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Original Article

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Baseline characteristics of an incident haemodialysis population in Spain: results from ANSWER—a multicentre, prospective, observational cohort study

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Abstract

Background. The ANSWER study aims to identify risk factors leading to increased cardiovascular morbidity and mortality in a Spanish incident haemodialysis population. This paper summarizes the baseline characteristics of this population.

Methods. A prospective, observational, one-cohort study, including all consecutive incident haemodialysis patients from 147 Spanish nephrology services, was conducted. Patients were enrolled between October 2003 and September 2004. Sociodemographic, clinical, laboratory and health care characteristics were collected.

Results. Baseline characteristics are described for 2341 incident haemodialysis patients [mean (SD) age 65.2 (14.5) years, 63% males]. The main cause of renal failure was diabetic nephropathy (26%). The majority of patients (57%) had a Karnofsky score of 80–100 and 27% were followed up by a nephrologist for ≤6 months. In total, 86% of the patients had hypertension, 43% had dyslipidaemia and 44% had a history of cardiovascular disease. Initial vascular access was obtained via a temporary catheter in 30% of patients, via a permanent catheter in 16% and via an arteriovenous fistula in 54%. Albumin levels were <3.5 g/dl in 43% of patients. Immediately prior to the onset of haemodialysis, the mean (SD) glomerular filtration rate (GFR) was 7.6 (2.8) ml/min/1.73 m^2, and only 6.7% of the patients were within the K/DOQI guidelines for all four bone mineral markers. In addition, a high proportion of patients had anaemia markers outside the EBPG guidelines (haemoglobin <11 g/dl, 59%, ferritin <100 or >500 ng/ml, 41% and saturated transferrin <20 or >40%, 50%) despite previous treatment with erythropoiesis-stimulating agents in 41% of cases.

Conclusions. There is excessive use of temporary catheters and a high prevalence of uraemia-related cardiovascular risk factors among incident haemodialysis patients in Spain. The poor control of hypertension, anaemia, malnutrition and mineral metabolism and late referral to a nephrologist indicate the need for improving the therapeutic management of patients before the onset of haemodialysis.

Keywords: cardiovascular; haemodialysis; malnutrition; risk factors; vascular access

Introduction

Haemodialysis has become an increasingly safe and well-tolerated therapy for patients with end-stage renal disease (ESRD). Nevertheless, life expectancy of dialysis patients remains significantly shorter than that of the general population with similar demographics [1]. There is also a high incidence of cardiovascular morbidity and mortality in this population [2,3]. Large, prospective, observational studies, including the Dialysis Outcomes and Practice Patterns Study (DOPPS) [4], and the United States Renal Data System Dialysis Morbidity and Mortality Wave 2 study [5,6] have provided important insights into the characteristics and likely prognosis of haemodialysis patients. A number of prospective epidemiological studies from several European countries have also described the incident haemodialysis population [7–15], which can help to assess the influence of a multitude of risk factors on the increased mortality among these patients. In this regard, the ANSWER study is currently underway in a large incident haemodialysis population in Spain.

The primary objective of the ANSWER study is to determine and quantify the risk factors influencing cardiovascular morbidity and mortality in incident haemodialysis patients in Spain. In addition, the study also aims to provide information on the baseline characteristics of the incident

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haemodialysis population; in this paper, we report these data and make comparisons with other incident and prevalent populations reported in the literature.

Subjects and methods

ANSWER is a multicentre, prospective, observational cohort study in incident haemodialysis patients all over Spain. Most dialysis facilities from Spain ($n = 235$) were invited to participate in the study, of which 147 (62.5%) centres agreed to participate. The local ethics committees approved the study and all patients enrolled in the study provided informed consent.

Patients

All incident haemodialysis patients (i.e. patients starting chronic haemodialysis treatment, who had received haemodialysis for ≤30 days) aged ≥18 years were eligible for inclusion in the study. Patients were excluded if they had undergone renal replacement therapy previously, were already receiving haemodialysis (≥30 days) or peritoneal dialysis, or had received a kidney transplant.

Following initiation of the study at each site in October 2003, patients were consecutively enrolled as they started haemodialysis treatment. Enrolment was stratified by region according to the incidence of haemodialysis in a reference population [16], in order to obtain a sample in which all Spanish regions would be represented in the same proportion as in the target population.

Patient assessments

Sociodemographic, clinical, laboratory (maximum 30 days before start of haemodialysis) and health care (concomitant drug therapy and haemodialysis characteristics) variables were recorded at baseline (within first 30 days of haemodialysis) and assessed at regular intervals during the study period, with all the study patients followed up for at least 2 years.

Variables recorded at baseline included waist measurement, smoking status (active smoker, non-smoker, ex-smoker), alcohol consumption (grams of alcohol [17]), employment status and education. The clinical variables assessed included history of renal failure and various comorbidities: diabetes, dyslipidaemia [cholesterol >220 mg/dl or low-density cholesterol (LDL-C) >100 mg/dl or treatment with statins], hypertension [systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or treatment with antihypertensives], parathyroidectomy, malnutrition (physician's subjective assessment) and cardiovascular disease (heart failure, left ventricular hypertrophy, cardiac arrhythmia, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease and any other diseases of the circulatory system). The Charlson age-comorbidity index [18,19], performance status [Karnofsky score (KS)] and health-related quality of life (QoL) assessed with the Medical Outcome Survey Short Form 36 (SF-36) questionnaire [20], previously validated for the Spanish population [21], were also recorded.

Parameters describing the patients' initial haemodialysis experience (first month after starting) were also obtained. Dialysis intolerance was defined as hypotension recorded at >50% of dialyses performed during the past month. The urea reduction ratio (URR) and Kt/V were calculated for each patient according to a standard formula (second-generation Daugirdas formula for eKt/V [22]). Glomerular filtration rate (GFR) was estimated according to the MDRD equation [23].

