Risk Factors Associated with Cardiovascular Morbidity and Mortality in Spanish Incident Hemodialysis Patients: Two-Year Results from the ANSWER Study

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Abstract
Aims: To identify factors associated with cardiovascular (CV) disease in hemodialysis. Methods: Multicenter, prospective, 2-year, observational study in 2,310 incident patients (3,496 patient-years). Multivariate Cox models determined baseline characteristics associated with CV disease. Results: Main factors associated with CV deaths (6.3/100 patient-years) were: high Charlson score (hazard ratio (HR) 3.6; 95% confidence interval (CI) 1.7–7.5 for ≥9 vs. ≤4); low Karnofsky score (KS; HR 2.2; 95% CI 1.5–3.3 for KS ≤50 vs. >70); female gender (HR 1.4; 95% CI 1.1–1.9); catheter access (HR 1.4; 95% CI 1.0–1.9); low (<3.5 g/dl) albumin (HR 2.5; 95% CI 1.8–3.3); ferritin deficiency (HR 1.6; 95% CI 1.2–2.2 for <100 vs. ≥100–500 ng/ml) and low body mass index (BMI; HR 1.6; 95% CI 1.2–2.2 for <20 vs. 20–25). A BMI of ≥30 was a protective factor (HR 0.6; 95% CI 0.4–0.9). Conclusions: There is a high CV risk, especially in older patients with high comorbidities, low BMI, low albumin or iron deficiency. Catheter access increases the CV death risk.

Introduction
Chronic kidney disease (CKD) and hemodialysis (HD) are associated with an increased risk of cardiovascular (CV) death [1–4], even at early stages [5, 6]. The increase is more pronounced in younger patients [7, 8]. About half the deaths of patients on dialysis are of CV origin [9]. Some studies have revealed an extremely high prevalence of clinical and echocardiographic manifestations of CV disease in patients initiating HD [10].

1 See appendix.
The increased presence of comorbidities and traditional risk factors, such as hypertension or diabetes mellitus, cannot entirely explain the high CV burden [11, 12]. There are other CKD-specific factors that must be taken into account. Uremic-related factors include albuminuria, hyperhomocysteinemia, elevated lipoprotein(a), interleukin-6, anemia, abnormal calcium/phosphate metabolism, extracellular fluid volume overload, electrolyte imbalance, oxidative stress, inflammation (C-reactive protein), malnutrition, thrombogenic factors, and altered nitric oxide/endothelin balance [13–16]. With regard to the dialysis technique, some of the proposed parameters that might modulate the CV risk are: use of high-flux dialyzers, endotoxin filters, hemodiafiltration, non-catheter access type, adequate dialysis doses, and longer or more frequent sessions [17].

The study of all these risk factors has been scarcely described in incident populations. The available results are not consistent and even contradictory in some cases, so results cannot be extrapolated. The Dialysis Outcomes and Practice Patterns study (DOPPS) [18, 19] demonstrated that the characteristics of incident populations and HD techniques differ from one country to another. Published studies include large populations from the US [20, 21], and small cohorts from Japan [22] and Europe [23]. The primary objective of the ANSWER study was to determine patients’ characteristics at HD initiation independently associated with CV morbidity and mortality, in order to find modifiable risk factors. The secondary objectives were to describe the incidence of CV events, deaths and hospitalizations for CV reasons throughout the study.

### Table 1. Dropout reasons and causes of death for the 2,310 incident patients from the ANSWER study (3,496.3 patient-years)

| Causes of death                  | n   |
|----------------------------------|-----|
| Cardiovascular                   | 221 (45.7%) |
| Infections                       | 88  (18.1%) |
| Neoplasia                        | 57  (11.8%) |
| Digestive problems               | 11  (2.3%)  |
| Other/unknown                    | 107 (22.1%) |

### Subjects and Methods

ANSWER is a prospective, observational cohort study in incident HD patients conducted at 147 centers across Spain. The study protocol was approved by local ethics committees and all patients provided their informed consent.

#### Study Population

Incident HD patients aged ≥18 years were eligible. Patients were excluded if they had undergone previous renal replacement therapy, were already receiving HD (≥30 days) or peritoneal dialysis, or had received a kidney transplant [24].

