Port J Nephrol Hypert 2014; 28(1): 13-19
Advance Access publication 24 February 2014

The Initiation of Dialysis: As Good as It Gets!

André Fragoso, Ana Paula Silva, Pedro Leão Neves

Department of Nephrology, Centro Hospitalar do Algarve. Faro, Portugal

Received for publication: 23/01/2014
Accepted: 27/01/2014

ABSTRACT

The quality of pre-dialysis care of chronic kidney patients has been shown to be associated with the outcome after renal replacement therapy. Referral to the nephrologist should be done on time. The renal care team has the best expertise to prepare patients to start dialysis, treat progression factors and complications of end-stage renal disease. The initiation of dialysis must be prepared and decided previously, and the choice of the dialysis modality discussed with the patients and their families, whenever possible. The establishment of a permanent dialysis access is crucial. The renal function at which patients must start treatment is under discussion. Probably the medical related conditions are more important than the level of renal function itself.

Keywords: Chronic kidney disease; dialysis initiation; pre-dialysis care.

RESUMO

A qualidade dos cuidados pré-diálise está associada com a morbilidade e mortalidade dos doentes, após o início da terapêutica de substituição renal. A referenciação aos Serviços de Nefrologia deve pois ser atempada. As equipas de Nefrologia são as mais capazes no sentido de preparar os doentes para a terapêutica dialítica, tratar os fatores de progressão da doença renal crónica e as complicações da doença renal crónica avançada. O início de diálise deve ser preparado e decidido previamente e, sempre que possível, a escolha da modalidade de tratamento discutida com o doente e a sua família. A construção de um acesso de diálise permanente é fundamental. O nível de função renal com a qual se deve iniciar terapêutica dialítica é motivo de atual de discussão. Seguramente que as morbilidades associadas à doença renal crónica terão maior relevância em termos de resultados, do que a função renal por si só.

Palavras-Chave: cuidados pré-diálise; doença renal crónica; início de diálise.

INTRODUCTION

The best timing for dialysis initiation has been subject of concern within the nephrology community in the last decades. Despite the advances in the treatment of end-stage chronic renal disease (ESRD), evidence from clinical practice has demonstrated that the morbidity and mortality rates remain high[1].

More important than time, in terms of glomerular filtration rate (GFR), is the patient's health condition that defines survival[2]. Early referral to the nephrologist and the type of vascular access at the beginning of renal replacement therapy (RRT) are relevant factors associated with survival [3,4].

The aim of this article is to discuss the appropriate time to start dialysis. It will be also suggested the way patients must be cared for to start dialysis in the best conditions and discussed the appropriate modality options.

BEFORE DIALYSIS

Dialysis gives an opportunity to chronic kidney disease (CKD) patients to extend their lives, despite an overall mortality far in excess of the general population[5]. Ideally, patients in advanced stages of their disease should be adequately prepared for dialysis. Therefore, a timely referral to nephrology is crucial, since an early referral and the quality of pre-dialysis care have been strongly correlated to the outcome after beginning RRT[5-7].

The definition of early referral varies in the literature from 1 to more than 12 months prior to RRT[4]. The *Kidney Disease Outcomes Quality Initiative* (KDOQI) guidelines recommend consultation and/or co-management with a kidney disease care team during CKD stage 3 and referral to a nephrologist in stage 4[8]. In our opinion, referral of CKD patients to the nephrologist should be done earlier, at stage 3, since these patients already need specialized nephrology care[4]. Indeed, nephrologists have better expertise to prepare patients for RRT, treat progression factors and also complications associated with advanced CKD[9]. More recently, *Kidney Disease: Improving Global Outcome* (KDIGO) guidelines also identified several factors associated with CKD progression that we should not overlook, such as the cause of CKD, level of GFR, albuminuria, age, sex, ethnicity, elevated blood pressure, hyperglycaemia, dyslipidaemia, smoking, obesity, history of cardiovascular disease and ongoing exposure to nephrotoxic agents[10].

