An Epidemiological Study of Hemodialysis Patients Based on the European Fresenius Medical Care Hemodialysis Network: Results of the ARO Study

Angel L.M. de Francisco^a Joseph Kim^b Stefan D. Anker^c Vasily Belozero^d Bernard Canaud^e
Charles Chazot^f Tilman B. Drüeke^g Kai-Uwe Eckardt^h Jürgen Floegeⁱ Florian Kronenberg^j
Iain C. Macdougall^k Daniele Marcelli^l Bart Molemans^m Jutta Passlick-Deetjen^l
Guntram Schernthanerⁿ Peter Stenvinkel^o David C. Wheeler^p Bruno Fouqueray^q
Pedro Aljama^r

^aServicio de Nefrología, Hospital Universitario Valdecilla, Santander, Spain; ^bDepartment of Epidemiology, Amgen Ltd., Uxbridge, UK; ^cDepartment of Cardiology, Applied Cachexia Research, Campus Virchow Klinikum, Charité, Berlin, Germany, and Center for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy; ^dDepartment of Health Economics, Amgen Inc., Thousand Oaks, Calif., USA; ^eService de Néphrologie, Dialyse et Soins Intensifs, Hôpital Lapeyronie, Montpellier, France; ^fCentre de Rein Artificiel, Tassin-la-Demi-Lune, et ^gFacultés de Médecine et de Pharmacie, Université de Picardie, Inserm ERI-12, Amiens, France; ^hDepartment of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, and ⁱDivision of Nephrology, RWTH University of Aachen, Aachen, Germany; ^jDivision of Genetic Epidemiology, Innsbruck Medical University, Innsbruck, Austria; ^kDepartment of Renal Medicine, King's College Hospital, London, UK; ^lDepartment of NephroCare Coordination, Fresenius Medical Care, Bad Homburg, Germany; ^mDepartment of Nephrology, Amgen Ltd., Uxbridge, UK; ⁿDepartment of Medicine I, Rudolfstiftung Hospital, Vienna, Austria; ^oDepartment of Renal Medicine, Karolinska Institute, Stockholm, Sweden; ^pCenter for Nephrology, Royal Free Campus, University College London Medical School, London, UK; ^qDepartment of Nephrology, Amgen (Europe) GmbH, Zug, Switzerland; ^rDepartment of Nephrology, Hospital Reina Sofia de Cordoba, Cordoba, Spain

Key Words

Anemia · Epidemiology · Hemodialysis · Mineral disorders · Mortality, practice patterns

Abstract

Background/Aims: ARO, an observational study of hemodialysis (HD) patients in Europe, aims to enhance our understanding of patient characteristics and practice patterns to improve patient outcome. **Methods:** HD patients (n = 8,963) from 134 Fresenius Medical Care facilities treated between 2005 and 2006 were randomly selected from 9 European

countries (Czech Republic, France, Hungary, Italy, Poland, Portugal, Spain, Slovak Republic and Slovenia) and Turkey. Information was captured on demographics, comorbidities, medications, laboratory and dialysis parameters, and outcome. **Results:** Patients were followed for 1.4 ± 0.7 years. Wide variation by country was observed for age, sex and diabetes as a cause of chronic kidney disease. Cardiovascular disease was present in 73% of patients. Dialysis parameters were homogeneous across countries. Arteriovenous fistulas were frequently used (73%). More incident patients had hemoglobin <11 g/dl than prevalent patients (50 vs. 33%, respectively). Phosphatemia and intact parathyroid hormone were similar between incident and prevalent patients (4.7 ± 1.2 mg/dl and 190 vs. 213 ng/l, respectively). Medication use varied widely by country. In total, 5% of patients underwent renal transplantation. Overall death rate was 124/1,000 pa-

Except for V.B., all authors are ARO-CKD Research Initiative Steering Committee Members.

tient-years. **Conclusion:** ARO revealed differences in HD practice patterns and patient characteristics in the 10 participating countries. Future ARO studies will fill gaps in the knowledge about the care of European HD patients.

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Introduction

Significant progress has been made in the care of patients with chronic kidney disease (CKD) over recent decades. Nevertheless, the prevalence of CKD requiring dialysis has been steadily increasing [1, 2], and the mortality rate in patients undergoing hemodialysis (HD) remains high [3]. Several epidemiological studies have been conducted in the United States to evaluate the patterns of clinical practice, the achievement of treatment guidelines and the occurrence of outcome in HD patients [4–7]. Due to the lack of other available data, the results have been extrapolated to other populations despite known differences in patient characteristics [3, 8, 9] and clinical practice patterns [9].

The only population-based study published to date that captures both US and European HD populations is the Dialysis Outcome and Practice Patterns Study (DOPPS) [4, 8, 10–12]. However, the generalizability of these results to the wider European HD population may be limited since only patients from Western Europe were selected. Other population-based studies have been carried out in European HD patients, including NECOSAD (Netherlands Cooperative Study on the Adequacy of Dialysis) [13–15] and COSMOS [16]. However, their findings may be limited since NECOSAD is a single-country study and COSMOS focuses on issues related to bone and mineral disorders. The ARO (Analyzing Data, Recognizing Excellence and Optimizing Outcome) CKD Research Initiative began in 2007 to improve HD patient outcome through better understanding of patient characteristics and practice of care in Europe. This study is based on a clinical database from European Fresenius Medical Care (EU-FME) dialysis centres. A unique strength of this study is that it includes not only patients from Western Europe but also patient populations from Eastern Europe and Turkey who have been largely neglected in other studies.

The aims of this report are to present the design and methodology of the ARO-CKD Research Initiative, and describe the population currently investigated with respect to patient characteristics, dialysis and biochemical parameters, medication use and patient outcome.

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Fig. 1. Open-cohort study design. The study includes incident (<6 months of dialysis at the time of enrolment) and prevalent (≥ 6 months of dialysis) hemodialysis patients. A prevalent dialysis patient who died or experienced a censoring event (lost to follow-up or successful renal transplant) over the course of the study was replaced with a randomly selected incident patient from the same dialysis facility. X = An event (e.g. death or successful renal transplant); LTF = a patient lost to follow-up.

