Clinical Kidney Journal, 2017, vol. 10, no. 1, 74–78

doi: 10.1093/ckj/sfw092
Advance Access Publication Date: 23 September 2016
Original Article

ORIGINAL ARTICLE

Course of chronic kidney disease in French patients

Nicolas Janus[1,2], Vincent Launay-Vacher[1,2], Laurent Juillard[3], Gilbert Deray[1,2], Thierry Hannedouche[4], Myriam Isnard-Rouchon[5], Stéphane Burtey[6], Philippe Vanhille[7], Jean-Paul Ortiz[8], Gérard Janin[9], Philippe Nicoud[10], Malik Touam[11] and Maurice Laville[12]

[1]Service ICAR, Néphrologie, Hôpital Pitié-Salpêtrière, Paris, France, [2]Néphrologie, Hôpital Pitié-Salpêtrière, Paris, France, [3]Néphrologie, Hôpital Edouard Herriot, Lyon, France, [4]Néphrologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [5]Néphrologie, AURA-Auvergne, Chamalières, France, [6]Aix-Marseille Université Centre de Néphrologie, Hôpital de la Conception, Marseille, France, [7]Néphrologie, Centre Hospitalier de Valenciennes, Valenciennes, France, [8]Néphrologie, Polyclinique Saint-Roch, Cabestany, France, [9]Néphrologie, Hôpital des Chanaux, Mâcon, France, [10]Néphrologie, Hôpitaux du Pays du Mont-Blanc, Sallanches, France, [11]Néphrologie, AURA-Paris, Paris, France and [12]Néphrologie, Hôpital Lyon Sud, INSERM U1060 CarMen, Université de Lyon, Pierre-Bénite, France

Correspondence and offprint requests to: Nicolas Janus; E-mail: nicolas.janus@psl.aphp.fr

Abstract

Background: In 1998, a French survey showed that the referral of patients with chronic kidney disease to a nephrologist was delayed, resulting in many emergency initiations of dialysis. In 2009, the ORACLE study aimed to describe the renal course of dialysis patients from their first nephrology visit to their first dialysis session.

Methods: The ORACLE study was a multicentre retrospective study of all patients who started chronic dialysis. Data were collected at the first nephrology visit and at the first dialysis session.

Results: In total, 720 patients were included (69 centres). At the first nephrology visit, the mean Cockcroft–Gault (CG) indicator was 31.8 mL/min (22.7 in 1998) and 52.4% of patients (73% in 1998) had a CG <30. The mean time between the first nephrology visit and the first dialysis session was 48 months (35 months in 1998).

Conclusion: In 2009, most patients were referred a long time before dialysis initiation, which likely allowed them to benefit from the impact of nephrology care on early outcomes when on dialysis. However, 34.2% of the dialysis sessions were still initiated under emergency conditions.

Key words: chronic renal insufficiency, dialysis, drug dosage management

Received: January 15, 2016. **Accepted:** August 5, 2016

Clinical Kidney Journal

Introduction

Chronic kidney disease (CKD) is a long-term condition and has been described as a progressive loss of kidney function over time. CKD is a silent disease in the early part of the process and has long been an underdiagnosed condition. CKD is significantly associated with high rates of cardiovascular (CV) events and CV mortality [1].

However, despite all efforts to alert the medical community and the authorities about its multiple detrimental consequences, late referral of CKD patients to the nephrologist still remains a frequent issue [2]. Early referral has a clear impact on patient mortality [3] and evidence shows that referral to a nephrologist more than 12 months prior to starting dialysis may improve outcomes, including long-term survival on dialysis [4]. Furthermore, studies have reported that early referral could slow down the progression of CKD [4–6]. Finally, only a few studies have described drug therapy in CKD patients at the first visit to a nephrologist. The AVENIR study investigated the appropriateness of pre-dialysis medications and assessed adherence to current guidelines for five aspects of CKD (hypertension/proteinuria, anaemia, bone disease, metabolic acidosis and dyslipidaemia). The study reported that during pre-dialysis nephrology follow-up, hypertension/proteinuria was managed appropriately in 72.4% of cases, anaemia in 56.2%, bone disease in 16.7%, metabolic acidosis in 60.2% and dyslipidaemia in 61.4%. The authors concluded that therapeutic care was suboptimal in their population [7, 8].

