

Coronary artery, cerebrovascular and peripheral vascular disease

Date written: December 2008

Final submission: March 2009

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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)

- Registry data and data from observational cohort studies suggest that coexisting vascular disease, whether it be coronary artery disease (CAD), peripheral vascular disease (PVD) or cerebrovascular disease is associated with increased mortality risk for patients on dialysis. Limited studies have addressed the effect of different levels of disease severity. Dialysis itself is associated with a significantly increased risk of worsening vascular disease and nephrologists should consider these factors when a decision is being made to commence dialysis and the patient should be adequately informed regarding the outcomes in people with these comorbidities.
- Clinical awareness of increased mortality associated with PVD, coronary artery and cerebrovascular disease stresses the need for intensive management of cardiovascular risk factors prior to and during dialysis treatment.

IMPLEMENTATION AND AUDIT

No recommendation.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for cardiovascular disease, coronary disease and myocardial ischaemia were combined with MeSH terms and text words for renal replacement therapy and dialysis. The search was carried out in Medline (1950–March, Week 3, 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search/es: 2 April 2008.

WHAT IS THE EVIDENCE?

Coronary artery and cerebrovascular disease

Patients with end-stage kidney disease (ESKD) are at high risk of developing cardiovascular disease (CVD), which is

considered the leading cause of mortality and morbidity in dialysis patients, accounting for 40–50% of deaths.¹ Although there have only been a few studies of CVD in a population with mild renal insufficiency, several authors have reported an elevated prevalence of CVD in patients starting dialysis compared with the general population.^{2–5}

On admission to dialysis, patients have a high prevalence of cardiovascular risk factors. According to the Lombardy registry,⁶ it was estimated that 17.4% of the incident patients admitted to dialysis have CAD (9.8%) or myocardial infarction (7.6%). Congestive cardiac failure (CCF) was reported in the same study to be 8.3%. In the United States Renal Data System Registry (USRDS),⁷ the prevalence of CVD in incident ESKD patients should be proportionally higher, as there is a higher proportion of diabetics, however, the proportion of patients affected by ischaemic heart disease is 3 times higher (40.0%) and the proportion of patients affected by CCF is 5 times higher at 36.0%. The difference between the registries cannot be attributed to diabetes alone.

In the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) report for 2007,⁸ 4.0% of incident Australian patients have CAD, 19.0% have PVD and 13.0% have cerebrovascular disease. Similarly, the rates for incident dialysis patients from New Zealand are 13.0%, 25.0% and 15.0%, respectively. An analysis performed by Roberts *et al.*⁹ using ANZDATA looked at adult incident dialysis patients between 1992 and 2002 and followed them to the end of 2003. During this time 18 113 patients were analysed. Patients with known CVD comprised 48.0% of the cohort and the remainder had no disease. In Australia, CVD was responsible for 51.0% of deaths. The age-specific cardiovascular mortality rate for patients without CVD at baseline was 2.3 (1.9–2.8) per 100 person years in those aged 35–44 years, and increased to 11.9 (10.5–13.5) per 100 person years for patients aged 75–84 years (Fig. 1). Respectively, these patients were 121 (98–149) and 5.7 (5.0–6.4) times more likely to die a cardiovascular death than people of similar age in the general population (Fig. 1). Similar findings were demonstrated in the New Zealand cohort.

Few studies have assessed mortality rates or risk predictors in the period immediately after initiation of dialysis. These studies^{10–16} suggest an increased mortality rate in the

first 90 days; however, it is not clear if this rise is limited to the first 90 days. All-cause and cause-specific mortality were examined in an incident United States cohort who began dialysis <30 days before enrolment into the Dialysis Outcomes and Practice Patterns Study (DOPPS) and had at least 1 day of follow-up ($n = 4802$).¹⁶ The risk of death was increased in the first 120 days compared with the period 121–365 days (27.5 vs 21.9 deaths per 100 person-years, $P = 0.002$). CAD was present in 51.8% of patients, cerebrovascular disease was present in 18.5% and other CVD was present in 29.1% of patients and CCF in 44.6%. Patients with CCF were at increased risk for mortality within 120 days of starting dialysis (adjusted HR 1.71 (1.35–2.17) $P < 0.05$) but not significantly different for other cardiovascular comorbid conditions. Similarly, in the 2007 USRDS report¹⁷ for incident 2004 patients, the overall mortality rate per 1000 patient years increased from 210.8 in month one to 307.8 in month three, ultimately falling to 246.1 in month 12. Overall, 1-year mortality rates were reported to be relatively stable since the 1990s.