Subjects and Methods

Source Population

The source population consisted of patients who underwent HD at selected FME facilities between the 1st of January 2005 and the 31st of December 2006. Anonymized patient data were captured using the European Clinical Database (EuCliD), which has been described elsewhere [17–19]. Informed consent was obtained from all patients by FME.

Selection of Participants

Patients were selected into this study using an open-cohort design [20] because it allowed the selection of a heterogeneous mix of patients (i.e. incident and prevalent dialysis patients). In addition, it maintained a fixed period of follow-up (i.e. 15,000 patient-years): each patient who died or experienced a censoring event (i.e. lost to follow-up or successful renal transplant) was replaced with a randomly selected incident patient from the same facility. Incident patients had undergone HD for less than 6 months at the start of the study; prevalent patients had undergone HD for 6 months or longer (fig. 1).

A random sample of HD patients was selected by (1) defining geographic strata based on the number of FME facilities within specific countries on January 1, 2005; (2) selecting a random sample of eligible facilities within each stratum, and (3) randomly selecting patients from these facilities. Eligible facilities were part of FME for at least 12 months prior to January 1, 2005, and remained in the network on December 31, 2006. Each center must have treated at least 25 patients as of December 1, 2005. A maximum of 25 sites were eligible for random selection within each country. Twenty-five sites were randomly chosen in Portugal and

Spain due to the higher number of centers; all eligible sites were included elsewhere. In total, patients were selected from 172 facilities in 11 countries (Czech Republic, France, Hungary, Italy, Poland, Portugal, Spain, Slovak Republic, Slovenia, Turkey and the United Kingdom).

A total of 11,153 patients (7,037 prevalent and 4,116 incident patients) were sampled and contributed approximately 15,000 patient-years of observation over a 2-year follow-up period (January 2005 to December 2006).

Variables of Interest

Demographic characteristics available for this study included age, gender, smoking history, height and weight both before and after dialysis. Information on medical history included the etiology of CKD, history of cardiovascular disease (CVD; defined as peripheral vascular disease, congestive heart failure, coronary artery disease, myocardial infarction, and/or angina, cerebrovascular accident and/or transient ischemic attack), history of diabetes (defined as a recorded history of diabetes or use of diabetic medication) and history of cancer.

Detailed information on dialysis vintage, dialysis access [arteriovenous (AV) fistula, AV graft, and temporary or permanent venous catheter], actual blood flow and dialysis adequacy (single-pool Kt/V) [21] was also obtained. All dialyzers were single use. Information on the dialyzer type was not available.

Laboratory data included circulating markers for anemia (hemoglobin and ferritin), bone and mineral metabolism [total calcium, phosphate and intact parathyroid hormone (iPTH)], lipid metabolism (cholesterol, high- and low-density cholesterol) and inflammation (C-reactive protein and albumin). There was no standard assay method to evaluate PTH.

Information on medication use included the name of the product, duration of use and the weekly dose. Data were available on phosphate binders, oral vitamin D (data on intravenous vitamin D were not available), calcimimetics, erythropoietin-stimulating agents (ESA), platelet inhibitors, statins, anti-hypertensives (including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), oral anticoagulants, insulin and oral anti-diabetics.

Outcome data were available for hospitalization, renal transplantation and death. Reasons for hospitalization and cause of death were coded according to the WHO International Classification of Diseases (10th Revision; ICD-10) coding scheme. Patients were considered lost to follow-up if they left a dialysis facility and failed to return within 45 days.

Statistical Analysis

Normally distributed variables were described using means and standard deviations; medians and interquartile ranges were used otherwise. Where appropriate, variables were grouped into clinically meaningful classes for further analysis. Bivariate comparisons were performed using Student's *t* test, a Wilcoxon rank sum test or a χ^2 test as appropriate. Mortality and hospitalization rates were calculated using Poisson regression. Adjusted mortality rates were derived by including age, gender and duration of dialysis treatment as covariates in the model.

Dialysis parameters, laboratory parameters and medication use were calculated based on the average monthly values recorded and reported as the average 6-month value.

All statistical analyses were performed using SAS for Windows (version 9.0; SAS, Cary, N.C., USA) and were reproduced independently by a second statistician.

Results

Of the 11,153 patients selected into the study, we excluded patients recruited from centers where the majority of data on key dialysis parameters (i.e. actual blood flow or Kt/V) were missing ($n = 1,352$). UK patients were also excluded because information on medication was not available ($n = 838$). The remaining 8,963 patients (3,396 incident and 5,567 prevalent patients) were included in the analysis. Patients were followed for 1.4 ± 0.7 years (incident patients: 1.0 ± 0.6 years, and prevalent patients: 1.6 ± 0.6 years), contributing to 12,194 patient-years of follow-up.

Demographics and Baseline Characteristics

Spain ($n = 1,707$), Turkey ($n = 1,600$) and Italy ($n = 1,586$) contributed the largest numbers of patients to the overall cohort (table 1). The youngest patients were from Turkey (56 ± 15 years) and the oldest patients from France (69 ± 15 years). The most common CKD etiology was glomerulonephritis (16%), followed by tubulointerstitial nephritis (14%), diabetic nephropathy (14%) and hypertension (13%). A history of CVD was present in 73% of patients (50% incident and 87% prevalent patients), ranging from 64% in France to 91% in Slovenia. The prevalence of diabetes was 25%, which varied by country from 15% in Spain to 42% in the Czech Republic.

Dialysis Parameters

Prevalent patients had undergone HD on average for 5 years prior to study entry (table 2). The mean actual blood flow in prevalent patients was 313 ± 48 ml/min, ranging from 260 ± 35 ml/min in Slovenia to 349 ± 48 ml/min in Italy. Mean actual blood flow was higher in prevalent than incident patients (313 vs. 283 ml/min). Kt/V ranged from 1.4 ± 0.3 in Hungary and Poland to 1.8 ± 0.3 in the Czech Republic. Consistent with the findings for actual blood flow, Kt/V was higher among prevalent patients than incident patients (1.7 ± 0.3 vs. 1.5 ± 0.3 , respectively). An AV fistula was the preferred mode of vascular access compared with AV graft or venous catheter across each country. Prevalent patients were significantly more likely to be dialyzed with an AV fistula than incident patients (78 vs. 64%).