Several studies also have shown that frequent[6,9] and optimal pre-dialysis care are associated with improved short- and long-term survival, being a valuable cost-effective measure to improve outcomes[9,11]. Conversely, late referral, generally defined as less than 1 to 4 months prior to RRT initiation[9], was shown to be an independent risk factor for early mortality on dialysis[9] and is also associated with greater morbidity, lower quality of life, increased costs and duration of hospital stay, more temporary vascular access, increased need for urgent dialysis and suboptimal management of end-stage renal disease and its systemic consequences[4,9,12,13]. In our department, there is a specialized pre-dialysis programme, with a multidisciplinary team, aimed at an integrated preparation to RRT in patients already in CKD stage 4 or 5. In our experience, patients followed in this programme start dialysis in better health condition and more often with a definitive vascular access (unpublished data).

Early care will also retard CKD progression, delaying the onset of RRT by correcting several factors associated with a faster progression of CKD abnormalities, such as hypertension and proteinuria[6,9]. There are other factors, such as anaemia, hyperuricaemia and mineral abnormalities, whose control is not obviously proven to retard renal insufficiency[10].

To prevent CKD progression and lower the cardiovascular risk, KDIGO guidelines propose a multifactorial intervention with angiotensin-receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) in diabetic adults with CKD and urine albumin excretion ≥ 30 mg/24 hours, or in non-diabetic adults with CKD and urine albumin excretion ≥ 300 mg/24 hours[10]. Those guidelines also advise that in the presence of micro-albuminuria the blood pressure target should be lower (BP < 130/80 mmHg)[10].

From a nutritional point of view, a reduced protein intake (0.8g/Kg/day) is recommended in CKD stages 4 and 5[10]. In diabetic patients, to delay the progression of micro vascular complications, a target

haemoglobin A1c about 7% is advised[10]. However, a higher target is tolerated in patients with co-morbidities or limited life expectancy and risk of hypoglycaemia[10]. KDIGO also recommend lowering salt intake to 2g per day of sodium unless contraindicated[10]. The use of statins, in earlier stages of CKD, has also been shown to decrease cardiovascular mortality after dialysis initiation, but the slowing down of renal failure is not obvious, with these agents, in randomized controlled trials[14]. There is insufficient evidence that lowering serum uric acid slows the progression of CKD, and, in consequence, the use of these agents is not recommended[10].

In our unit, those nutritional targets described above are achieved with the support of a nutritionist integrated in the multidisciplinary team. We follow the KDIGO recommendations and our patients receive expert dietary advice and information in the context of an education programme, tailored to the severity of CKD[10]. Lifestyle changes are not forgotten and physical activity compatible with the cardiovascular status and tolerance is encouraged. We also strongly advise against smoking habits and encourage smokers to attend the tobacco cessation clinic.

There are several complications associated with loss of kidney function, anaemia, mineral bone changes and cardiovascular complications being the most important issues that must be managed by the pre-dialysis team[9]. The prevalence of anaemia increases as GFR declines[10], contributing to left ventricular failure, congestive heart failure, cognitive impairment and lower quality of life[9]. In the last 30 years, a major transition occurred in the treatment approach of CKD-related anaemia. The advent of erythropoietin therapy was a remarkable breakthrough regarding the management of CKD patients[10]. Nevertheless, the appropriate haemoglobin target, in pre-dialysis stages, is still under discussion. Recent studies have consistently shown that the normalization of haemoglobin level may have detrimental effects[9] and, consequently, erythropoietin should be used only when haemoglobin is lower than 10 g/dl and discontinued when haemoglobin rises above 11.5g/dl[10].

Chronic kidney disease-mineral bone disorder is a systemic condition characterized by abnormalities in bone and mineral metabolism and extra-skeletal calcifications that can cause fractures, bone pain, vascular calcification, cardiovascular disease, and ultimately, death[9]. KDIGO guidelines suggest the regular evaluation of phosphorous, calcium, vitamin D and parathyroid hormone (PTH) levels in stages 3 to 5 of CKD[10]. It is also recommended that phosphorous and calcium levels should be maintained in the normal range. Regarding PTH, its optimal level is not known and the prescription of vitamin D supplements or analogues is not advised in CKD patients not on dialysis, in the absence of suspected or documented deficiency[10].