The USRDS data were recently used to analyse the outcomes of non-fatal myocardial infarction and cardiac death in incident dialysis patients from the years 1997–2001 ($n = 214, 890$).¹⁸ Multivariate analyses were performed employing Cox proportional hazards models using demographics, comorbidities, laboratory variables, body mass index, prior erythropoietin use and mode of dialysis. The relative risk of non-fatal myocardial infarction in patients with prior CAD compared with those without was 1.57 (95% CI: 1.5–1.65) and cardiac death was 1.16 (95% CI: 1.14–1.18). The 5-year cumulative incidence of non-fatal myocardial infarction was 8.1% and 6.0% and cardiac death was 48.3% and 40.2%, in patients with and without prior CAD, respectively.

The degree of clinical severity of each comorbid condition may also impact on patient survival; however, minimal published data are available pertaining to this issue. This could be important since new haemodialysis patients with ischaemic heart disease and class I heart disease would be equally weighted with patients with class IV disease. In a study by Varghese *et al.*,¹⁹ the clinical and angiographic findings in 158 consecutive patients (84 diabetic and 74 non-diabetic patients) with ESKD were evaluated. Only patients who were already on a maintenance dialysis programme or were being considered for transplantation were included so this was not a true incident population. Coronary angiography was indicated either because of ischaemic chest pain or as part of a routine pre-transplant evaluation. Diabetic patients had more adverse risk factors for CAD yet there was no significant difference in the prevalence of CAD between the diabetic and non-diabetic patients (67% vs 55%, $P = 0.15$), but triple vessel disease was significantly more common in diabetic patients (27% vs 12%, $P = 0.005$). The prognostic or functional significance of this finding has not been further evaluated. In a small study by Joki *et al.*,²⁰ the authors performed coronary angiography in patients with or without angina within 1 month of initiation of dialysis. These investigators found that within 2 years of initiation of dialysis, the survival rate in patients

with CAD was 60.0% compared with 100.0% in patients without CAD, implying that CAD plays a significant role in the short-term survival of diabetic haemodialysis patients.

Adequately powered prospective interventional studies that attempt to reduce cardiovascular risk factors are limited in dialysis patients and the ones that have been conducted, such as the 4D,²¹ AURORA,²² CHOIR²³ and CREATE studies, have failed to show a survival benefit. An excellent review of the role of statins in dialysis patients was recently conducted by Navaneethan *et al.*²⁴ and ongoing adequately powered studies such as the SHARP study²⁵ should provide more insights into the efficacy of statins in reducing mortality rates in dialysis patients. Furthermore, the potential mechanisms underlying the deleterious outcomes associated with efforts to correct renal anaemia remain unproven, and the CHOIR and CREATE studies highlight the potential adverse effects of exposure to high doses of erythropoietic stimulating agents.

The question also arises whether adequate risk factor intervention exists in this population. Dialysis patients may have different needs than patients with CVD and no renal impairment. Herzog *et al.*²⁶ showed a significant early survival advantage for dialysis patients who received coronary bypass grafting using an internal mammary artery, compared with saphenous vein grafting. This advantage was present in all-cause mortality (ACM) as well as in cardiac mortality (CM). Furthermore, after evaluating more than 5000 dialysis patients who had aortic, mitral, or combined aortic/mitral valve replacements and comparing survival, Herzog *et al.* showed that the Kaplan–Meier all-cause survival was not different between the non-tissue and tissue-based valve replacement patients. Cardiac death was also indistinguishable between the two groups, suggesting that the use of bio-prosthetic valves may be indicated to reduce the requirements for anti-coagulation and potentially reduce haemorrhagic complications.