Bone mineral markers [intact parathyroid hormone (iPTH), phosphorus, total calcium and calcium–phosphorus product (Ca × P)] were assessed according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) target ranges [24]. Anaemia markers (haemoglobin, haematocrit, ferritin and saturated transferrin) were assessed according to the European Best Practice Guidelines (EBPG) [25].

Statistical analysis

Summary statistics were calculated for continuous and categorical endpoints. Differences between subgroups were assessed using chi-square tests for categorical variables and Student's *t*-test or the Mann–Whitney *U*-test for continuous variables (according to normality). The Bonferroni method [26] was applied for adjusting the significance level in these analyses. Differences were considered significant at $P < 0.00022$ (0.05/228). Differences between means and odds ratios with respect to the reference subgroup, together with their 95% confidence interval, are displayed only for the variables with significant results. The calculations were performed using SPSS® 14.0.

Results

Sociodemographic characteristics and aetiology of kidney disease

A total of 2406 incident patients undergoing dialysis were enrolled from 147 hospital nephrology services and associated haemodialysis centres throughout Spain between 1 October 2003 and 30 September 2004. Sixty-five patients were excluded from analysis, as they did not meet the inclusion criteria. The resulting sample, 2341 patients, accounts for ∼58% of the total incident patients during the study period (according to the 2003 and 2004 estimates of the incidence of haemodialysis in Spain of the National Registry [27,28]).

Table 1 summarizes the patient demographics and baseline characteristics. Most patients were elderly (29% over 75 years), male (63%) and overweight [59% had body mass index (BMI) >25 kg/m^2]. The education level was low (38% had no primary education). The most common reason for renal failure was diabetic nephropathy (26%), and 27% of patients had been followed up by a nephrologist for <6 months prior to the onset of haemodialysis (24% in the subgroup with diabetic nephropathy and 26% in the subgroup with vascular nephropathy). The prevalence of hepatitis C virus positive patients was 5.4%.

Table 1. Baseline sociodemographic, clinical and haemodialysis characteristics of the study population

	Mean (SD) or *N* (%)		Mean (SD) or *N* (%)
Mean age (years) (SD) ($n = 2336$)	65.2 (14.5)	Hypertension ($n = 2283$)	1975 (86%)
18–44	258 (11%)	Diagnosed <1 year before[a] ($n = 1174$)	152 (13%)
45–64	663 (28%)	Previous cardiovascular disease[b] ($n = 2341$)	1038 (44%)
65–74	744 (32%)	Ischaemic CV Disease	701 (30%)
≥75	671 (29%)	Ischaemic heart disease	355 (15%)
Gender ($n = 2341$)		Peripheral vascular disease	272 (12%)
Male	1470 (63%)	Cerebrovascular disease	263 (11%)
Race ($n = 2323$)		Heart failure	401 (17%)
Europid	2275 (98%)	Cardiac arrhythmia	248 (11%)
Other	48 (2%)	Other diseases of the circulatory system	141 (6%)
Mean BMI (kg/m^2) (SD) ($n = 2050$)	26.6 (5.3)	Left ventricular hypertrophy ($n = 2341$)	374 (16%)
BMI <20 kg/m^2	146 (7%)	Dyslipidaemia[c] ($n = 2261$)	973 (43%)
20≤BMI<25 kg/m^2	701 (34%)	Diagnosed <1 year before[a] ($n = 514$)	108 (21%)
25≤BMI<30 kg/m^2 (overweight)	787 (39%)	Diabetes mellitus ($n = 2285$)	823 (36%)
		Diagnosed <1 year before[a] ($n = 466$)	19 (4%)
BMI ≥30 kg/m^2 (obesity)	416 (20%)	Malnutrition ($n = 2246$)	251 (11%)
Mean WC in males (cm) (SD) ($n = 424$)	96.5 (17.2)	Parathyroidectomy ($n = 2266$)	15 (0.7%)
Mean WC in females (cm) (SD) ($n = 253$)	93.6 (16.9)	Solid or non-solid tumour ($n = 1992$)	223 (11%)
Abd.ob. males (WC ≥ 102 cm)	144 (34%)	Median Karnofsky score, (P25–P75)[d] ($n = 2160$)	80 (60–80)
Abd.ob. females (WC ≥ 88 cm)	167 (66%)	<50	68 (3%)
Reasons for renal failure ($n = 2280$)		50–70	861 (40%)
Diabetic nephropathy	596 (26%)	80–100	1231 (57%)
Reno-vascular and hypertensive renal disease	383 (17%)	Mean of Charlson score (SD)[e] ($n = 2249$)	6.2 (2.4)
Glomerulonephritis	260 (11%)	2–6	1223 (55%)
Polycystic kidney disease	166 (7%)	7–8	648 (29%)
Chronic pyelonephritis	140 (6%)	≥9	378 (16%)
Systemic	90 (4%)	SF-36[f] ($n = 847$)	
Hereditary	15 (1%)	Mean PCS (SD)	36.4 (9.9)
Unknown aetiology	482 (21%)	Mean MCS (SD)	39.9 (13.0)
Other	148 (7%)		
Mean duration of predialysis nephrologist follow-up (months) (SD) ($n = 2212$)	36.8 (34.9)	Haemodialysis technique ($n = 2087$)	
≤6 months	610 (27%)	Conventional	2047 (98%)
7–12 months	216 (10%)	Special[g]	40 (2%)
>12 months	1386 (63%)	HD frequency, session/week ($n = 2109$)	
Tobacco use ($n = 2187$)		3 session/week	2053 (97%)
Non-smoker	756 (35%)	Other	56 (3%)
Former smoker	1181 (54%)	Mean HD duration (hours/session) (SD) ($n = 2091$)	3.6 (0.7)
Current smoker	250 (11%)	Membrane type ($n = 2085$)	
Alcohol consumption ($n = 2159$)		Low-flux	1158 (56%)
None	1908 (88%)	High-flux	927 (44%)
Any	251 (12%)	Heparin ($n = 1695$)	
Employment status ($n = 2151$)		Low molecular weight	804 (47%)
Retired	1328 (62%)	Standard	891 (53%)
Disabled	308 (14%)	Vascular access ($n = 2124$)	
Active	271 (13%)	Permanent catheter	347 (16%)
Unemployed	244 (11%)	Temporary catheter	642 (30%)
Educational status ($n = 2063$)		IAVF-distal	644 (31%)
Cannot read or write	138 (7%)	IAVF-proximal	441 (21%)
Can read or write	643 (31%)	PTFE graft	50 (2%)
Primary education	903 (44%)	Blood pressure before HD session	
Secondary education	266 (13%)	Mean SBP (mmHg) (SD) ($n = 1457$)	140.5 (21.7)
University studies	113 (5%)	Mean DBP (mmHg) (SD) ($n = 1458$)	75.4 (12.2)
Hepatitis B (+) ($n = 2306$)	25 (1%)	Mean interdialysis weight gain (kg) (SD) ($n = 1499$)	1.07 (0.95)
Hepatitis C (+) ($n = 2296$)	119 (5%)	Mean urea reduction ratio (%) (SD) ($n = 1079$)	62.3 (12.2)
HIV (+) ($n = 2290$)	16 (0.7%)	Mean (eKt/V) (SD) ($n = 1044$)	1.17 (0.53)