Cardiovascular disease must be a matter of great concern when dealing with CKD patients. It is the main cause of morbidity and mortality in dialysis patients[9].

Hypertension, a cause and consequence of CKD, must be preferentially managed with an ACEI or ARB, as these drugs show clear benefits, regarding the progression of renal failure and cardiovascular outcomes[10]. We also suggest a thorough cardiovascular assessment, if possible, since it will save time if the patient is a candidate for kidney transplantation. This cardiovascular evaluation is also easier to be performed before the dialysis initiation.

In the pre-dialysis programme it is also necessary to educate the patient regarding potential nephrotoxic agents like non-adjusted or prescribed medications, metformin, antibiotics, non-steroid anti-inflammatory drugs and radio contrast agents, among others[10].

Chronic kidney disease patients also have more risk of infection and KDIGO guidelines recommend annual influenza vaccine, polyvalent pneumococcal vaccine and immunization against hepatitis B[10]. This last immunization shows greater success when done in the pre-dialysis period[15].

Preparation for dialysis should begin early enough to inform patients about the available modalities, their risks and benefits[16]. The establishment of a permanent functioning access is crucial. In peritoneal dialysis (PD), timely insertion of a peritoneal catheter with adequate PD training is required, and in patients choosing haemodialysis (HD), early creation and maturation of an arteriovenous vascular access is mandatory, when possible[11,12,16-18]. The arteriovenous fistula is considered the vascular access of choice[8,10], since it confers benefits, after HD initiation, in terms

of morbidity and mortality. Central venous catheters are associated with significantly higher rates of infectious complications, as well as more long-term non-infectious complications, compared with permanent vascular access[7].

The two dialytic modalities, HD and PD, show a considerable variety of distribution both within and between different countries[19,20] suggesting a strong influence of non-medical factors[20,21]. In the United States, the current modality split is approximately 93% HD and 7% PD[17]. In Portugal, the distribution is similar with 9.5% of CKD patients on PD in 2012 (Portuguese Society of Nephrology Registry).

Although PD continues to be underutilized in many countries[18], starting patients on PD as their initial treatment modality seems to be appropriate. The concept "PD first" implies that, when feasible, PD should be offered as the first dialytic modality[18]. Peritoneal dialysis and haemodialysis should be considered complementary rather than opponent techniques. It must be kept in mind the long-term goals of the patient[18,22], and PD as the initial treatment modality seems appropriate for several reasons. It preserves better residual renal function[21], has the convenience of home therapy, has a flexible schedule, increases freedom and improves quality of life[18]. Dialytic therapies still inflict a tremendous burden on health care resources around the world and PD has shown to be less expensive than HD as the initial renal replacement modality choice in most countries[17,21]. Nephrologists should take into account all the advantages and disadvantages of both PD and HD, in order to best meet the needs of the patient. Such a balanced approach will lead to longer patient survival, with improved quality of life at a lower cost[22].

It is important to notice that older age should not have a crucial importance in the choice of the dialytic modality. In fact, surveys have shown that age *per se* is not a contraindication for PD – In older patients it can provide better hemodynamic stability, steady-state metabolic control and hypertension control. On the other hand, permanent vascular access can be problematic in the elderly. However, the associated morbidity and social conditions that go along with ageing can make home dialysis more difficult. The dialysis modality choice in elderly patients should be individualized, dependent on the co-morbidity, cognitive function, social support and functional status[23].

In our region, Algarve, we achieved 12% prevalence on peritoneal dialysis in the year 2000, but nowadays, although the continuous efforts of our renal team in "Low Clearance" clinic, we only have 5% of patients on PD. This low prevalence in PD is probably related to the high prevalence of old patients without familiar or social support and, in contrast, our sunny coastal region takes away the younger patients from this modality for social and leisure reasons.

WHEN TO START DIALYSIS

In recent years, the appropriate moment to begin dialysis treatment has been the object of debate in the nephrology literature. This discussion involves not only time in terms of renal function, but also time in terms of patient morbidity.

