peritoneal dialysis.

Gøransson and Bergam performed a retrospective study of 242 patients commencing RRT.<sup>46</sup> Early referral was defined as >3 months, and late referral as <3 months, prior to initiation of dialysis. Patients were further stratified into three groups, depending on the years in which they started dialysis. Late referral patients were older, had worse biochemistry and were less likely to be taking medications for hypertension and calcium-phosphate control. Forty-three per cent of early referral patients started dialysis with an AV fistula whereas all late referral patients commenced with temporary venous access. Duration of hospitalization was prolonged in the late referral group (31 days) compared with 7 days in the early referral group. Mortality at 3 months did not differ between the two late and early referral groups.

Heaf studied 255 dialysis patients and 64 predialysis patients in an attempt to create an algorithm to allow optimal timing of predialysis access.<sup>47</sup> Acute dialysis was associated with increased hospitalization (17.9 vs 9.0 days) and mortality at 90 days (14% vs 6%). In a subsequent prospective study of 178 patients, use of the algorithm led to increased dialysis access placement and reduction in acute dialysis from 50% to 23%.

Holland and Lam studied a retrospective cohort of 201 predialysis patients.<sup>48</sup> Independent predictors of in-hospital dialysis initiation were age (OR 1.038, 95% CI: 1.011–1.065), congestive heart failure (OR 2.877, 95% CI: 1.205–6.871) and shorter predialysis follow-up time (OR 0.945, 95% CI: 0.920–0.971). Every month lost due to late referral increased the risk of in-hospital commencement of dialysis by 5.5%.

Jones *et al.* reviewed the GFR decline of 726 new patients with CKD stages 3–5 referred over a 6-year period.<sup>49</sup> The rate of decline slowed from 5.4 mL/min per 1.73 m<sup>2</sup> per year to 0.35 mL after nephrological referral. This was associated with a reduction in blood pressure and improved survival (HR 0.55, 95% CI: 0.40–0.75).

Khan *et al.* analysed a retrospective cohort of 109 321 US Medicaid/Medicare patients who started dialysis between 1995 and 1998.<sup>50</sup> Only 50% had received nephrological care in the 24 months preceding dialysis. Higher mortality was associated with age and visits to generalists and non-renal specialists. Compared with patients with three or more 'months of nephrology care' in the 6 months preceding commencement of dialysis, mortality was increased in those with no nephrological care in the 24 months preceding dialysis (HR 1.51), no care in the 6 months preceding dialysis (HR 1.28) and only 1–2 'months of nephrology care' in the 6 months prior to dialysis initiation (HR 1.23).

Ledoux *et al.* defined late referral as presentation to nephrology services less than 3 months prior to starting dialysis.<sup>51</sup> In their cohort of 62 patients, biochemical indices were worse and initial duration of hospitalization increased

in late referrals, however, 4-year mortality was not increased.

Lenz *et al.*, in a retrospective study of 170 patients starting dialysis, found that 92% started with temporary venous access.<sup>52</sup> Absence of adequate predialysis care, failure to recover from acute renal failure and non-compliance with scheduled clinic appointments were the main reasons for this. He further suggested that the velocity of eGFR loss rather than a given level of renal impairment may be a better trigger for access referral.

Lhotta *et al.* divided a cohort of 75 patients into 33 early referral and 42 late referral (defined as GFR <20 mL/min per 1.73 m<sup>2</sup>).<sup>53</sup> Late referred patients had higher comorbidity. By univariate analysis, comorbidity and age were significantly associated with mortality, whereas in multivariate analysis, only comorbidity was associated with higher 2-year mortality. Late referral was associated with reduced survival but only with univariate analysis and did not reach statistical significance.

Lin *et al.* studied 115 patients with type 2 diabetes mellitus commencing dialysis.<sup>54</sup> Of these, 53 were early referrals (seen >6 months before dialysis) and 62 late referrals. Early referred patients had better survival at 5 years (72.4% vs 35.2%,  $P < 0.05$ ) and better residual renal function ( $P < 0.001$ ).

Marron *et al.* studied 621 patients who commenced dialysis in Spain in 2002.<sup>55</sup> Permanent access at initiation of dialysis was considered as planned (49% of patients). Seventy-six per cent of patients had more than 3 months of predialysis follow up but only half of these received predialysis education. Education was associated with a planned start (73.4% vs 26%) and more peritoneal dialysis (31% vs 8.3%). Non-planned start was associated with older age, fewer nephrology visits, less education and more haemodialysis.

In 2006, Marron *et al.* also reviewed 1504 patients who commenced RRT in Spain in 2003.<sup>56</sup> Fifty-four per cent of patients had planned initiation of dialysis; they were younger, had a longer period of predialysis follow up, more predialysis education, were more likely to have permanent access and more commonly were on peritoneal dialysis (27% vs 8%) all with  $P < 0.001$ .