Therefore, the challenge for healthcare professionals is to improve patient management through early diagnosis and referral. In 1998, a French survey of 700 patients found that the referral of patients with renal insufficiency to a nephrologist was delayed and that in many cases dialysis was initiated in emergency (not programmed) conditions [9].

Eleven years later, the French national study ORACLE aimed to describe the course of renal disease in CKD patients from their first nephrology visit to their first chronic dialysis session. The major objectives of the ORACLE study were to describe the profile of patients at the first nephrology visit and at the first dialysis session, to observe the course of renal disease in CKD patients and to compare these data with those of the previous 1998 study.

Materials and methods

ORACLE was a national retrospective multicentre study. Because the names of the 1998 survey centres were not available, the participating centres for ORACLE were selected according to the geographic localization of the 1998 survey centres and a similar proportion of public versus private centres. Finally, the 1998 survey centres were selected to provide a representative sample of French centres. For all participating centres, nephrologists were asked to complete a case report form for all patients starting chronic dialysis ($n = 702$) from 1 April 1997 to 31 July 1997. Patients <15 years, patients with a past medical history of dialysis and patients initiating chronic dialysis in another centre were not included. The aims of the 1998 study were the same as those of the ORACLE study. For the ORACLE study, all the participating centres were asked to provide a list of patients who started chronic dialysis (either haemodialysis or peritoneal dialysis) between 1 April 2009 and 31 July 2009 in one of the participating centres in France.

The study consisted of retrospective data collection from the medical files of dialysis patients, focusing on the first chronic dialysis session and on the first visit to a nephrologist. Patients undergoing dialysis for acute renal failure, with a past medical history of dialysis, renal transplantation and/or under 18 years of age were not included in the ORACLE study.

The data collected were as follows: age, weight, creatinine and haemoglobin (Hb) levels, comorbidities (diabetes, arterial hypertension, dyslipidaemia, CV disease and cancer; all from the medical file) and the time between the first nephrology visit and the initiation of the dialysis. Renal function was assessed both with the Cockcroft–Gault (CG) formula for the estimation of creatinine clearance (CrCl) and the abbreviated Modification of Diet in Renal Disease (aMDRD) formula for the estimation of the glomerular filtration rate (GFR). The data collected were roughly the same between the two studies, with some exceptions.

The main data were compared with those of the survey conducted in 1998. However, the comparison between the two study populations could not be performed for renal function assessed with the aMDRD formula as this was not available in 1998. The comparison was also not possible for the classification of CKD, which had changed between 1998 and 2009. The mean annual (12 month) decrease in renal function was calculated as follows: (CrCl at the first chronic dialysis session – CrCl at the first visit) × 12/(time between the first nephrology visit and the first dialysis session).

Furthermore, because the database of the first study was not available (only the results summarized in a study report were available), no statistical analyses were performed on the databases for the comparison of the two studies. However, all the means, sizes of the populations, number of patients presenting a characteristic (comorbidities, CG <15 mL/min etc.) and standard deviations were available. Therefore, it was possible to make comparisons of the means/frequencies between the two studies using *t*-test and χ^2 test.

Multiple linear regressions were used to identify risk factors associated with a higher annual variation of GFR. All factors were measured at the first visit. A P-value <0.05 was considered significant.

Ethical statement

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For France, the ethical approvals were obtained from the CCTIRS and the CNIL. This article does not contain any studies with animals performed by any of the authors. Because ORACLE was a retrospective study, no formal consent was required.

Results

A total of 720 patients from 69 centres in France were retrospectively included. Patients referred for the first time to a nephrologist (first nephrology visit) were older in 2009 (66.2 versus 62.5 years in 1998; Table 1). Furthermore, 61.9% of these patients were over 65 years (versus 53% in 1998). Nearly two-thirds (64.3%) were men (versus 60.6% in 1998).

First nephrology visit

Patients had a higher mean CrCl (CG) at the first visit in 2009 (31.8 versus 22.7 mL/min in 1998; Table 2). Furthermore, patients presenting with CKD 4-5ND (CrCl <30 mL/min) were less numerous in 2009 (52.4%) than in 1998 (73%), despite the fact that the patients were older in 2009 (66.2 years) than in 1998 (62.5 years).