Dialysis therapy evolved from a lifesaving therapy, in the 1960s, to a true chronic therapy that prolongs the life of chronic kidney patients with an acceptable quality[24]. At the same time, the better availability of treatment, the increased population longevity and the Western diabetes and hypertension pandemic, contributed to the huge increment of patients on dialysis therapy, since the early days.

The right time to start dialysis has been a matter of debate, not only due to its possible relationship with morbidity and mortality, but also for economic reasons[25,26].

The advantages of an early start were first proposed by Bonomini and colleagues in the late 1970s[27]. In their study, patients that initiated RRT with higher glomerular filtration rate (GFR), showed a 12-year better survival (77% vs. 51%). However, the authors did not adjust the survival rate for age and comorbidities. These results have been confirmed by Korevaar and co-workers[28]. These investigators found an increased risk, not statistically significant, for late starters (75% vs. 84% survival), with an adjusted HR of 1.66 (CI0.95 – 2.66). On the contrary, some authors also showed that early starters have lower survival[29-31]. In a retrospective study, including patients (n = 275) followed after an estimated GFR of 20 ml/min, Traynor *et al.* verified that early dialysis starters had an increased risk of death (HR, 1.1)[29]. Also in a retrospective analysis, using the US Renal

Data System database, from 1995 to 2006, Wright *et al.* divided the population into two groups: those who started dialysis with an estimated (eGFR) › 15 ml/min (n = 99 231) and those who began with an eGFR ‹ 5 ml/min (n = 113 510). Compared with the reference group (GFR › 5 and ‹ 10 ml/min), the early starters showed an increased mortality (HR, 1.44) and the late starters a decreased mortality (HR, 0.88)[30]. Finally, in a review article, Rosansky *et al.* examined US dialysis data and publications relevant to the early vs. late start phenomenon. They concluded that mortality while on dialysis therapy may be higher in those subjects with early start and that the comorbidities present at the time of dialysis initiation do not appear to be a major driving force for early start patients[31]. In their opinion, comorbidities in the early start group also do not explain the excess in mortality[31].

Notwithstanding, the evidence demonstrates that patients initiate RRT at higher GFRs, in the last decades[32]. The percentage of starters with GFR › 10 ml/min in diabetic and non-diabetic patients rose from 25% to 55% and from 16% to 48%, respectively, between 1996 and 2008 in the USA[33]. In Canada, between 2001 and 2007, the mean estimated GFR, at the beginning of dialysis, increased from 9.3 to 10.2 ml/min, and the proportion of early starters (defined as those with GFR › 10.5 ml/min) increased from 28% to 36%[34]. In a study including nine European Registries, it was also found that the eGFR at the beginning of dialysis increased between 1999 and 2003, from 7.9 to 8.6 ml/min[35].

Further than these undeniable data, we must be cautious when analysing the influence of the GFR at the beginning of dialysis treatment on mortality.

First of all, most of the studies were observational or retrospective. There is one single prospective, randomized, controlled study that deserves special attention[36]. We will discuss it below. Second, the renal function (GFR) was not measured, but rather estimated in the majority of the studies. We think that this is the major limitation of all clinical studies, including the IDEAL[36]. As pointed out by Botev *et al.*, the MDRD or Cockcroft-Gault (CG) equations have limitations for correct estimation of the GFR[37]. They estimated GFR by those formulas and compared them with inulin measured GFR in 2208 patients. The performance of both formulas was evaluated in the five CKD stages. The ability of MDRD and CG equations to precisely classify the patients in stage 5, was only 60% and 43.8%, respectively. Moreover, in stage five, MDRD and CG clearly overestimated the true GFR[37]. The estimated GFR uses the creatinine in the denominator of the equation. Consequently, patients with low muscle mass will have higher estimated GFR values. Accordingly, there is an inverse relationship between muscle mass and eGFR, but not with measured GFR (mGFR)[38]. The investigators of the NECOSAD Group concluded that "estimation of GFR by equations using plasma creatinine in the denominator cannot be used for this purpose in patients with ESRD, because the effect of GFR on plasma creatinine is overruled by that of muscle mass". In view of that, it is not a surprise that measured renal function at the initiation of dialysis was not correlated with mortality, contrary to eGFR (higher levels associated with increased mortality)[38]. Third, one important bias is introduced by the fact that older patients, with higher comorbidities, start dialysis earlier[34,39]. Furthermore, in a recent meta-analysis that included 15 cohorts (n = 1,079,917), it was found that higher eGFR was associated with increased mortality, only in haemodialysis patients, not in peritoneal patients[40]. In this same analysis, conversely, in those studies that measured the GFR, early starting was associated with decreased mortality[40].