Baseline demographic characteristics are described for 2341 incident haemodialysis patients recruited from 147 nephrology centres in Spain. Values are expressed as number of patients and percentages on the valid sample indicated in parentheses for each variable.

N = number of patients; SD = standard deviation; p25 = percentile 25; p75 = percentile 75; WC = waist circumference; Abd. ob. = abdominal obesity; IAVF = internal arteriovenous fistula; PTFE = polytetrafluoroethylene; SBP = systolic blood pressure; DBP = diastolic blood pressure; CV = cardiovascular; HD = haemodialysis.

[a]Percentage calculated for the hypertensive, dyslipidaemic or diabetic patients with information available, respectively.

[b]Excluding left ventricular hypertrophy.

[c]Cholesterol >220 mg/dl or LDL-C >100 mg/dl or treatment with statins.

[d]On a scale 0–100, with 100 = the normal ability to carry out daily activities.

[e]Age adjusted; on a scale 0–37, with 37 = the highest comorbidity.

[f]SF-36 Physical Component Summary Scale (PCS) and Mental Component Summary Scale (MCS) are calculated based on *T* transformations, so that the mean score of the general Spanish population is 50 and the standard deviation is 10 (a value between 45 and 55 is considered 'normal', between 40 and 45 'somewhat worse' and <40 'worse' than 70% of the general population).

[g]Short daily haemodialysis or nocturnal haemodialysis.

Comorbidities, functional status, medications and quality of life

Comorbidities were common, particularly hypertension (86%), with almost all hypertensive patients being non-controlled (89% with SPB $\geq$140 mmHg or DBP $\geq$90 mmHg), despite most of them receiving antihypertensive treatment (80%). There was also a high frequency of previous cardiovascular disease (44%) and dyslipidaemia (43%) (Table 1). The prevalence of diabetes mellitus was 10% higher than that of diabetic nephropathy. Approximately 1 in 10 patients had developed a tumour.

As expected, the use of concomitant medications reflects the comorbidities in this population (Table 2). Half of the patients were treated with iron supplements either before (47%) or after (53%) the initiation of haemodialysis. Most patients were receiving or were starting treatment with erythropoiesis-stimulating agents (ESA, 80%) and phosphate binders (71%). Of the patients on ESAs, 52% were treated prior to dialysis initiation (62% in the subgroup with >6 months of predialysis nephrological care versus 38% in the $\leq$6 months group, $P < 0.0001$) and 48% began ESA treatment at the time of dialysis initiation. The use of beta-blockers was lower than expected in view of the comorbidities (24% of total sample, 16% as antihypertensive treatment and 8% as cardiovascular therapy).

The presence of comorbidities [mean of Charlson Index of 6.2 (SD 2.4)] resulted in a severely decreased quality of life when compared with the general Spanish population (Table 1). Over half of the patients (57%) had a Karnofsky score between 80 and 100. Younger patients had a better functional status [mean KS of 82 (SD 14) for patients <65 years] than the older patients [71 (16) for patients $\geq$65 years, $P < 0.0005$].

Blood chemistry

Table 3 summarizes the patients' baseline blood chemistry values. A high proportion of diabetic patients had uncontrolled glycaemia (48% >126 mg/dl, 34% with HbA1c >7%), whereas LDL-C was mostly within the normal range and high-density lipoprotein (HDL)-cholesterol was below the normal range in one-third of cases. The nutritional status of the patients was quite poor (43% had albumin levels <3.5 g/dl) and the inflammation status was highly variable (SD 6.2 mg/dl for the C-reactive protein). The mean GFR prior to dialysis onset was 7.6 (SD 2.8) ml/min/1.73 m^2 and the mean 24-h diuresis was 1602 (SD 920) ml.