Table 1. Patient baseline characteristics by country

Characteristics	Czech Republic (n = 320)	France (n = 352)	Hungary (n = 1,278)	Italy (n = 1,586)	Poland (n = 163)	Portugal (n = 1,244)	Slovak Republic (n = 545)
Prevalent dialysis vintage, n (%)	184 (57.5)	196 (55.7)	748 (58.5)	1,064 (67.1)	84 (51.5)	836 (67.2)	354 (65.0)
Age, years	66.3 ± 13.2	68.9 ± 15.0	62.2 ± 14.4	65.7 ± 14.0	62.4 ± 14.9	64.5 ± 15.2	58.1 ± 13.6
Body mass index	26.5 ± 6.0	24.9 ± 5.3	25.1 ± 5.7	25.4 ± 4.7	26.3 ± 4.8	25.2 ± 4.3	26.4 ± 5.3
Gender							
Female	162 (50.6)	145 (41.2)	650 (50.9)	648 (40.9)	70 (42.9)	501 (40.3)	220 (40.4)
Male	158 (49.4)	207 (58.8)	628 (49.1)	938 (59.1)	93 (57.1)	743 (59.7)	325 (59.6)
Etiology of CKD							
Hypertension/vascular	44 (13.8)	90 (25.6)	80 (6.3)	269 (17.0)	8 (4.9)	190 (15.3)	12 (2.2)
Glomerulonephritis	66 (20.6)	104 (29.5)	259 (20.3)	207 (13.1)	36 (22.1)	175 (14.1)	237 (43.5)
Diabetic nephropathy	60 (18.8)	8 (2.3)	57 (4.5)	300 (18.9)	26 (16.0)	250 (20.1)	12 (2.2)
Tubulointerstitial nephritis	85 (26.6)	28 (8.0)	225 (17.6)	176 (11.1)	38 (23.3)	154 (12.4)	218 (40.0)
Polycystic kidney disease	13 (4.1)	21 (6.0)	73 (5.7)	120 (7.6)	8 (4.9)	83 (6.7)	27 (5.0)
Miscellaneous	8 (2.5)	50 (14.2)	51 (4.0)	34 (2.1)	5 (3.1)	42 (3.4)	6 (1.1)
Unknown/missing	44 (13.8)	51 (14.5)	533 (41.7)	480 (30.3)	42 (25.8)	350 (28.1)	33 (6.1)
Diabetes mellitus	134 (41.9)	82 (23.3)	328 (25.7)	386 (24.3)	57 (35.0)	323 (26.0)	180 (33.0)
History of cardiovascular disease	257 (80.3)	224 (63.6)	904 (70.7)	1,091 (68.8)	144 (88.3)	943 (75.8)	491 (90.1)
History of cancer	31 (9.7)	19 (5.4)	99 (7.7)	84 (5.3)	18 (11.0)	81 (6.5)	30 (5.5)

Baseline includes the 6 months of data collection for any parameter measured. Continuous variables are reported using means ± SD. Categorical variables are reported as n (%). Prevalent dialysis vintage was defined as having undergone >6 months of hemodialysis at the start of the study. Miscellaneous = Rare causes of CKD with no standard diagnosis; missing = the cause of CKD was not recorded;

unknown = the cause of CKD is unknown. The tabulation for cardiovascular disease (any) includes outcome according to identified ICD-10 codes (angina, coronary artery disease, myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular accident).

Table 2. Distribution of dialysis parameters during the first 6 months of follow-up by dialysis vintage and country

	Czech Republic (n = 320)	France (n = 352)	Hungary (n = 1,278)	Italy (n = 1,586)	Poland (n = 163)	Portugal (n = 1,244)	Slovak Republic (n = 545)
<i>Incident patients</i>	(n = 136)	(n = 156)	(n = 530)	(n = 522)	(n = 79)	(n = 408)	(n = 191)
Actual blood flow, ml/min	282.0 ± 37.7	–	263.8 ± 51.5	313.5 ± 59.1	266.8 ± 68.5	292.6 ± 48.8	258.2 ± 50.2
Kt/V	1.6 ± 0.3	1.6 ± 0.4	1.3 ± 0.3	1.5 ± 0.3	1.3 ± 0.3	1.5 ± 0.3	1.4 ± 0.3
Dialysis access							
AV fistula	87 (64.0)	64 (41.0)	319 (60.2)	423 (81.0)	53 (67.1)	245 (60.0)	114 (59.7)
AV graft	4 (2.9)	1 (0.6)	0	6 (1.1)	5 (6.3)	43 (10.5)	1 (0.5)
Catheter, temporary	15 (11.0)	0	108 (20.4)	32 (6.1)	16 (20.3)	39 (9.6)	4 (2.1)
Catheter, permanent	25 (18.4)	27 (17.3)	49 (9.2)	53 (10.2)	2 (2.5)	72 (17.6)	27 (14.1)
Other/missing	5 (3.7)	64 (41.0)	54 (10.2)	8 (1.5)	3 (3.8)	9 (2.2)	45 (23.6)
<i>Prevalent patients</i>	(n = 184)	(n = 196)	(n = 748)	(n = 1,064)	(n = 84)	(n = 836)	(n = 354)
Duration of dialysis treatment, years	4.2 ± 4.5	6.5 ± 7.4	4.2 ± 3.7	6.4 ± 6.1	3.7 ± 3.8	5.2 ± 4.4	3.9 ± 3.6
Actual blood flow, ml/min	320.2 ± 41.4	–	302.3 ± 39.9	348.5 ± 48.4	294.5 ± 61.7	309.2 ± 46.1	286.3 ± 42.0
Kt/V	1.8 ± 0.2	1.8 ± 0.4	1.5 ± 0.2	1.7 ± 0.2	1.5 ± 0.2	1.7 ± 0.3	1.5 ± 0.2
Dialysis access							
AV fistula	131 (71.2)	95 (48.5)	571 (76.3)	961 (90.3)	70 (83.3)	565 (67.6)	282 (79.7)
AV graft	9 (4.9)	4 (2.0)	0	21 (2.0)	6 (7.1)	139 (16.6)	0
Catheter, temporary	26 (14.1)	2 (1.0)	42 (5.6)	14 (1.3)	5 (6.0)	55 (6.6)	10 (2.8)
Catheter, permanent	8 (4.3)	16 (8.2)	77 (10.3)	57 (5.4)	1 (1.2)	66 (7.9)	26 (7.3)
Other/missing	10 (5.4)	79 (40.3)	58 (7.8)	11 (1.0)	2 (2.4)	11 (1.3)	36 (10.2)