The only prospective, randomized study that addressed the question of the relationship between time of initiation of dialysis and mortality was the IDEAL study[36]. There was no difference, regarding survival, between early and late starters, in this study. Additionally there were some facts that influenced the final results. First of all, 76% of the patients randomized to the late start group began dialysis before time. Once it was used the eGFR, patients with lower muscle mass and fluid overload had necessarily higher eGFR. At the beginning of treatment, early and late starters showed an eGFR of 9.0 and 7.2 ml/min, respectively, far from the study initial targets. What could happen to the late starters if they began dialysis with an eGFR between 5 and 7 ml/min as was decided previously?

As far as we know, there is no clear evidence that GFR level at the beginning of dialysis, is independently related to morbidity and mortality. There are many observational and retrospective studies and most of them make use of an inadequate method

to measure renal function. The unique prospective, randomized study failed, possibly due to its design and/or evolution.

However, regarding the guidelines, the EBPG (European Best Practice Guidelines) and the UK guidelines recommend the initiation of treatment when the GFR is below 15 ml/min, and never to start, if possible. with a GFR ‹ 6 ml/min[41,42]. The KDOQI and CARI advocate the initiation when GFR is around 10 ml/min[43,44] and the Canadian guidelines do not propose any specific GFR value[45].

Concerning clinical indications to start dialysis, there are clear ones, known by all nephrologists, such as: fluid overload, uremic pericarditis, resistant hyperkalemia, or coagulopathy. In our opinion, it is dangerous and unethical to wait for such late uremic signs and symptoms to start dialysis treatment. There are other symptoms, like nausea, vomiting and deterioration of the nutritional status that can be used to orientate the beginning of dialysis, and are used by most nephrologists. However, nephrologists are also sensible to the GFR level and use it as an indicator to start dialysis[46]. In terms of GFR, undoubtedly it is necessary more research in the field. We do not have any objective score to measure uraemia that could be used to initiate RRT[56]. The measurement of renal function is clearly advised by EBPG, instead of eGFR. Consequently, randomized controlled studies must be carried out appropriately, without the bias introduced in the IDEAL study and using probably a composite uraemic score (clinical plus mGFR) as suggested by Tattersall and colleagues[47].

The correct time to initiate dialysis is under debate, also because of economic issues. The cost-effectiveness of early dialysis was evaluated in the IDEAL study. It was found that direct dialysis costs were clearly higher in the early start group[48]. Nevertheless, a higher total costs to the health care system of early dialysis initiation has never been demonstrated.

The purpose of this article was to discuss how patients must be cared for before dialysis and that a true alternative must be offered in terms of dialysis modality. We also gave our point of view regarding the early vs. late renal replacement therapy initiation issue. In our opinion, we should support the "PD first" concept and, at the same time, not decide to treat late based in the statement "that it is not bad and it is less expensive". The risk to select this way is to treat later (and worse) the old and the frail! Even though there are supporters of the non-dialytic management for elderly renal patients[49], the evidence, at least in terms of survival, is that dialysis is better than conservative treatment[50].

Conflict of interest statement: None declared. The results presented in this paper have not been published previously in whole or in part except in abstract form.