McLaughlin *et al.* performed an economic evaluation of early versus late referral using a Markov (decision analysis tree) model.<sup>57</sup> Early referral occurred when the creatinine clearance was 20 mL/min. In the model, early referral produced cost savings, improved survival, led to more life-years free of RRT and reduced duration of hospitalization. These findings were not reversed with a sensitivity analysis using published US and Canadian data.

Navaneethan *et al.* in a retrospective analysis of 204 patients, defined early referral as GFR >15 mL/min and late referral as <15 mL/min.<sup>58</sup> Twenty-two per cent were referred late with non-diabetic status (OR 2.42) and Charlson comorbidity index (OR 1.17) as significant associations. Not surprisingly, late referrals had worse biochemical indices and less permanent vascular access at initiation of dialysis. The late referral group had twice as many deaths but this did not reach statistical significance.

Obialo *et al.*, in a study of 460 patients, defined late referral as 1–3 months before initiation of dialysis (37%), ultra-late as <1 month (46%) and early as >3 months (17%).<sup>59</sup> Mortality (over a 4-year period) was 40% for ultra-late, 26% for late and 15% for early patients. Temporary venous catheter use was 92%, 70% and 39%, respectively. Delayed referral was associated with poor socioeconomic status, denial and lack of awareness.

Orlando *et al.* performed a retrospective study of 1553 patients and defined CKD as a creatinine of >1.4 mg/dL.<sup>60</sup> Patients with nephrology care progressed to more advanced CKD stages more slowly than those with only primary care. Survival was better in CKD stages III and IV for patients who had nephrology care (HR 0.80 and 0.75, respectively). There were insufficient numbers to analyse stage V patients.

Owen *et al.* designed and implemented a predialysis clinical pathway, which led to improved outcomes with late referrals (GFR <10 mL/min) falling from 29% to 6%.<sup>61</sup> As a consequence, median time to initiation of dialysis improved from <1 to 14 months and permanent access at the time of initial dialysis increased from 24% to 83%.

Paris *et al.* studied 1137 patients from 15 centres starting dialysis.<sup>62</sup> Early referral was defined as >2 months before initiation of dialysis. Eighty-six per cent of these had permanent access and 44% commenced with peritoneal dialysis. Units with structured predialysis education programmes had higher rates overall of permanent access (66.3% vs 48.2%) and more patients on peritoneal dialysis (40% vs 22%).

Peña *et al.* investigated 178 patients who started haemodialysis and survived at least 3 months.<sup>63</sup> Patients with acute kidney injury were excluded. Early referral was defined as >4 months before dialysis commencement (139 early and 39 late). Late referral was associated with a worse clinical and metabolic state and was an independent risk factor for mortality in the first 2 years.

Roderick *et al.* in a retrospective study of 361 patients identified 124 (35%) as late referrals (<4 months before starting dialysis).<sup>64</sup> Of these, 84 were referred <1 month before starting dialysis. There was evidence of CKD in all late referrals. Late referrals were older with more comorbidities, worse biochemistry, less permanent access, were more likely to start on haemodialysis rather than predialysis and had a higher rate of hospitalization ( $P = 0.001$ ) and death at 6 months ( $P = 0.002$ ).

Roubicek *et al.* in a study of 270 patients defined 177 as early referral (>16 weeks before the start of dialysis) and 93 as late (<16 weeks).<sup>65</sup> The late referral group had higher short-term morbidity (emergency dialysis, acute pulmonary oedema, severe hypertension, use of temporary vascular access and duration of hospitalization). However, in this retrospective study, survival at 3 months, 12 months and 5 years was the same for the two groups.

Sabath *et al.* studied 163 patients commencing predialysis with 94 defined as early referrals (>3 months before first dialysis) and 69 as late referrals (<3 months).<sup>66</sup> Early referral patients had a shorter duration of hospitalization in the first 6 months, fewer emergency catheter placements and better biochemistry and haemoglobin.

Schwenger *et al.* reviewed 280 patients. Of these, 137 were late referral (<17 weeks prior to starting dialysis) and 143 early referral (>17 weeks prior). The median time of referral was 17 weeks.<sup>67</sup> Late referred patients had a higher incidence of temporary vascular access and increased mortality at 12 months (34.2% vs 5.5%).

In a subsequent paper, Schwenger *et al.* from Heidelberg<sup>68</sup> reported on a group of 254 consecutive patients with late referral defined as less than 8 weeks before initiation of dialysis. A total of 196 patients were aged <75 years (84 late referrals and 122 early) and 58 were aged 75 years or older (35 late referrals and 23 early). The older patient group had higher 1-year mortality (31% vs 19%). Late referral was associated with greater mortality in both groups (34% vs 9% in the younger group and 42% vs 16% in the older group). The RR for death in the older group was 1.80 and 2.2 in the younger group. Because of the higher frequency of late referral in older patients this accounted for a large proportion of excess mortality.