Continuous variables are reported using means ± SD. Categorical variables are reported using n (%). – = Missing data; K = dialyzer clearance of urea; t = dialysis time; V = patient's total body water. Incident patients were on HD therapy <6 months at the start of the study; prevalent patients were on HD therapy for ≥6 months. The last mode of dialysis access used at the 6-month follow-up is listed.

Slovenia (n = 168)	Spain (n = 1,707)	Turkey (n = 1,600)	Total (n = 8,963)
130 (77.4)	897 (52.5)	1,074 (67.1)	5,567 (62.1)
64.0 ± 12.2	65.9 ± 14.6	56.4 ± 14.5	63.0 ± 14.9
26.5 ± 5.0	25.3 ± 4.8	24.8 ± 4.5	25.4 ± 4.8
75 (44.6)	636 (37.3)	705 (44.1)	3,812 (42.5)
93 (55.4)	1,071 (62.7)	895 (55.9)	5,151 (57.5)
17 (10.1)	163 (9.5)	316 (19.8)	1,189 (13.3)
42 (25.0)	232 (13.6)	111 (6.9)	1,469 (16.4)
24 (14.3)	109 (6.4)	371 (23.2)	1,217 (13.6)
38 (22.6)	145 (8.5)	125 (7.8)	1,232 (13.7)
13 (7.7)	71 (4.2)	57 (3.6)	486 (5.4)
5 (3.0)	115 (6.7)	46 (2.9)	362 (4.0)
29 (17.3)	872 (51.1)	574 (35.9)	3,008 (33.6)
41 (24.4)	263 (15.4)	448 (28.0)	2,242 (25.0)
153 (91.1)	1,241 (72.7)	1,086 (67.9)	6,534 (72.9)
17 (10.1)	145 (8.5)	31 (1.9)	555 (6.2)

Hemoglobin

The mean hemoglobin value achieved was 11.3 g/dl, ranging from 10.4 g/dl in the Slovak Republic to 11.9 g/dl in the Czech Republic, Slovenia and Spain (table 3). Incident patients were more likely to have a hemoglobin level <11 g/dl (50 vs. 33%) and were less likely to have a hemoglobin level >13 g/dl than prevalent patients (7 vs. 12%).

Other Laboratory Parameters

Table 4 shows that prevalent patients had higher levels of total serum calcium than incident patients (9.2 ± 0.9 vs. 8.9 ± 0.8 mg/dl, respectively). Phosphatemia was similar in incident and prevalent patients (4.7 ± 1.2 mg/dl) despite wide variation across countries. iPTH values were comparable in incident and prevalent patients (190 vs. 213 ng/l).

Ferritin levels were consistently higher in prevalent patients than incident patients (475 vs. 267 μ g/l, respectively). C-reactive protein levels were relatively comparable between incident and prevalent patients, whereas serum albumin levels were higher in prevalent than incident patients, with a wide variation by country (3.9 ± 0.5 vs. 3.7 ± 0.5 g/dl, respectively).

Medication Use

Statin use varied widely and the prevalence was generally low (13%). Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use ranged from 6% in Turkey to 41% in Poland, while less than one third of patients were treated with another anti-hypertensive drug. At least 76% of patients were on ESA therapy, with the exception of Turkey (59%; table 5). In addition, incident patients were more likely to have received ESA than prevalent patients (82 vs. 76%). The frequency of phosphate binder use ranged from 24% in Italy to 76% in Poland and the type varied by country. Likewise, the use of oral vitamin D sterols differed widely across the countries (from 3% in Turkey to 52% in the Czech Republic).

Patient Outcome

During the study period (2005–2006), there were 1,678 deaths, 42% of which were attributed to CVD (table 6). The overall crude mortality rate was 138 deaths per 1,000 patient-years, which was higher for incident than for prevalent patients (158 vs. 130 deaths per 1,000 patient-years). When adjusted for age, gender and duration of dialysis, the death rate was 124 per 1,000 patient-years, ranging from 73 (Slovenia) to 182 per 1,000 patient-years (Slovak Republic).

Slovenia (n = 168)	Spain (n = 1,707)	Turkey (n = 1,600)	Total (n = 8,963)
(n = 38)	(n = 810)	(n = 526)	(n = 3,396)
226.1 ± 46.7	286.4 ± 37.3	274.8 ± 42.1	283.1 ± 51.1
1.3 ± 0.3	1.4 ± 0.3	1.5 ± 0.3	1.5 ± 0.3
29 (76.3)	521 (64.3)	329 (62.5)	2,184 (64.3)
1 (2.6)	3 (0.4)	7 (1.3)	71 (2.1)
7 (18.4)	105 (13.0)	75 (14.3)	401 (11.8)
1 (2.6)	101 (12.5)	73 (13.9)	430 (12.7)
0	80 (9.9)	42 (8.0)	310 (9.1)
(n = 130)	(n = 897)	(n = 1,074)	(n = 5,567)
6.2 ± 5.4	5.0 ± 5.2	4.5 ± 3.5	5.0 ± 4.9
260.0 ± 34.9	303.1 ± 41.8	312.4 ± 35.1	313.1 ± 47.7
1.6 ± 0.3	1.6 ± 0.2	1.7 ± 0.3	1.7 ± 0.3
116 (89.2)	628 (70.0)	946 (88.1)	4,365 (78.4)
4 (3.1)	3 (0.3)	13 (1.2)	199 (3.6)
6 (4.6)	61 (6.8)	22 (2.0)	243 (4.4)
1 (0.8)	114 (12.7)	46 (4.3)	412 (7.4)
3 (2.3)	91 (10.1)	47 (4.4)	348 (6.3)