References

1. Foley RN, Hakim RM. Why Is the mortality of dialysis patients in the United States much higher than the rest of the world? J Am Soc Nephrol 2009;20(7):1432-1435
2. de Jager DJ, Grootendorst DC, Jager KJ, *et al.* Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA 2009;302(16):1782-1789
3. Lorenzo V, Martin M, Rufino M, Hernández D, Torres A, Ayus JC. Predialysis nephrologic care and a fuctioning arteriovenous fistula at entry are associated with better survival in incident hemodialyis patients: an observational study. Am J Kidney Dis 2004;43:999-1007
4. Cabrita A, Neves PL. Early referral: still a challenge ten years after the millenium. Port J Nephrol Hypert 2011;25(3):191-193
5. Jungers P, Massy ZA, Nguyen-Khoa, *et al.* Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. Nephrol Dial Transplant 2001;16(12):2357-2364
6. Wavamunno MD, Harris DC. The need for early nephrology referral. Kidney Int Suppl 2005;94: S128–S132
7. Saggi, SJ, Allon M, Bernardini J, *et al.* Considerations in the optimal preparation of patients for dialysis. Nat Rev Nephrol 2012;8(7):381–389
8. National Kidney Foundation: K-DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1-266
9. Sijpkens YWJ, Berkhout-Byrne NC, Rabelink TJ. Optimal predialysis care. NDT Plus 2008;1(4): iv7–iv13
10. *Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.* KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1-150
11. Karkar A. The value of pre-dialysis care. Saudi J Kidney Dis Transpl 2011;22(3):419-427
12. Owen JE, Walker RJ, Edgell L, *et al.* Implementation of a pre-dialysis clinical pathway for patients with chronic kidney disease. Int J Qual Health Care 2006;18(2):145-151
13. Marrón B, Ortiz A. Sequera P. Impact of end-stage renal disease care in planned dialysis start and type of renal replacement therapy–a Spanish multicentre experience. Nephrol Dial Transplant 2006;21(Suppl 2):ii51–ii55
14. Baigent C, Landray MJ, Reith C, *et al.* The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet 2011;377(9784): 2181–2192.
15. Grzegorzewska AE. Hepatitis B vaccination in chronic kidney disease: review of evidence in non-dialyzed patients. Hepat Mon 2012;12(11):e7359
16. Oliver MJ, Verrelli M, Zacharias JM. Choosing peritoneal dialysis reduces the risk of invasive access interventions. Nephrol Dial Transplant 2012;27(2):810–816
17. Liebman SE, Bushinsky DA, Dolan JG, Veazie P. Differences between dialysis modality selection and initiation. Am J Kidney Dis 2012;59(4):550–557

18. Chaudhary K, Sangha H, Khanna R. Peritoneal dialysis first: rationale. Clin J Am Soc Nephrol 2011;6(2):447–456

19. Foley RN. Comparing the incomparable: hemodialysis versus peritoneal dialysis in observational studies. Perit Dial Int 2004;24(3):217–221

20. Blake PG. Free modality choise: Aspiration or illusion? Perit Dial Int 2009;29(2):133-134

21. Hingwala J, Diamond J, Tangri N, *et al.* Underutilization of peritoneal dialysis: the role of the nephrologist's referral pattern. Nephrol Dial Transplant 2013;28(3):732–740

22. Thodis E, Passadakis P, Vargemezis V, Oreopoulos DG. Peritoneal dialysis: better than, equal to, or worse than hemodialysis? Data worth knowing before choosing a dialysis modality. Perit Dial Int 2001;21(1):25-35

23. Berger JR, Hedayati SS. Renal replacement therapy in the elderly population. Clin J Am Soc Nephrol 2012;7(6):1039–1046

24. Neves PL, Nunes I, Jardim J, *et al.* Qualidade de vida em hemodiálise: factores determinantes. Rev Port Nefrol Hipert 1995;9:149-161

25. Liberek T, Warzocha A, Galgowska J, Taszner K, Clark WF, Rutkowski B. When to initiate dialysis – is an early start always better? Nephrol Dial Transplant 2011;26(7);2087-2091

26. DiMicco L, Torraca S, Pota A, *et al.* Setting dialysis start at 6.0 ml/min/1.73 m2 eGFR – a study on safety, quality of life and economic impact. Nephrol Dial Transplant 2009;24(11):3434-3440

27. Bonomini V, Vangelista A, Stefoni S. Early dialysis in renal substitutive programs. Kidney Int Suppl 1978;/8):S112-S116

28. Korevaar JC, Jansen MA, Dekker FW, *et al.* When to initiate dialysis: effect of proposed US guidelines on survival. Lancet 2001;358;(9287)1046-1050