Table 1. Description of ORACLE population and the 1998 survey population

Characteristics	1998	ORACLE	Test[a] (P)
Age at the first visit[b] (years)	62.5/65.3 ± 15.8	66.2/70 ± 15.9	0.35
Age at the first dialysis[b] (years)	64.4/66.3 ± 15.8	70.2/74 ± 15.9	0.31
Gender (male)	60%	64.3	0.11
Time between the first visit and the first dialysis[b] (years)	2.9/1.2 ± 4.2	4.0/3.0 ± 4.6	0.31
Number of consultations between the first visit and the first dialysis[b]	9.6/4.3 ± 13.9	10.8/9.0 ± 10.2	0.39
Characteristics at the first visit			
Body mass index[b] (kg/m^2)	–	27.9/27.2 ± 6.2	–
Serum creatinine[b] (μmol/L)	411.0/346.5 ± 280.1	294.2/236 ± 190.2	0.98
eGFR (aMDRD)[b] (mL/min/1.73 m^2)	–	26.7/21.9 ± 19.0	–
CrCl (CG)[b] (mL/min)	22.7/16.3 ± 19.8	31.8/26.0 ± 20.7	0.11
CrCl (CG) <30; <15 mL/min	73%; 43%	52.4%; 16.1%	<0.0001; <0.0001
Hb[b] (g/dL)	10.7/10.6 ± 2.3	11.4/11.5 ± 2.2	0.44
Hb <10.0 g/dL	37%	18.4%	<0.0001
Cardiovascular disease			
Ischaemic cardiomyopathy	19%	18.2%	0.72
Heart failure	17%	6.5%	<0.0001
Cerebrovascular disease	8%	7.5%	0.73
Other	–	12.9%	–
Other comorbidities			
Arterial hypertension	82%	77.6%	0.06
Diabetes	28%	38.6%	<0.0001
Dyslipidaemia	–	29.9%	–
Cancer	7%	12.9%	0.0008
Smoking (active)	–	20.4%	–
Characteristics at the first dialysis			
Body mass index[b] (kg/m^2)	–	27.4/26.3 ± 6.2	–
Serum creatinine[b] (μmol/L)	743/705 ± 257.0	592.9/550 ± 266.4	0.98
eGFR (aMDRD)[b] (mL/min/1.73 m^2)	–	9.5/8.6 ± 4.6	–
CrCl (CG)[b] (mL/min)	8.7/8.2 ± 4.2	11.7/10.6 ± 4.9	0.25
CrCl (CG) <15; <10; <5 mL/min	90%; 69%; 7%	70.1%; 39.2%; 3.8%	<0.0001; <0.0001; 0.01
Unplanned initiation of the first HD session	33%	34.2%	0.66
Hb[b] (g/dL)	9.1/9.0 ± 1.5	10.2/10.1 ± 1.7	0.40
Hb <10.0 g/dL	69%	38.8%	<0.0001
Other comorbidities			
Arterial hypertension	–	86.0%	–
Diabetes	–	41.8%	–
Dyslipidaemia	–	37.5%	–
Cancer	–	19.7%	–
Smoking (active)	–	20.7%	–

eGFR, estimated glomerular filtration rate; CG, Cockcroft–Gault; CrCl, creatinine clearance; Hb, haemoglobin; aMDRD, abbreviated Modification of Diet in Renal Disease.
[a]t-test for the comparisons of the mean or χ^2 test for the comparisons of the percentage.
[b]Mean/median ± standard deviation.

When using the aMDRD formula, the prevalence in the ORACLE study of GFR <30 mL/min/1.73 m^2 and GFR <15 mL/min/1.73 m^2 was 63.6 and 23.6%, respectively (Table 2).

In 2009, the parameters assessing anaemia were better (Table 1). The mean Hb level increased by 0.7 g/dL (11.4 g/dL in 2009 versus 10.7 g/dL in 1998) and 18.4% of the patients had an Hb <10.0 g/dL versus 37% in 1998.

First dialysis session

Patients at the first dialysis session had a higher mean CrCl in 2009 (11.7 versus 8.7 mL/min in 1998; Table 2). Furthermore, patients with a CrCl <15 mL/min were less numerous in 2009 (70.1 versus 90.0% in 1998). When estimating renal function using the aMDRD formula for the ORACLE patients, the percentage of patients with a GFR <15 mL/min/1.73 m^2 at the initiation of dialysis reached 85.4%. In 2009, 34.2% of the dialysis sessions were initiated in emergency conditions (versus 33% in 1998). Most patients were haemodialysed (90.7% in 2009 versus 83% in 1998).