Anaemia and mineral metabolism

A large proportion of patients were outside the EBPG targets for haematological parameters related to the management of anaemia (haemoglobin <11 g/dl in 59%). Ferritin and saturated transferrin levels were decreased in 31% and 39% of patients, respectively. Most patients were also outside the K/DOQI guideline target ranges for bone mineral markers (Table 4). Overall, only 6.7% of the patients were within the four K/DOQI target ranges at the same time. The population means were also outside the K/DOQI guideline target ranges for iPTH and phosphorus, but not for total albumin-adjusted calcium or Ca $\times$ P, probably due to the large percentage of patients with low total calcium levels.

Baseline haemodialysis characteristics

Baseline haemodialysis variables are detailed in Table 1. The majority of patients received three haemodialysis sessions per week with a mean of 3.6 h of dialysis per session. Similar proportions of patients had high-flux or low-flux membranes and similar proportions received low-molecular-weight or standard heparin. Vascular access in patients at the start of haemodialysis was achieved by using either catheter (46%) or arteriovenous fistula (AVF) (52%) and in a small proportion of patients using polytetrafluoroethylene AVF (2%).

Characteristics of the patients with initial vascular access via a catheter

The patients with initial vascular access via a permanent catheter were older and had worse nutritional status, more comorbidities (higher Charlson index) and worse residual renal function (lower 24-h diuresis) than patients with a temporary catheter or an AVF (Table 5). The subgroup with temporary catheters was characterized by greater use of low-molecular-weight heparin and a higher degree of anaemia, hypocalcaemia and hyperphosphataemia (Table 5).

Characteristics of patients with late referral to the nephrologist

In the subgroup analyses, patients who were referred to the nephrologist <6 months before the start of dialysis had worse functional and nutritional status, a lower degree of dyslipidaemia and hypertension (and more recently diagnosed) and worse residual renal function (higher creatinine and lower 24-h diuresis) than patients who referred >12 months ago (Table 6). As expected, systemic aetiologies (e.g. myeloma and vasculitis) were also related to the late referral to the nephrologist. Anaemia, hyperferritinaemia and uncontrolled mineral metabolism (hypocalcaemia and hyperphosphataemia) were much more frequently observed in the late referral group. Vascular access was obtained via an AVF in only 25% of patients who were referred late compared with 52–64% in the other subgroups.

Characteristics of patients with previous ischaemic cardiovascular disease

The presence of previous ischaemic cardiovascular disease in the incident dialysis population was related to all the classic cardiovascular risk factors in the general population (advanced age, male gender, former or current smoker, diabetes mellitus, history of dyslipidaemia or hypertension) except obesity (Table 7). It is notable that despite a higher percentage of dyslipidaemia and lower HDL-C levels, the mean total cholesterol was lower in the patients with previous cardiovascular disease. This inverse relationship was not due to the greater use of statins in

Table 2. Use of concomitant medications at haemodialysis initiation

	Valid *N*	*N* (%)		Valid *N*	*N* (%)
Erythropoiesis-stimulating agents[a]	2267	1814 (80%)	Antihypertensives	2269	1815 (80%)
Rhu-Epo	1814	996 (54%)	Calcium antagonists	1815	1101 (61%)
Darbepoetin alfa	1814	818 (45%)	α-blockers	1815	563 (31%)
Iron[b]	2254	1127 (50%)	ACE inhibitors	1815	554 (31%)
Intravenous[c]	1106	774 (70%)	ARA II	1815	543 (30%)
Oral[c]	1106	332 (30%)	β-blockers	1815	352 (19%)
Phosphate binders	2232	1585 (71%)	Diuretics	1815	342 (19%)
CO_3Ca	1585	1091 (69%)	α /β-blockers	1815	130 (7%)
Sevelamer	1585	298 (19%)	Other	1815	53 (3%)
Calcium acetate	1585	269 (17%)	Cardiovascular drugs	2250	990 (44%)
$Al(OH)_3$	1585	121 (8%)	Nitrates	990	249 (25%)
Vitamin D analogues/metabolites	2216	687 (31%)	β-blockers	990	184 (19%)
Calcitriol	687	666 (97%)	Antiarrhythmic drugs	990	101 (10%)
Other	687	17 (2%)	Digital	990	78 (8%)
Vitamins	2267	476 (21%)	Other	990	378 (38%)
Folic acid	476	421 (88%)	Antithrombotics	2259	655 (29%)
Vitamin C	476	198 (42%)	Anticoagulants	2112	169 (8%)
Hypoglycaemics	2236	626 (28%)	Hypolipidaemics	2228	713 (32%)
Insulin	626	540 (86%)	Statins	713	676 (95%)
Oral antidiabetics	626	86 (14%)	Fibrates	713	41 (6%)

Values are expressed as percentages on patients receiving the corresponding therapeutic group, except for major categories, calculated on total valid sample. The valid *N* for each percentage is shown in the second and fifth columns. Total sample size, 2341.
N = number of patients; ACE = angiotensin-converting enzyme; ARAII = angiotensin II receptor antagonist.
[a]Among patients on ESA, 52% were treated previously to HD initiation.
[b]Among patients on iron, 47% were treated previously to HD initiation.
[c]Percentages calculated for the subgroup of patients receiving iron with information available.