29. Traynor JP, Simpson K, Geddes CC, Deighan CJ, Fox JG. Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. J Am Soc Nephrol 2002;13(8):2125-2132

30. Rosansky SJ, Clark WF, Eggers, Glassock RJ. Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful? Kidney Int 2009;76(3):257-261

31. Wright S, Klausner D, Baird B, *et al.* Timing of dialysis initiation and survival in ESRD. Clin J Am Soc Nephrol 2010;5(10):1828-1835

32. US Renal Data Report. Am J Kidney Dis 2013 (suppl 1): e215-e228

33. US Renal Data System National Kidney Foundation. United States Renal Data System. 2007 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. *Am J Kidney Dis* 2008; 51: S1–S304

34. Clark WF, Na, Rosansky SJ, *et al.* Association between estimated glomerular filtration rate at initiation of dialysis and mortality. CMAJ 2011;183(1):47-53

35. Stel VS, Dekker FW, Ansell D, *et al.* Residual renal function at the start of dialysis and clinical outcomes. Nephrol Dial Transplant 2009;24:3175-3182

36. Cooper BA, Brangley P, Bulfore L, *et al.* A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 2010;363(7):609-69

37. Botev R, Mallié J-P, Couchoud C, *et al.* Estimating glomerular filtration rate: Cockcroft-Gault and Modification of Diet in Renal Disease formulas compared to renal inulin clearance. Clin J Am Soc Nephrol 2009;4(5):899-906

38. Grootendorst DC, Michels WM, Richardson JD, *et al*, for the NECOSAD Study Group. The MDRD formula does not reflect GFR in ESRD patients. Nephrol Dial Transplant 2011;26(6):1932-1937

39. Lassalle M, Labeeuw M, Frimat L, *et al*, for REIN Registry. Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival. Kidney Int 2010;77(8):700-707

40. Susantitaphong P, Altamimi S, Ashkar M, *et al.* GFR at Initiation of dialysis and mortality in ckd: a meta-analysis. Am J Kidney Dis 2012;59(6):829-840

41. Dombros N, Dratwa M, Feriani M, *et al.* European best practice guidelines. 2 The initiation of dialysis. Nephrol Dial Transplant 2005;20 [Suppl 9]: ix3-ix7

42. Kelly S, Stanley M, Harris D. The CARI Guidelines. Level of Renal Function at Which to Iniate Dialysis. Nephrology 2005; 18: 546-560

43. KDOQI. Clinical Practice Guidelines for Hemodialysis Adequacy. Guideline 1: Initiation of Dialysis. Am J Kidney Dis 2006; 48 (suppl 1): S13-S16

44. UK Guidelines. Farrington K, Warwick G. Planning, Initiating and Withdrawal of RRT. 2012

45. Levin A, Hemmelgarn B, Culleton B, *et al.* Guidelines for the management of chronic kidney disease. CMAJ 2008;179(11):1154-1162

46. Mehrotra R, Rivara M, Himmelfarb J. Initiation of dialysis should be timely: neither early nor late. Semin Dial 2013;26(6):644-649

47. Tattersall J, Dekker F, Heimburger O, *et al.* When to start dialysis: updated guidance following publication of the initiating dialysis early and late (IDEAL) study. Nephrol Dial Transplant 2011;26(7):2082-2086

48. Harris A, Cooper BA, Li JJ, *et al.* Cost-effectiveness of initiating dialysis early: a randomized controlled trial. Am J Kidney Dis 2011;57(5):707-715

49. Rosansky SJ. The sad truth about early initiation of dialysis in elderly patients. JAMA 2012;307(18):1919-1920

50. Dasgupta I, Rayner HC. Dialysis versus conservative management of elderly patients with advanced chronic kidney disease. Nat Clin Pract Nephrol 2007;3(9):480-481

Correspondence to:
Professor Dr. Pedro Leão Neves
Department of Nephrology, Centro Hospitalar do Algarve
Rua Leão Penedo, 800-386
Faro, Portugal
E-mail: pleaon@hotmail.com