Stoves *et al.* retrospectively studied all 1260 patients who received dialysis from 1980 to July 1999 at St James Hospital in Leeds.<sup>69</sup> Group A commenced dialysis <90 days after referral and group B >90 days. Survival at 4 months was 87% in group A and 94% in group B with survival at 1 year being 74% versus 87% and survival at 5 years being 31% versus 55%. Fewer group A patients were listed for transplantation. By multifactorial analysis, age, diabetes, serum albumin, transplant listing and time of referral were significant predictors of survival.

Wasse *et al.* used Medicare and Medicaid data from 5042 US dialysis patients to analyse reasons for persistent use of CVC 90 days after dialysis initiation.<sup>70</sup> At 90 days, 59.4% were still using a CVC, 25.4% an AV graft and only 15.2% a fistula. Age, sex, race and cardiovascular comorbidity were associated with persistence of catheter use. The authors suggested that this could be due to late access referral or primary access failure.

White *et al.* looked at another aspect of timely referral – whether or not allowing participation in a predialysis clinic could improve quality of life.<sup>71</sup> A total of 74 patients attended a predialysis multidisciplinary clinic and 46 did not. The former showed improvement in 4 of 8 physical Quality of Life scores at 6 months after start of dialysis, even when adjusted for comorbidities and other variables.

Winkelmayer *et al.* defined late referral as less than 90 days prior to starting dialysis.<sup>72</sup> Medicare and Medicaid data identified all adult patients in New Jersey who commenced dialysis between 1990 and mid-1996 (3014 patients). Late referral was associated with old age, race, lack of comorbidity and management by a general internist rather than a primary care doctor or other subspecialist.

Winkelmayer *et al.* also looked at potential associations between late referral and choice of dialysis modality.<sup>73</sup> Late referral was defined as less than 90 days before first dialysis. Timing of referral did not influence the initial dialysis modality; however, late referral patients commencing predialysis were more likely to switch to haemodialysis than early referred patients (HR 1.47).

Winkelmayer *et al.* performed a propensity analysis of late versus early nephrologist referral and dialysis mortality.<sup>74</sup> Late referral was again defined as less than 90 days before initiation of dialysis. There was a 36% excess mortality in late referrals which was, however, limited to the first 3 months (HR 1.75, 95% CI: 1.48–2.08) and was an independent risk factor for death.

Winkelmayer *et al.* further looked at the effect of late referral on access to transplantation.<sup>75</sup> A cohort of 3014 incident patients on RRT was studied. Due to the old age of this population, only 35 received a kidney transplant. Thirty-two of these were matched with 197 controls with similar comorbidity and demographic data. Late referral (<90 days) in this retrospective case–control study was associated with a significant reduction in transplantation (OR 0.22, 95% CI: 0.05–0.97). Socioeconomic status and comorbidity were also significantly associated with a reduced rate of transplantation.

Finally, Wu *et al.* analysed 52 type 2 diabetic patients commencing predialysis at his institution in Taiwan over a 2-year period.<sup>76</sup> Late referral was defined as less than 6 months before starting dialysis (36 patients) versus 16 early referrals. Survival (extended out to 5 years) was better in the early referral group (RR 0.42, 95% CI: 0.152–0.666) and was independent of age, glycaemic control and residual renal function.

## SUMMARY OF THE EVIDENCE

Most data come from retrospective studies. Prospective studies are limited and RCT unlikely due to logistic and ethical concerns. A systemic review demonstrates that late referral leads to worse patient outcomes (mortality and increased duration of hospitalization). Early referral provides the opportunity for optimal care by a nephrologist-led multidisciplinary team.

## WHAT DO THE OTHER GUIDELINES SAY?

**Kidney Disease Outcomes Quality Initiative:** In general patients with eGFR <30 should be referred, or earlier if the 'clinical action plan' cannot be carried out.

**UK Renal Association:** GFR should be calculated using the four-variable Modification of Diet in Renal Disease equation. A GFR of <15 merits immediate referral, 15–29 urgent referral and 30–59 routine referral. Patients with stage IV and V kidney disease should be discussed with a nephrologist.

**Canadian Society of Nephrology:** Measure or calculate creatinine clearance for patients with a serum creatinine of >200 µmol/L. Measure creatinine clearance by 24-hour urine collection with a concurrent serum creatinine or calculate it using the Cockcroft–Gault formula. Refer patients with a creatinine clearance of <30 mL/min to a nephrologist for opinion regarding management of renal failure.

**European Best Practice Guidelines:** No recommendation.

**International Guidelines:** No recommendation.

## SUGGESTIONS FOR FUTURE RESEARCH

Estimated GFR at the time of referral should be correlated with the time interval between referral and initiation of dialysis to suggest an optimal eGFR range to allow adequate predialysis management.

## CONFLICT OF INTEREST

Grant Luxton has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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