Table 3. Blood chemistry at baseline

	N	Mean (SD)		*N* patients (%)
Glucose (mg/dl)	2138	113 (46)	≥126 mg/dl[a]	367 (48%)
HbA1c (%)	568	6.2 (1.5)	>7%[a]	124 (34%)
Cholesterol (mg/dl)	1961	171 (46)	>200 mg/dl	451 (23%)
Cholesterol HDL (mg/dl)	1269	47 (18)	<40 mg/dl	457 (36%)
Cholesterol LDL (mg/dl)	1162	102 (37)	>160 mg/dl	93 (8%)
Triglycerides (mg/dl)	1914	134 (70)	>200 mg/dl	268 (14%)
Albumin (g/dl)	1796	3.5 (0.6)	<3.5 g/dl	771 (43%)
			3.5–4.0 g/dl	694 (39%)
			>4.0 g/dl	331 (18%)
Creatinine (mg/dl)	2175	6.9 (2.5)		
Serum urea (mg/dl)	2043	184 (69)		
High-sensitivity C-reactive protein (mg/dl)	313	5.3 (6.2)/3 (0.9, 7)[b]	>7.5 mg/dl	72 (23%)
Vitamin B12 (pg/ml)	583	512 (204)		
Lipoprotein A (mg/dl)	321	56 (47)	>30 mg/dl	184 (58%)
Homocysteine (μmol/l)	361	25.9 (13)	>18 μmol/l	253 (70%)
Fibrinogen (g/l)	533	5.3 (1.9)	>4.5 g/l	331 (62%)
Potassium (mmol/l)	2177	4.9 (0.8)		
Magnesium (mg/dl)	627	2.2 (0.5)		
ALT (U/l)	1957	21 (40)		
AST (U/l)	1929	20 (34)		
Alkaline phosphatase (U/l)	1714	129 (92)		
GFR (ml/min/1.73 m^2)	1559	7.6 (2.8)	<10 ml/min/1.73 m^2	1294 (83%)
24-h diuresis (ml)	1370	1602 (920)		

Percentages calculated on valid sample for each variable (indicated in the second column), unless otherwise specified.
N = sample size of the described variable; SD = standard deviation.
[a]% of diabetic patients with determination available ($n = 765$ for glucose, $n = 360$ for HbA1c).
[b]Median (P25, P75).

the cardiovascular group (42% versus 58% in the non-cardiovascular groups). Table 7 also shows greater catheter use, worse residual renal function and nutritional status, and a lower degree of hyperphosphataemia in this subgroup of patients.

Discussion

ANSWER is the first large, prospective, observational study of incident haemodialysis patients in Spain, which will help to clarify, together with other recent ongoing

Table 4. Haematological and bone mineral markers parameters at baseline

	N	Mean (SD)	*N* patients (%)		
			<11	≥11	
Haemoglobin (g/dl)	2198	10.6 (1.7)	1289 (59%)	909 (41%)	
			<33	33–36	≥37
Haematocrit (%)	2201	32.0 (5.2)	1244 (57%)	447 (20%)	510 (23%)
			<100	100–500	>500
Ferritin (ng/ml)	1718	236 (238)	529 (31%)	1015 (59%)	174 (10%)
			<20	20–40	41–100
Saturated transferrin (%)	1219	25.3 (13.8)	479 (39%)	611 (50%)	129 (11%)
			Low	Normal[a]	High
			<150	150–300	>300
iPTH (pg/ml)	1556	348 (259)	425 (27%)	468 (30%)	663 (43%)
			<3.5	3.5–5.5	>5.5
Phosphorus (mg/dl)	2109	5.6 (1.7)	129 (6%)	999 (47%)	981 (47%)
			<8.4	8.4–9.5	>9.5
Adjusted calcium (mg/dl)[b]	1787	9.1 (1.0)	325 (18%)	846 (48%)	616 (34%)
			na	≤55	>55
Ca × P (mg^2/dl^2)	1759	51 (15)	na	1158 (66%)	601 (34%)

Percentages calculated on valid sample for each variable (indicated in the second column).
N = sample size; na = not applicable.
[a]'Normal' represents the K/DOQI guideline target range for bone mineral markers.
[b]Adjusted with the following formula: Adjusted Ca = calcium + 0.8 *(4-albumin).

Table 5. Differences in clinical and sociodemographic characteristics of incident haemodialysis patients grouped by the type of initial vascular access (only those variables with significant differences with respect to AV fistula patients are displayed)

	Permanent catheter (*N* = 347, 16%)	Temporary catheter (*N* = 642, 30%)	AV fistula[a], reference (*N* = 1085, 52%)	*P*-value*
Age (years)	4.5 (2.3; 5.6)	1.1 (−0.4; 2.4)	0	<0.0001
Weight (kg)	−4.4 (−5.8; −2.1)	−2.22 (−3.4; −0.5)	0	0.0002
Karnofsky score	−10 (−12; −7.9)	−7 (−8.5; −5.4)	0	<0.0001
Charlson index	1.2 (0.9; 1.4)	0.6 (0.3; 0.8)	0	<0.0001
CKD aetiology = diabetic nephropathy	1.6 (1.2; 2.1)	1.5 (1.2; 1.9)	1	<0.0001
CKD aetiology = glomerulonephritis	0.5 (0.3; 0.8)	0.7 (0.5; 1.0)	1	<0.0001
CKD aetiology = polycystic kidney disease	0.3 (0.1; 0.5)	0.2 (0.1; 0.4)	1	<0.0001
CKD aetiology = systemic	3 (1.6; 5.5)	2.6 (1.5; 4.4)	1	<0.0001
Employment status = retired	1.4 (1.0; 1.8)	1 (0.8; 1.3)	1	0.0002
Haemodialysis duration (hours/session)	0.1 (0.01; 0.18)	0.2 (0.13; 0.26)	1	<0.0001
Low-molecular-weight heparin	0.8 (0.6; 1.1)	1.5 (1.2; 1.8)	1	<0.0001
Diabetes mellitus	1.6 (1.2; 2.0)	1.5 (1.2; 1.9)	1	<0.0001
Hypertension	0.4 (0.3; 0.6)	0.7 (0.5; 0.9)	1	<0.0001
Hypertension diagnosed <1 year before[b]	1.6 (0.9; 2.7)	2.3 (1.5; 3.4)	1	0.0002
Malnutrition	2.6 (1.8; 3.8)	1.6 (1.1; 2.2)	1	<0.0001
Albumin (g/dl)	−0.4 (−0.47; −0.32)	−0.4 (−0.44; −0.36.)	0	<0.0001
C-reactive protein (mg/dl)	0.3 (−2.2; 3.0)	3.3 (0.9; 5.8)	0	0.0001
Triglycerides (mg/dl)	21 (8; 35)	10 (0; 20)	0	<0.0001
Creatinine (mg/dl)	0.1 (−0.2; 0.4)	0.8 (0.5; 1.2)	0	<0.0001
Serum urea (mg/dl)	−12 (−21.5; −2.4)	9 (1.6; 16.3)	0	<0.0001
24-h diuresis (ml)	−474 (−285; −663)	−342 (−181; 503)	0	<0.0001
Haemoglobin <11 g/dl	1.9 (1.5; 2.5)	2.6 (2.1; 3.2)	1	<0.0001
Ferritin ≥ 500 ng/ml	2 (1.3; 3.3)	2.7 (1.8; 4.0)	1	<0.0001
Ca <8.4 mg/dl	1.4 (0.9; 2.0)	1.8 (1.4; 2.4)	1	0.0002
PO_4 >5.5 mg/dl	1.1 (0.9; 1.5)	1.4 (1.1; 1.7)	1	0.0001