Course of renal disease between the first nephrology visit and the first chronic dialysis

The mean time between the first nephrology visit and the first dialysis session was 4 years (48 months) in the ORACLE study. It was shorter in 1998, with a mean time of 2.9 years (35 months). During the follow-up of the patients after the first nephrology visit, the mean number of nephrology visits per patient was 10.8 in the ORACLE study versus 9.6 in the 1998 survey. Consequently, ORACLE patients were seen 2.7 times per year (every 4.4 months) compared with 3.3 times per year (every 3.6 months) in 1998. Finally, the mean annual decrease in CrCl was −4.9 mL/min/year in 2009 versus −4.8 mL/min/year in 1998.

Finally, the decrease in Hb level was lower in 2009 than in 1998: −1.2 g/dL in 2009 versus −1.6 g/dL in 1998.

Table 2. Stages of renal insufficiency in ORACLE population and the 1998 survey population

	1998		ORACLE	
Stage of renal insufficiency	First visit (%)	First dialysis (%)	First visit (%)	First dialysis (%)
Cockcroft–Gault formula (mL/min)				
50–30	14.0	2.0	23.2	0.8
30–10	46.0	23.0	46.8	48.8
<10	27.0	69.0	5.6	39.2
No data	6.0	6.0	13.3	11.2
aMDRD formula[a] (mL/min/1.73 m^2)				
60–90	–	–	3.9	0.0
30–59	–	–	23.5	0.4
15–29	–	–	40.0	7.8
<15	–	–	23.6	85.4
No data	–	–	8.2	6.4

aMDRD, abbreviated Modification of Diet in Renal Disease.
[a]Not available for the first study conducted in 1998.

Discussion

The mean time between the first visit and the first dialysis session was longer in 2009 (13 months). This difference was not found to be statistically significant ($P > 0.05$), but it highlighted that patients who started dialysis in 2009 were under the care of a nephrologist for a longer period of time than those who started dialysis in 1998 and that ORACLE patients were followed from an earlier time point in their illness trajectory but were no less likely to start dialysis in an unplanned fashion.

However, this major outcome was mostly explained by the fact that patients saw a nephrologist at a higher GFR: the mean CrCl was 31.8 mL/min in 2009 versus 22.7 mL/min in 1998, corresponding to an increase in CrCl of 9.1 mL/min between the two studies. In contrast, the mean annual decrease in CrCl did not actually improve between the two studies (−4.8 versus −4.9 mL/min/ per year in 1998 and 2009, respectively). The limitation is that the trend for the 1998 survey (−4.8 mL/min/year) was calculated based on the mean CrCl at the first nephrology visit, at the first dialysis session and the mean time between these two periods (calculation based on three means) and not using the individual patient data. Furthermore, CrCl at the inception of dialysis was globally higher in the 2009 cohort than in 1998. It is likely that nephrologists did not use the estimation of the renal function based on the CG formula as the criterion for the initiation of maintenance dialysis in 2009. This could explain the fact that ~30% of dialysis initiations were made at CrCl >15 mL/min in the ORACLE study. However, the difference in estimated GFR using either the CG or the MDRD formula would translate into a time lag of several months without initial maintenance dialysis. Such an effect could also explain changes in epidemiology towards an increase in the incidence of patients starting dialysis programmes. Finally, it is important to note that the classification of CKD was not the same in 1998 as in 2009. As a result, the clinical practices could have been different. It is also important to note that the ORACLE study only included patients who started chronic dialysis and not those who did not.

Another important point is the representativeness of the studies. The patients in the ORACLE study were compared with the patients of the French REIN cohort (www.agence-biomedecine.fr), available on the website of the French biomedicine agency. Globally, the trends were similar, except that ORACLE included more cancer patients (+9%). Furthermore, the prevalence of heart failure was quite different in the two studies (Table 1). Finally, the 1998 study report (not published) specified that a comparison was made between the participating centres and all the centres in France.

The ORACLE study reported some key messages. Patients were referred to nephrologists with a better renal function, but this was not statistically significant, and 34.2% of the dialysis sessions were still initiated as emergency measures. It is also important to consider the management of anaemia and other comorbidities in these patients according to the recommendations available.