Table 3. Achieved hemoglobin levels during the first 6 months of follow-up by dialysis vintage and country

All patients	Czech Republic (n = 320)	France (n = 352)	Hungary (n = 1,278)	Italy (n = 1,586)	Poland (n = 163)	Portugal (n = 1,244)	Slovak Republic (n = 545)
Hemoglobin, g/dl	11.9 ± 1.4	11.4 ± 1.2	11.1 ± 1.3	11.2 ± 1.2	11.1 ± 1.2	11.8 ± 1.3	10.4 ± 1.1
Incident patients	(n = 121)	(n = 147)	(n = 326)	(n = 443)	(n = 75)	(n = 327)	(n = 183)
<11 g/dl	43 (35.5)	63 (42.9)	168 (51.5)	247 (55.8)	44 (58.7)	121 (37.0)	144 (78.7)
11–12 g/dl	29 (24.0)	47 (32.0)	89 (27.3)	153 (34.5)	19 (25.3)	101 (30.9)	31 (16.9)
>12–13 g/dl	36 (29.8)	30 (20.4)	49 (15.0)	35 (7.9)	11 (14.7)	75 (22.9)	5 (2.7)
>13 g/dl	13 (10.7)	7 (4.8)	20 (6.1)	8 (1.8)	1 (1.3)	30 (9.2)	3 (1.6)
Prevalent patients	(n = 171)	(n = 157)	(n = 83)	(n = 926)	(n = 79)	(n = 748)	(n = 336)
<11 g/dl	19 (11.1)	46 (29.3)	23 (27.7)	286 (30.9)	25 (31.6)	120 (16.0)	235 (69.9)
11–12 g/dl	31 (18.1)	54 (34.4)	35 (42.2)	421 (45.5)	35 (44.3)	228 (30.5)	85 (25.3)
>12–13 g/dl	80 (46.8)	44 (28.0)	20 (24.1)	148 (16.0)	15 (19.0)	266 (35.6)	11 (3.3)
>13 g/dl	41 (24.0)	13 (8.3)	5 (6.0)	71 (7.7)	4 (5.1)	134 (17.9)	5 (1.5)

Continuous variables are reported using means ± SD. Categorical variables are reported as n (%). Incident patients were on HD therapy <6 months at the start of the study; prevalent patients were on HD therapy for ≥6 months. Reported values of achieved hemoglobin levels were calculated using average monthly values of hemoglobin.

Table 4. Laboratory parameters during the first 6 months of follow-up by country

Parameters	Czech Republic (n = 320)	France (n = 352)	Hungary (n = 1,278)	Italy (n = 1,586)	Poland (n = 163)	Portugal (n = 1,244)	Slovak Republic (n = 545)
<i>Incident patients</i>	(n = 136)	(n = 156)	(n = 530)	(n = 522)	(n = 79)	(n = 408)	(n = 191)
Calcium, mg/dl	8.9 ± 0.7	9.0 ± 0.7	8.9 ± 0.8	8.8 ± 0.7	8.8 ± 0.8	8.8 ± 0.8	9.0 ± 0.7
Phosphate, mg/dl	4.7 ± 1.1	4.9 ± 1.3	4.8 ± 1.2	4.6 ± 1.1	4.6 ± 1.1	4.5 ± 1.2	4.8 ± 1.2
iPTH, ng/l	174 (93, 316)	168 (99, 274)	158 (87, 304)	211 (115, 361)	232 (116, 323)	208 (112, 379)	202 (110, 347)
Ferritin, µg/l	468 (310, 710)	264 (123, 438)	287 (151, 596)	210 (109, 357)	354 (184, 785)	234 (136, 366)	311 (194, 550)
CRP, mg/l	12 (6, 22)	12 (5, 25)	7 (4, 17)	8 (4, 20)	11 (6, 20)	9 (3, 19)	8 (3, 22)
Serum albumin, g/dl	3.4 ± 0.6	3.4 ± 0.6	3.8 ± 0.5	3.7 ± 0.6	3.9 ± 0.7	3.9 ± 0.7	3.6 ± 0.5
Cholesterol, mmol/l	4.7 ± 1.2	4.5 ± 1.3	4.7 ± 1.2	4.2 ± 1.1	4.5 ± 1.4	4.3 ± 1.1	4.6 ± 1.0
<i>Prevalent patients</i>	(n = 184)	(n = 196)	(n = 748)	(n = 1,064)	(n = 84)	(n = 836)	(n = 354)
Calcium, mg/dl	9.3 ± 0.7	9.2 ± 0.6	9.5 ± 0.8	9.2 ± 0.7	8.8 ± 0.7	9.4 ± 1.4	9.5 ± 0.7
Phosphate, mg/dl	4.9 ± 1.2	4.8 ± 1.4	5.1 ± 1.3	4.4 ± 1.1	4.9 ± 1.1	4.8 ± 1.3	5.3 ± 1.4
iPTH, ng/l	162 (89, 259)	188 (119, 340)	108 (31, 309)	247 (113, 450)	209 (98, 411)	246 (128, 448)	335 (146, 768)
Ferritin, µg/l	944 (620, 1243)	403 (184, 682)	575 (361, 956)	314 (146, 534)	979 (531, 1241)	393 (269, 562)	537 (353, 977)
CRP, mg/l	10 (6, 18)	11 (6, 20)	8 (2, 22)	7 (3, 16)	9 (4, 26)	8 (4, 14)	8 (3, 16)
Serum albumin, g/dl	3.6 ± 0.5	3.6 ± 0.7	3.9 ± 0.5	3.9 ± 0.5	4.2 ± 0.7	4.2 ± 0.6	3.8 ± 0.4
Cholesterol, mmol/l	4.8 ± 1.1	4.6 ± 1.0	4.6 ± 1.3	4.1 ± 0.9	4.7 ± 1.2	4.4 ± 1.1	4.6 ± 1.0

Incident patients were on HD therapy <6 months at the start of the study; prevalent patients were on HD therapy for ≥6 months. All values are reported using means ± SD, except for iPTH, ferritin and C-reactive protein (CRP), where medians (interquartile ranges) are reported (conversion for mg/dl to mmol/l: multiply by 0.2495).