The presence of cerebrovascular disease in long-term haemodialysis patients is associated with significant morbidity and mortality. In DOPPS, approximately 18.0% of patients undergoing dialysis in the United States had a history of CVD, defined as stroke, transient ischaemic attack or carotid endarterectomy.²⁷ Seliger *et al.*²⁸ analysed the USRDS and National Hospital Discharge Survey data, and determined there was a 4- to 10-fold increased risk of either an ischaemic or haemorrhagic stroke in dialysis patients compared with the general population. The presence of CVD was also found to be an independent predictor of subsequent death in European, Japanese and US dialysis patients²⁷ and in this population, the 2-year mortality rate after a stroke is 64.0%.²⁹

Peripheral vascular disease

Compared with other forms of CVD, relatively little attention has been given to the overall prevalence of PVD in patients with ESKD and its effect on long-term prognosis. A large international cohort of patients on haemodialysis was recently evaluated by the DOPPS team.³⁰ This prospective,

observational study of 29 873 haemodialysis patients involved both DOPPS I and DOPPS II and detailed descriptions of the DOPPS design have previously been published.³¹ A prevalent cross-section population was initially chosen and with the exception of only 3722 patients that were new to haemodialysis, the remainder of patients were prevalent patients. The total sample was thus a predominantly prevalent population. Associations between baseline clinical variables and PVD were evaluated by logistic regression analysis and Cox regression models were used to test the association between PVD and risk for ACM, CM and hospitalization. At baseline, PVD was defined as including at least one of the following conditions: (1) prior diagnosis of PVD; (2) intermittent claudication; (3) critical limb ischaemia encompassing rest pain, skin necrosis and gangrene, including recurrent skin infections; (4) surgical revascularization for PVD; (5) amputation for PVD; and (6) aortic aneurysm or surgery for aortic aneurysm.

The prevalence of PVD in the total population was 25.3%, but there was significant geographic variation among the 12 DOPPS countries, from 12.0% in Japan to 38.0% in Belgium and 32.7% in Australia and New Zealand. Significant correlates of PVD included age, male sex, diabetes, hypertension, smoking and duration of haemodialysis. PVD patients had a significantly higher risk of ACM (HR 1.36, $P < 0.0001$) and CM (HR = 1.43, $P < 0.0001$). These results were consistent across the regions, but in Japan both patients with and without PVD had a better survival than their counterparts in Europe and the United States. The effect of diagnosis of PVD on survival in haemodialysis patients is shown in Figure 2 by region. Although this graph shows DOPPS II results only, DOPPS I results were similar.

A diagnosis of PVD also had a significant impact on all-cause hospitalization (HR = 1.19, $P < 0.0001$) and hospitalization for a major cardiovascular event (HR = 2.05, $P < 0.0001$). As the investigators point out, the results are even more worrying when it is considered that the increased risk in mortality and morbidity in patients with PVD was also seen in patients without prior CVD and despite a higher use of statins and aspirin in this group (21.8% vs 12.9%, $P < 0.001$, and 33.5% vs 20.0%, $P < 0.0001$), respectively. Although this study has limitations which the authors acknowledge, it highlights that a subgroup of patients may benefit from aggressive therapeutic intervention.

The incidence of PVD is not well known in patients with diabetes mellitus but it is presumed that diabetic patients have an increased risk of PVD. In a recent Japanese study, 613 incident haemodialysis patients were divided into two groups: patients with diabetes mellitus ($n = 342$) and without diabetes ($n = 271$).³² These patients were screened with ankle-brachial pressure index (ABI) measurements annually. If the ABI was abnormal or they had ischaemic symptoms, ultrasonographic and/or angiographic examinations of the lower limbs were performed. During the follow-up period (51 ± 33 months), 20.0% of patients had PVD and 3.0% underwent amputation. Eight-year event-free survival for PVD and amputation was significantly lower in diabetic patients than for those without diabetes (67.0% vs 90.0%, $P < 0.0001$; 92.0% vs 98.0%, $P = 0.018$, respectively). On

Cox multivariate analysis, diabetes was a strong predictor for PVD (HR 7.04, 95% CI: 2.99–16.67, $P < 0.0001$) and for amputation (HR 8.54, 95% CI: 1.03–71.42, $P = 0.046$). However, there were no differences seen in the 8-year event-free survival for amputation (84.0% vs 88.0%, $P = 0.24$) and in death (46.0% vs 61.0%, $P = 0.75$) for patients with PVD who underwent revascularization, suggesting that interventions at an earlier stage of PVD may improve clinical outcomes even in patients with diabetic ESKD.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

There is a need for further prospective interventional studies to improve outcomes and to develop strategies for the identification and treatment of clinically silent cardiovascular disease in patients starting dialysis.