Acknowledgements

We are indebted to the physicians who took time from their busy work schedules to participate in the ORACLE Study Group: M. Al Badawy, N. Albeiriss, W. Arkouche, C. Beauchamp, S. Benarbia, H. Berbagui, Y. Berland, P. Bindi, R. Boudet, L. Boudier, M. Bouiller, J. Brasseur, E. Bruce, I. Brunak, B. Canaud, G. Cardon, C. Chazot, G. Choukroun, B. Coevoet, C. Combe, O. Dahmani, F. De Groc, V. de Précigout, F. Dehais-Goffinet, G. Deray, N. Diab, J. Dion, P. Donnadieu, P. Dubot, A. Faure, P. Fontanier, M. François, L. Gaëlle, C. Gazangel, D. Glotz, O. Grezard, T. Hachache, A. Haddj El Mrabet, M. Hadj-Abdelkader, T. Hannedouche, J. Haultier, M. Hoffman, F. Ibrahil, G. Janin, D. Jaubert, J. Jaulin, C. Jolimoy, B. Jonon, J. Jourdan, L. Juillard, E. Kernaonet, C. Klein, Z. Koochaki, F. Kuentz, I. Landru, M. Laville, M. Le Bot, H. Leray, E. MacNamara, J. Marc, F. Marquiny, K. Maurizi, F. Metivier, P. Michel, R. Montagnac, H. My, M. Rouchon-Isnard, P. Nicoud, H. Nivet, J. Ortiz, V. Panescu, P. Philippe, A. Pruna, A. Ratsimbazafy, E. Robin, L. Rouillon, J. Rottembourg, J. Ryckelynck, M. Souid, F. Taghzouti, B. Temperville, M. Touam, D. Touzard, P. Vanhille, L. Vrigneaud, L. Yver, and P. Zaoui. We extend special thanks to Roche for independently promoting the study. The results presented in this paper have not been published previously in whole or part, except in abstract form.

Authors' contributions

N.J. participated in the design of the study, the collection of the data, the statistical analysis and the redaction of the article, and has given final approval of the version to be published. V.L.-V. participated in the design of the study, the interpretation of data and the redaction of the article and has given final approval of the version to be published. L.J. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. G.D. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. T.H. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. M.R.-I. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. S.B. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. P.V. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. J.-P.O. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. G.J. participated in the design of the

study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. P.N. participated in the design of the study; the interpretation of data and the redaction of the article, and has given final approval of the version to be published. M.T. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published. M.L. participated in the design of the study, the interpretation of data and the redaction of the article, and has given final approval of the version to be published.

Conflict of interest statement

N.J.: Roche, Pfizer, Fresenius Medical Care, Leo; V.L.-V.: Roche, Vifor Pharma, Gilead, Sanofi, Pfizer, HAS, InCA, ANSM; L.J., T.H., M.R.-I., J.-P.O., G.J. and M.T.: nothing to declare; G.D., P.V. and M.L.: Roche; S.B.: Alexion, Amgen, Roche; P.N.: BBraun Avitum.

References

1. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296–1305
2. Jungers P. Late referral: loss of chance for the patient, loss of money for society. *Nephrol Dial Transplant* 2002; 17: 371–375
3. Smart NA, Titus TT. Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. *Am J Med* 2011; 124: 1073–1080.e2
4. Black C, Sharma P, Scotland G *et al*. Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *Health Technol Assess* 2010; 14: 1–184
5. Orlando L, Owen W, Matchar D. Relationship between nephrologist care and progression of chronic kidney disease. *N C Med J* 2007; 68: 9–16
6. Martínez-Ramírez HR, Jalomo-Martínez B, Cortés-Sanabria L *et al*. Renal function preservation in type 2 diabetes mellitus patients with early nephropathy: a comparative prospective cohort study between primary health care doctors and a nephrologist. *Am J Kidney Dis* 2006; 47: 78–87
7. Thilly N, Boini S, Kessler M *et al*. Chronic kidney disease: appropriateness of therapeutic management and associated factors in the AVENIR study. *J Eval Clin Pract* 2009; 15: 121–128
8. Thilly N, Boini S, Kessler M *et al*. Management and control of hypertension and proteinuria in patients with advanced chronic kidney disease under nephrologist care or not: data from the AVENIR study (AVantagE de la Nephroprotection dans l'Insuffisance Renale). *Nephrol Dial Transplant* 2009; 24: 934–939
9. Nicoud P, Foret M, Kessler M *et al*. From referral to nephrologist. *Nephrol Dial Transplant* 1999; 14: A124 (abstract)