Effect measures are expressed as a difference in means for quantitative variables and odds ratio for qualitative variables, together with their 95% confidence interval, with respect to the reference subgroup (AV fistula as initial vascular access). For qualitative variables with more than one category, the odds ratio has been calculated with respect to the absence of the displayed category.
N = sample size; CKD = chronic kidney disease.
*Bonferroni-corrected significance limit: $P < 0.00022$ (0.05/228).
[a]2% patients with PTFE graft not included in the subgroup analysis.
[b]Only analysed in the subgroup of hypertensive patients where the information was available, *N* = 1034.

Table 6. Differences in clinical and sociodemographic characteristics of incident haemodialysis patients grouped by duration of predialysis nephrological care (only those variables with significant differences with respect to >12 months patients are displayed)

	≤6 months ($N = 610$, 27%)	7–12 months ($N = 216$, 10%)	>12 months, reference ($N = 1386$, 63%)	*P*-value*
Karnofsky scale	−4.1 (−5.6; −2.3)	−2.5 (−4.3; 0.3)	0	0.0001
BMI (kg/m^2)	−0.9 (−1.4; −0.3)	−0.6 (−1.4; 0.2)	0	<0.0001
CKD aetiology = diabetic nephropathy	0.8 (0.6; 1.0)	1.5 (1.1; 2.1)	1	<0.0001
CKD aetiology = glomerulonephritis	0.6 (0.4; 0.9)	0.5 (0.2; 0.8)	1	0.0002
CKD aetiology = chronic pyelonephritis	0.5 (0.3; 0.9)	0.9 (0.5; 1.7)	1	0.0002
CKD aetiology = polycystic kidney disease	0.2 (0.1; 0.4)	0.2 (0; 0.5)	1	<0.0001
CKD aetiology = systemic	3.2 (2.0; 5.1)	1.4 (0.6; 3.2)	1	0.0002
Vascular access = IAVF	0.1 (0.1; 0.2)	0.6 (0.4; 0.8)	1	<0.0001
Diabetes diagnosed <1 year before[a]	15.7 (3.4; 72.4)	15.9 (3.1; 81.0)	1	<0.0001
Dyslipaemia	0.5 (0.4; 0.6)	0.7 (0.5; 1.0)	1	<0.0001
Dyslipidaemia diagnosed <1 year before[b]	12.3 (7.1; 21.3)	17.7 (8.7; 35.8)	1	<0.0001
Hypertension	0.3 (0.2; 0.4)	0.5 (0.3; 0.7)	1	<0.0001
Hypertension diagnosed <1 year before[c]	16.4 (10.3; 26.0)	12 (6.8; 21.4)	1	<0.0001
Malnutrition	2 (1.5; 2.7)	1.3 (0.8; 2.1)	1	<0.0001
Albumin (g/dl)	−0.3 (−0.37; −0.22)	−0.1 (−0.21; 0.01)	0	<0.0001
Creatinine (mg/dl)	1.1 (0.8; 1.3)	−0.3 (−0.61; 0.01)	0	<0.0001
24-h diuresis (ml)	−378 (−492; −263.9)	−142 (−306.3; 22.3)	0	<0.0001
Haemoglobin <11 g/dl	3.2 (2.5; 4.0)	0.9 (0.7; 1.2)	1	<0.0001
Ferritin ≥500 ng/ml	2.7 (1.9; 3.8)	1.2 (0.6; 2.1)	1	<0.0001
Ca <8.4 mg/dl	1.9 (1.4; 2.5)	0.8 (0.5; 1.3)	1	<0.0001
PO_4 >5.5 mg/dl	1.6 (1.3; 1.9)	0.8 (0.6; 1.1)	1	<0.0001

Effect measures are expressed as a difference in means for quantitative variables and odds ratio for qualitative variables, together with their 95% confidence interval, with respect to the reference subgroup (predialysis nephrological care >12 months). For qualitative variables with more than one category, the odds ratio has been calculated with respect to the absence of the displayed category.
N = sample size; CKD = chronic kidney disease.
*Bonferroni-corrected significance limit: $P < 0.00022$ (0.05/228).
[a]Only analysed in the subgroup of diabetic patients where the information was available, $N = 460$.
[b]Only analysed in the subgroup of dyslipidaemic patients where the information was available, $N = 512$.
[c]Only analysed in the subgroup of hypertensive patients where the information was available, $N = 1156$.

studies in Europe (the Netherlands [7,8], France [10–12], Italy [13,14] and Sweden [15]) and North America (CHOICE [29], Wave-2 USRDS [30–32]), the risk factors associated with cardiovascular morbidity and mortality in these patients. The ANSWER study enrolled all consecutive incident haemodialysis patients, whereas most other haemodialysis studies have excluded patients who did not survive the first 3 months [7,14,29,31] or have included 'prevalent' patients (DOPPS [33], MAR [34]). Studies of 'incident' populations are needed to verify the previously described associations for 'prevalent' populations, because those studies suffered from the bias of not enrolling patients with higher cardiovascular risk, that is, those who die in the first months after dialysis onset.