A total of 3,254 patients had at least one hospitalization episode during the course of follow-up. The first hospitalization rate was 344 events per 1,000 patient-years and was higher for incident patients than for prevalent patients (445 vs. 306 events per 1,000 patient-years).

Nearly 5% (438/8,963) of patients had a successful renal transplant during the study, ranging from 1.8% in Turkey to 7.9% in Spain. Twelve percent (1,058/8,963) of patients were lost to follow-up; 65% (5,789/8,963) of patients completed the study.

Slovenia (n = 168)	Spain (n = 1,707)	Turkey (n = 1,600)	Total (n = 8,963)
11.9 ± 1.0	11.9 ± 1.4	10.6 ± 1.4	11.3 ± 1.4
(n = 37)	(n = 703)	(n = 421)	(n = 2,783)
8 (21.6)	227 (32.3)	327 (77.7)	1,392 (50.0)
18 (48.6)	204 (29.0)	71 (16.9)	762 (27.4)
9 (24.3)	166 (23.6)	18 (4.3)	434 (15.6)
2 (5.4)	106 (15.1)	5 (1.2)	195 (7.0)
(n = 130)	(n = 810)	(n = 935)	(n = 4,375)
14 (10.8)	122 (15.1)	535 (57.2)	1,425 (32.6)
47 (36.2)	225 (27.8)	244 (26.1)	1,405 (32.1)
54 (41.5)	272 (33.6)	92 (9.8)	1,002 (22.9)
15 (11.5)	191 (23.6)	64 (6.8)	543 (12.4)

Slovenia (n = 168)	Spain (n = 1,707)	Turkey (n = 1,600)	Total (n = 8,963)
(n = 38)	(n = 810)	(n = 526)	(n = 3,396)
9.1 ± 0.7	9.0 ± 0.7	8.7 ± 0.8	8.9 ± 0.8
5.0 ± 1.2	4.7 ± 1.2	4.5 ± 1.1	4.7 ± 1.2
181 (124, 336)	196 (102, 335)	160 (68, 331)	190 (100, 343)
449 (243, 601)	227 (128, 354)	360 (215, 584)	267 (147, 457)
9 (2, 14)	8 (4, 17)	8 (4, 15)	9 (4, 19)
3.8 ± 0.5	3.8 ± 0.5	3.7 ± 0.4	3.7 ± 0.5
4.1 ± 0.8	4.1 ± 0.9	4.4 ± 1.1	4.4 ± 1.1
(n = 130)	(n = 897)	(n = 1,074)	(n = 5,567)
9.3 ± 0.6	9.3 ± 0.7	8.9 ± 0.7	9.2 ± 0.9
4.8 ± 1.1	4.7 ± 1.2	4.7 ± 1.1	4.7 ± 1.2
237 (127, 425)	200 (99, 355)	156 (65, 334)	213 (103, 408)
676 (546, 849)	375 (249, 570)	790 (521, 1167)	475 (273, 792)
5 (1, 12)	7 (4, 16)	7 (2, 14)	7 (3, 15)
4.1 ± 0.3	3.9 ± 0.4	3.9 ± 0.3	3.9 ± 0.5
4.6 ± 0.9	4.1 ± 1.0	4.5 ± 1.2	4.4 ± 1.1

Discussion

The ARO-CKD Research Initiative was designed to improve patient outcome by investigating HD patients selected from the FME network. The results of this study in patients randomly selected from 9 European countries

and Turkey suggest that patient characteristics and treatment patterns vary widely across Europe, which may be explained in part by differences in comorbid conditions, availability of healthcare resources and variability in physician training.

For instance, there was a wide age distribution across the 10 countries, the mean age ranging from 56 years in Turkey to 69 years in France. We also found that overall the proportion of patients with glomerulonephritis as the primary cause of CKD (16%) was comparable to previous findings [22]. The diagnosis of CKD etiology, however, was somewhat inconsistent within the cohort: only 2% of patients in the Slovak Republic had a diagnosis of diabetic nephropathy despite a 33% prevalence of diabetes. Likewise in the Czech Republic, 19% had diabetic nephropathy while 42% of patients had diabetes. The discrepancy between diabetic nephropathy as the etiology of CKD and a diagnosis of diabetes may be attributable to misclassification, differences in case definitions, age at CKD diagnosis or the requirement for a confirmatory biopsy in the diagnosis of CKD etiology.

Practice patterns in the population differed from EuroDOPPS: fewer patients had an AV fistula in our cohort compared with EuroDOPPS (73 vs. 80%, respectively) [23]. There was also variation in the dialysis quality indicators: patients in this study had a slightly higher Kt/V than EuroDOPPS patients (1.5 vs. 1.4, respectively), but they were treated with a lower actual blood flow (283 vs. 296 ml/min) [10]. The average hemoglobin level (11 g/dl) achieved was consistent with previously reported findings from EuroDOPPS [12]. However, the average serum phosphate level achieved was 4.7 mg/dl, which is slightly lower than in EuroDOPPS (5.5 mg/dl) [10]. Serum albumin levels were consistent with those from EuroDOPPS, which also reported a mean of 3.9 g/dl.

There were minor differences in mortality rates between our study and EuroDOPPS [11]: the crude mortality rates for both Spain and Italy were lower in this study than in EuroDOPPS (11 vs. 15 deaths per 100 patient-years, respectively). However, the reported mortality rate in France was similar to that in EuroDOPPS (13 vs. 14 deaths per 100 patient-years, respectively). Results from this study and EuroDOPPS reported an average length of stay in hospital of 11 days [11].