CONFLICT OF INTEREST

Eugenie Pedagogos 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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APPENDICES

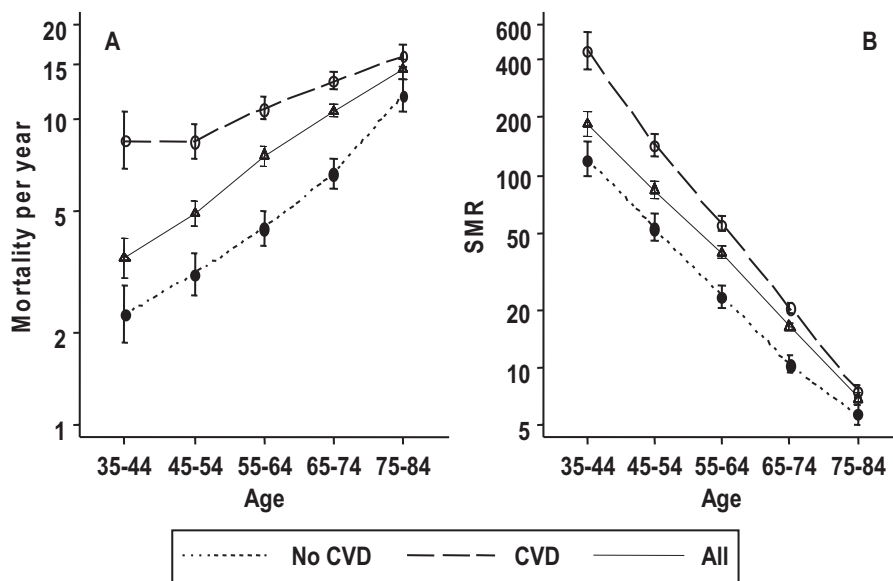


Fig. 1 Australian patients stratified by the presence of clinically evident cardiovascular disease (CVD) on starting dialysis. Panel A shows the age-specific cardiovascular mortality rates and panel B shows the age-specific standardized mortality ratio (SMR) for cardiovascular death. Source: ANZDATA Registry.⁹

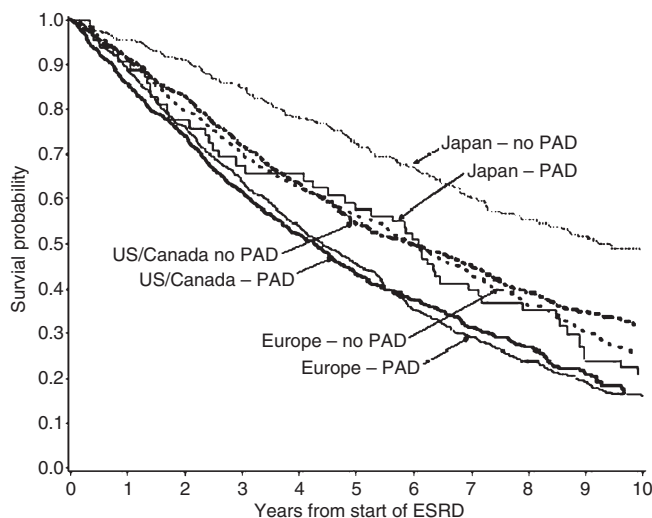


Fig. 2 Adjusted survival curves based on mean covariate values for the DOPPS II United States/Canada ($n = 4158$), Europe ($n = 6395$), and Japan ($n = 2286$) PAD and non-PAD patients. Adjusted Cox regression model was based on time from end-stage renal disease (ESRD) and left-truncated at study entry. The model was stratified by PAD and region to adjust for differences in the baseline hazard function across time for each stratum level. Source: Reproduced with permission. Rajagopalan *et al.* Peripheral arterial disease in patients with end-stage renal disease: Observations from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Circulation* 2006; **114**: 1914–22.