The sociodemographic characteristics of our cohort are similar to those reported for other European incident populations. The mean age and percentage of patients older than 65 or 75 years in our sample are similar to those reported in other European countries [8–10,14]) and the USA [35].

About a quarter of the patients developed renal failure due to diabetic nephropathy. This figure is similar to that reported in other European studies [12,13,16,36–38]. The prevalence of vascular nephropathy in the present study is also similar to that reported in other Spanish and Italian studies [13,16], but it seems slightly lower than the prevalence reported from the Netherlands [8] or France [9,10,12]. Our results support the findings of López Revuelta and colleagues [16] that the aetiology of chronic kidney disease in European incident haemodialysis populations is different from the aetiology among the incident population in the USA, where diabetes and hypertension account for >70% of cases, compared with <50% in Europe.

Due to the high mean age of the study population and significant prevalence of comorbidities, the functional status was moderately affected, consistent with findings of previous Spanish studies in the incident haemodialysis population [38]. Interestingly, the functional status in our patients is better than that of incident patients in the UK of similar mean age [39,40], but is similar to that of American patients, who were an average of 10 years younger [41]. The gender distribution in both the UK and US samples was different from ours (more males in the UK and US samples), but the worse functional status of the UK sample may be related to the higher proportion of unplanned initiation of haemodialysis in that population (44–47%) [39,40]. The QoL results revealed severely affected physical and

Table 7. Differences in clinical and sociodemographic characteristics of incident haemodialysis patients grouped by the presence of previous ischaemic cardiovascular disease (only those variables with significant differences are displayed)

	With previous ischaemic CVD ($N = 1640$, 70%)	Without previous ischaemic CVD, reference ($N = 701$, 30%)	P-value*
Age (years)	7.3 (5.9; 8)	0	<0.0001
Karnofsky score	−7.4 (−8.4; −5.5)	0	<0.0001
Charlson index	2.3 (2.1; 2.4)	0	<0.0001
Male gender	2 (1.6; 2.5)	1	<0.0001
CKD aetiology = diabetic nephropathy	2.5 (2.0; 3.0)	1	<0.0001
CKD aetiology = vascular nephropathy	2.4 (1.9; 3.0)	1	<0.0001
Former smoker	1.8 (1.4; 2.3)	1	<0.0001
Current smoker	1.7 (1.2; 2.3)	1	<0.0001
Employment status = retired	2.5 (2.0; 3.1)	1	<0.0001
Vascular access = IAVF	0.6 (0.5; 0.7)	1	<0.0001
Diabetes mellitus	2.7 (2.2; 3.2)	1	<0.0001
Dyslipidaemia	2.3 (1.0; 2.7)	1	<0.0001
Hypertension	2.7 (1.9; 3.7)	1	<0.0001
Hypertension diagnosed >5 years before[a]	2.1 (1.6; 2.8)	1	<0.0001
HbA1c (%)	0.5 (0.2; 0.7)	0	0.0002
Albumin (g/dl)	−0.1 (−0.16; −0.03)	0	0.0002
Cholesterol (mg/dl)	−8 (−12.3; −3.6)	0	<0.0001
HDL-cholesterol (mg/dl)	−4.5 (−7.2; −1.7)	0	<0.0001
Creatinine (mg/dl)	−0.8 (−1; −0.5)	0	<0.0001
24-h diuresis (ml)	−185 (−285; −84.9)	0	<0.0001
PO_4 > 5.5 mg/dl	0.7 (0.6; 0.8)	1	0.0002

Effect measures are expressed as a difference in means for quantitative variables and odds ratio for qualitative variables, together with their 95% confidence interval, with respect to the reference subgroup (non-previous ischaemic cardiovascular disease). For qualitative variables with more than one category, the odds ratio has been calculated with respect to the absence of the displayed category.
N = sample size; CKD = chronic kidney disease; CVD = cardiovascular disease.
*Bonferroni-corrected significance limit: $P < 0.00022$ (0.05/228).
[a]Only analysed in the subgroup of hypertensive patients where the information was available, $N = 1174$.

mental health, similar to previous reports of Spanish incident haemodialysis patients [42,43].

Regarding the use of catheter as first vascular access, we found fewer shunts than reported in the DOPPS study for Spain. This may be attributed to the differences among recruiting facilities [44,45]. The fact that there are many more facilities participating in the ANSWER study (147 compared with 20 in the DOPPS) probably provides a more confident estimate of the real situation of vascular access in Spain. Furthermore, our results are in agreement with previous studies in Spain, in which between 46% and 51% of incident patients were found not to have permanent AVF access [46,47], and this proportion has remained stable during the past few years [48].

Although a minimum nephrological follow-up of 6 months prior to haemodialysis onset is recommended, late referral has been reported for about a quarter of Spanish incident patients, similar to previous findings from other European countries [9,49,50]. The high proportion of catheter use in the late referral group, also described in DOPPS [51], highlights the need for early referral as far as possible. A shorter time of nephrologist follow-up has been associated with higher mortality in haemodialysis patients independent of catheter vascular access [52], indicating the presence of other negative factors in these patients. The worse clinical status at the onset of haemodialysis in the late referral subgroup may contribute to this phenomenon [53,54].