As expected, we found that incident patients had a higher death rate than prevalent patients (158 vs. 130 deaths per 1,000 patient-years). This difference may reflect survival bias. While incident patients often experience a period of instability during the initial months of dialysis, prevalent patients represent survivors who on

Table 5. Medication use during the first 6 months of follow-up by country

Medication type	Czech Republic (n = 320)	France (n = 352)	Hungary (n = 1,278)	Italy (n = 1,586)	Poland (n = 163)	Portugal (n = 1,244)	Slovak Republic (n = 545)
Statins	94 (29.4)	64 (18.2)	146 (11.4)	123 (7.8)	32 (19.6)	168 (13.5)	48 (8.8)
ACE inhibitors or ARB	58 (18.1)	69 (19.6)	407 (31.8)	201 (12.7)	67 (41.1)	379 (30.5)	163 (29.9)
Other anti-hypertensives	135 (42.2)	110 (31.3)	572 (44.8)	317 (20.0)	91 (55.8)	424 (34.1)	278 (51.0)
Insulin	83 (25.9)	55 (15.6)	172 (13.5)	157 (9.9)	42 (25.8)	122 (9.8)	53 (9.7)
Anti-diabetics – oral	9 (2.8)	11 (3.1)	69 (5.4)	13 (0.8)	5 (3.1)	46 (3.7)	11 (2.0)
ESA use							
All patients	292 (91.3)	273 (77.6)	1,063 (83.2)	1,198 (75.5)	152 (93.3)	1,052 (84.6)	436 (80.0)
Incident patients	126 (92.6) (n = 136)	125 (80.1) (n = 156)	438 (82.6) (n = 530)	427 (81.8) (n = 522)	72 (91.1) (n = 79)	355 (87.0) (n = 408)	145 (75.9) (n = 191)
Prevalent patients	166 (90.2) (n = 184)	148 (75.5) (n = 196)	625 (83.6) (n = 748)	771 (72.5) (n = 1,064)	80 (95.2) (n = 84)	697 (83.4) (n = 836)	291 (82.2) (n = 354)
Vitamin D – oral	166 (51.9)	144 (40.9)	337 (26.4)	581 (36.6)	37 (22.7)	218 (17.5)	259 (47.5)
Phosphate binders – overall	190 (59.4)	116 (33.0)	456 (35.7)	376 (23.7)	124 (76.1)	811 (65.2)	211 (38.7)
Sevelamer only	31 (16.3)	96 (82.8)	41 (9.0)	226 (60.1)	8 (6.5)	180 (22.2)	–
Calcium only	124 (65.3)	8 (6.9)	374 (82.0)	58 (15.4)	93 (75.0)	443 (54.6)	194 (91.9)
Combination	35 (18.4)	7 (6.0)	40 (8.8)	60 (16.0)	23 (18.5)	188 (23.2)	13 (6.2)
Cinacalcet	–	16 (4.5)	–	8 (0.5)	–	–	1 (0.2)

Categorical variables are reported using n (%). – = Missing data; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker. Incident patients were on HD therapy <6 months at the start of the study; prevalent patients were on HD therapy for ≥6 months.

Table 6. Patient outcome during the entire study period by country (2005–2006)

Patient outcome	Czech Republic (n = 320)	France (n = 352)	Hungary (n = 1,278)	Italy (n = 1,586)	Poland (n = 163)	Portugal (n = 1,244)	Slovak Republic (n = 545)
Crude death rate							
n/1,000 patient-years	191	191	161	141	175	122	164
Age-, gender-, duration of dialysis-adjusted death rate ¹	144	134	145	121	147	103	182
Deaths, n (%)	78 (24.4)	87 (24.7)	286 (22.4)	315 (19.9)	35 (21.5)	219 (17.6)	124 (22.8)
Cardiovascular	38 (48.7)	30 (34.5)	69 (24.1)	148 (47.0)	24 (68.6)	74 (33.8)	76 (61.3)
Infections	15 (19.2)	6 (6.9)	13 (4.5)	8 (2.5)	4 (11.4)	33 (15.1)	12 (9.7)
Cancer	8 (10.3)	5 (5.7)	9 (3.1)	44 (14.0)	2 (5.7)	20 (9.1)	12 (9.7)
Other/unknown	17 (21.8)	46 (52.9)	195 (68.2)	115 (36.5)	5 (14.3)	92 (42.0)	24 (19.4)
First hospitalization rate							
n/1,000 patient-years	1,049	492	187	290	1,847	324	763
Hospitalization ² – n (%)	223 (69.7)	153 (43.5)	279 (21.8)	531 (33.5)	143 (87.7)	452 (36.3)	335 (61.5)
Average duration of hospitalization per admission, days	11.6 ± 10.0	7.2 ± 8.1	9.5 ± 9.0	9.7 ± 9.3	8.9 ± 12.5	11.9 ± 20.5	10.4 ± 8.9
Successful renal transplant	18 (5.6)	13 (3.7)	61 (4.8)	72 (4.5)	12 (7.4)	62 (5.0)	29 (5.3)
Lost to follow-up	28 (8.8)	38 (10.8)	47 (3.7)	154 (9.7)	16 (9.8)	124 (10.0)	51 (9.4)
Completed follow-up	196 (61.3)	214 (60.8)	884 (69.2)	1,045 (65.9)	100 (61.3)	839 (67.4)	341 (62.6)

Continuous variables are reported using means ± SD. Categorical variables are reported as n (%). Adjustment for age, gender and duration of dialysis was performed by including these as covariates in a Poisson regression model.

¹ One patient was excluded from the adjusted death rate calculations due to an outlying value.

² Number of patients with at least 1 hospitalization over the course of the study period.