With respect to kidney function at haemodialysis onset in our patients, the GFR was lower in our patients compared with reports from previous studies in Spain and other European countries [49,50,55], and 8 in 10 patients were below the limit of 10 ml/min recommended by the K/DOQI guidelines [56]. These data suggest a delayed onset of haemodialysis in our settings. Initiation of haemodialysis above this limit may prolong survival according to the NECOSAD study [57]. Other haemodialysis quality indicators, such as the low initial eKt/V, also suggest inadequate haemodialysis onset although almost half the patients are using high-flux membranes.

About 10% of the population had history of neoplasia. This figure is a bit higher than that reported for the Spanish DOPPS cohort (6%), but agrees with the 9% of the EURO-DOPPS [36] prevalent patients and also with the 11% reported for the incident French population [10] (although that study considered only active neoplasia).

The antecedents of cardiovascular disease in our sample were, as expected, very common. The prevalence of ischaemic heart disease was similar to that in Italy, France and Sweden [11,14,15,58], but lower than that in the UK, Germany and the USA [58,35]. The prevalence of peripheral vascular disease was similar to that in Sweden and

the USA [14,35], but lower than the prevalence in France, Germany, Italy and the UK [9,11,58]. The prevalence of heart failure was similar to that in France, Germany and Italy [9,58], but lower than the prevalence in the UK and the USA [58,35]. Finally, the prevalence of cerebrovascular disease was a little higher than or similar to that in Italy, France, Sweden and the USA [9,11,13,15,35]. The differences in these prevalences must be viewed with caution, as they may be related to different disease definitions or methods of collection.

With regard to the prevalence of classic cardiovascular risk factors, the majority of patients had uncontrolled hypertension, despite almost all patients receiving antihypertensive treatment. Diabetes affected one-third of our patients, similar to other European studies [12,15], and far from one-half in the USA [59,35]. Glycaemic control was poor, and 1 in 5 patients were obese. Both the proportion of obese patients and the mean BMI were highly consistent with the findings from almost all previously described incident European and North American populations [7,15,32,35,50,59]. However, malnutrition was less prevalent in our sample than in the Netherlands or Sweden [7,15]. This discordance is probably due to an underestimation of malnutrition by Spanish physicians, as one-third of our patients had low albumin levels. The high prevalence of other emergent cardiovascular risk factors (hyperhomocysteinaemia, hyperfibrinogenaemia and elevated lipoprotein (a)) in our sample with respect to the general Spanish population [60] agrees with previous results in maintenance [61] and incident [10] haemodialysis patients. Since this is a cross-sectional analysis, the causal relationship between all these findings and cardiovascular status cannot be verified. Future data will produce more reliable results regarding the predictive value of the collected variables.

Anaemia-related target ranges, which are strongly predictive of reduced mortality in chronic kidney disease [2,6], were achieved by a relatively low percentage of patients. Despite almost 1 in 2 patients receiving ESAs prior to haemodialysis onset, >50% were anaemic, and more than one-third had iron deficiency, which suggests incorrect ESA administration and insufficient correction of iron stores. Less than 1 in 10 patients were within the K/DOQI targets for all four bone and mineral metabolism parameters, iPTH being the most uncontrolled. These findings correlate with those from the NECOSAD study [7]. Data from prevalent populations indicate that the degree of control of bone mineral disease is not better after the onset of haemodialysis [62]. Studies of the recently available therapies (calcimimetics, calcium-free P-chelating agents or new vitamin D analogues) may help to resolve this issue in the near future.

With regard to the classic cardiovascular risk factors, the expected associations with previous smoking, dyslipidaemia, hypertension and diabetes were observed in patients with a history of cardiovascular disease. However, the cholesterol levels were lower in the group with cardiovascular disease, which could be related to the worse nutritional status in those patients.

This cohort study has some limitations. The non-random (but consecutive) patient selection may have resulted in some selection bias. However, the extended inclusion period and the fact that the final sample represents more than half of all incident Spanish patients during this period [27,28] support the validity of the recruited cohort. In addition, as enrolment at each site was stratified according to the incidence of haemodialysis in a reference population, the 2341 patients in the study were considered to be representative of the target population in Spain.

For the purposes of international comparisons, our study confirms that there are important differences in the prevalence of cardiovascular and mortality risk factors, especially with respect to North American populations. Spain has an extremely high rate of renal transplantation (47% of patients on renal replacement therapy in 2004 [28] versus 29% in the USA [63]). This should be taken into account when comparing the prospective cardiovascular morbidity and mortality results in the future.

In summary, the ANSWER study provides valuable new data, thus adding to our knowledge of the characteristics of incident haemodialysis patients in Spain and Europe. Most patients present at an advanced age and have hypertension, diabetes and previous cardiovascular disease. Their functional status is moderately affected, considering the high mean age. Our results also show that in the Spanish setting, haemodialysis is started too late and that patients are also referred too late to the nephrologist (late referral for 1 in 4 patients with diabetic and vascular nephropathy). Also, not enough effort was made to place a permanent AVF before haemodialysis onset in patients referred >6 months ago, and such efforts must be specially made in older and diabetic patients.

This study has also revealed an extremely high prevalence of emergent and uraemia-related cardiovascular risk factors and poor glycaemic control, low HDL-C, hypertension, anaemia, malnutrition, hypo- and hyperparathyroidism, hyperphosphataemia and hypo- and hypercalcaemia. These results reflect the need for improving the therapeutic management of incident dialysis patients before the onset of haemodialysis.

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