Slovenia (n = 168)	Spain (n = 1,707)	Turkey (n = 1,600)	Total (n = 8,963)
31 (18.5)	361 (21.1)	123 (7.7)	1,190 (13.3)
46 (27.4)	348 (20.4)	97 (6.1)	1,835 (20.5)
64 (38.1)	518 (30.3)	156 (9.8)	2,665 (29.7)
15 (8.9)	2 (0.1)	148 (9.3)	849 (9.5)
5 (3.0)	26 (1.5)	37 (2.3)	232 (2.6)
160 (95.2)	1,460 (85.5)	938 (58.6)	7,024 (78.4)
36 (94.7)	726 (89.6)	329 (62.5)	2,779 (81.8)
(n = 38)	(n = 810)	(n = 526)	(n = 3,396)
124 (95.4)	734 (81.8)	609 (56.7)	4,245 (76.3)
(n = 130)	(n = 897)	(n = 1,074)	(n = 5,567)
74 (44.0)	343 (20.1)	42 (2.6)	2,201 (24.6)
89 (53.0)	981 (57.5)	818 (51.1)	4,172 (46.5)
13 (14.6)	282 (28.7)	38 (4.6)	915 (21.9)
61 (68.5)	425 (43.3)	733 (89.6)	2,513 (60.2)
15 (16.9)	270 (27.5)	47 (5.7)	698 (16.7)
–	11 (0.6)	–	36 (0.4)

Slovenia (n = 168)	Spain (n = 1,707)	Turkey (n = 1,600)	Total (n = 8,963)
78	143	96	138
73	107	115	124
22 (13.1)	306 (17.9)	206 (12.9)	1,678 (18.7)
13 (59.1)	119 (38.9)	107 (51.9)	698 (41.6)
1 (4.5)	28 (9.2)	15 (7.3)	135 (8.0)
1 (4.5)	11 (3.6)	12 (5.8)	124 (7.4)
7 (31.8)	148 (48.4)	72 (35.0)	721 (43.0)
391	491	150	344
76 (45.2)	772 (45.2)	290 (18.1)	3,254 (36.3)
10.2 ± 9.1	12.9 ± 19.3	12.1 ± 12.6	11.1 ± 14.6
8 (4.8)	135 (7.9)	28 (1.8)	438 (4.9)
3 (1.8)	153 (9.0)	444 (27.8)	1,058 (11.8)
135 (80.4)	1,113 (65.2)	922 (57.6)	5,789 (64.6)

average had undergone HD for 5 years prior to the study. In line with this assumption, prevalent patients had a higher actual blood flow and Kt/V than incident patients, and they were also more likely to be dialyzed with an AV fistula.

This European study population differed with regard to patient characteristics and practice patterns from US patient populations. For instance, 55% of patients in USRDS (United States Renal Data System) and 36% of patients in DOPPS were reported to have diabetes [24], in contrast to the 25% prevalence of diabetes reported in our study. Moreover, AV fistula use was much more common in this study compared with the US DOPPS population, in both men (76 vs. 41%) and women (69 vs. 22%). In addition, an unexpected finding in the ARO population was that incident patients had a higher ESA use than prevalent patients (82 vs. 76%). We also found differences in mortality rates, which were higher in the US DOPPS cohort [25] (22 vs. 14 deaths per 100 patient-years, respectively). In another US report, Tentori et al. [26] reported that the overall mortality rate in patients treated by the Dialysis Clinic Inc. was lower (17 deaths per 100 patient-years) than that of the 2002 USRDS HD prevalent cohort (21 per 100 patient-years) [27]. However, any apparent differences in mortality should be interpreted with caution due to the lack of adjustment for potentially confounding variables.

To our knowledge, this is the first large epidemiological study to include patients from Eastern Europe and Turkey, who have largely been unaccounted for in previous studies. Consistent with the findings by Levi et al. [28], our study demonstrated large differences in the prevalence of CVD history between Eastern and Western Europe. The strength of this study lies in the granularity of data, particularly with respect to dialysis parameters (actual blood flow and Kt/V) and laboratory parameters. For example, DOPPS contains hemoglobin values measured on a quarterly (DOPPS I and DOPPS II) or a monthly (DOPPS III) basis [3, 29], whereas this study evaluated all available measures on hemoglobin.

Study limitations of ARO are that the data were captured from a single private dialysis provider (FME) and data from the UK and Germany were omitted, which restricts the generalizability of our findings. Another limitation was that 44 centers were excluded as a result of inadequate capture of data on key dialysis parameters. Selection bias could theoretically have been introduced into the study if these centers also provided lower quality of care. However, this is unlikely since the missing data were a result of technical issues in the data transfer process and not related to patient selection.

The data captured in ARO are similar in content to widely published databases in the USA, such as the FMC North America database [30] and the DaVita database [31], both of which include longitudinal patient level data on a wide variety of clinical and laboratory parameters captured during the course of routine care of patients within a single network of dialysis providers. In contrast, however, the ARO database is markedly different from patient registries, such as the ERA-EDTA registry [32], which provides a cross-sectional survey of patient data on an annual basis by linking both national and local renal registries based throughout Europe.

An advantage of databases such as ARO over patient registries is that they provide better granularity in terms of the clinical and laboratory parameters. An important limitation of patient registries is that they often lack data on parameters that may be important confounding factors, and are therefore less useful for answering study questions that require multivariable adjustment. We also found some differences in laboratory parameters which were statistically significant, but clinically unimportant, as a result of the large sample size in the study population. Another advantage of ARO is that it contains longitudinally collected data, which allows time-to-event analysis. A major strength of patient registries lies in the generalizability of results, since patients tend to be more representative of the population of patients from which they were sampled.

The results of this study may help to identify areas for improvement in terms of practice of care. Despite the high prevalence of CVD in the study population, only a minority of these patients received a CVD-related medication at baseline. This may reflect the current lack of evidence concerning the effect of these medications on CVD-related outcome in the HD population, or that trials have failed to demonstrate a benefit (i.e. statins). Thus, in accordance with findings from DOPPS [33], the prevalence of statin use was low. In fact, the results of the 4D trial of HD patients [34] and the more recent AURORA trial [35] suggest that CVD in CKD patients differs from that in the general population and that statins are not equally protective. However, others have interpreted the low use of statins in some patients, such as those with a history of myocardial infarction, as under-use [36].

Future studies arising from the ARO initiative will aim to fill gaps in knowledge in the current literature concerning the optimal management of European HD patients. Two recently published papers from ARO described the management of patients with anemia [37] and those with secondary hyperparathyroidism [38].

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