#### Outcomes and Covariates

All CV events were recorded throughout the 2 years of follow-up, including whether hospitalization was required. CV events comprised: congestive heart failure, cardiac arrhythmia, ischemic heart disease, cerebrovascular event, peripheral arterial disease, and other cardiac events (cholesterol embolism, mesenteric infarction or ischemia, cardiac arrest of unknown cause, other cardiac causes, excluding left ventricular hypertrophy). All deaths were also recorded, including main causes of death, as determined by the nephrologist. Patients were withdrawn if they discontinued HD.

At baseline visit (within the first 30 days of HD initiation) sociodemographic, clinical, laboratory and health care (concomitant drug therapy and HD characteristics) variables were collected [24].

#### Statistical Analysis

Summary statistics were calculated for continuous and categorical endpoints. A Poisson distribution was used to calculate 95% confidence intervals for the incidence rates [25]. Outcomes in subgroups defined by previous CV history were compared using the Mann-Whitney test.

Using univariate Cox regression models, we selected all baseline characteristics that were associated with each outcome at a p value of <0.15. Then, all selected variables were entered into multivariate models (except components of the Charlson score, i.e. age or previous myocardial infarction). Continuous variables were dichotomized according to cutoff points of clinical relevance or categorized using quintiles. Missing values were imputed using the SPSS Missing Values Analysis module expectation maximization algorithm. A sensitivity analysis was performed using patients with non-missing values for all variables. No notable differences were found and thus results are presented with the missing values replaced. All the calculations were performed using SPSS® 14.0 (SPSS Inc, Chicago, Ill., USA).

#### Results

### Baseline Characteristics of Incident Patients and Follow-Up Data

Baseline characteristics of the cohort have been previously described [24]. Of 2,310 patients, 1,035 (44.8%) dropped out before 2 years (table 1). The main reasons...
were death (n = 484, 20.9%) and kidney transplantation (n = 335, 14.5%). Mortality rate was approximately constant over time (12.7/100 patient-years in the first 120 days versus 14.1 between days 121–730). The main cause of death was CV disease.

**Description of CV Mortality, CV Events and Hospitalizations for CV Reason**

The rate of CV events was 45.2/100 patient-years (table 2). Approximately 1 of every 2 CV events (42%) resulted in hospitalization, and 14% resulted in death (table 2). The mean duration of CV hospitalization was 10.5 (SD 16.4) days. The 3 outcomes were equally distributed during the 2 years (no significant differences in the respective hazard rates, data not shown).

CV mortality was mainly due to sudden death (responsible for 23.5% of CV deaths), followed by ischemic heart disease (21.7%), cerebrovascular disease (19%), heart failure (10%), peripheral vascular disease (9.5%), mesenteric infarction (8.6%), cardiac arrhythmia (2.7%), and other cardiac causes (5%). Among all events, the more frequent were ischemic heart disease (337 events, 9.6/100 patient-years), followed by cardiac arrhythmias (330 events, 9.4/100 patient-years), peripheral vascular disease (294 events, 8.4/100 patient-years), heart failure (219 events, 6.3/100 patient-years) and cerebrovascular disease (173 events, 4.9/100 patient-years). Other cardiac causes explained the remaining 227 events (6.5/100 patient-years).

Patients with a previous history of CV disease (1,037 patients, 44.9%) displayed three times more CV deaths than patients without previous events (166 [16%] vs. 55 [4.3%], respectively, p < 0.001), and the percentage of individuals suffering a CV event or hospitalization was almost double in this subgroup (490 patients with CV event [47.2%], and 260 with CV hospitalization [25.1%] vs. 224 [17.6%] and 120 [9.4%], respectively, p < 0.001 in both cases). The time until the first CV event was shorter in patients with previous CV events (7.1 [SD 5.9] vs. 8.5 [SD 6.4] months, p < 0.05).

**Independent Predictors of CV Mortality**

Multiple comorbidities, low Karnofsky score, low albumin level, and anticoagulant use were strongly associated with CV death (table 3). Other characteristics also associated with a higher probability of CV mortality were female gender and low body mass index (BMI <20). Obesity (BMI ≥30) was inversely associated with CV death. Catheter as vascular access and HD intolerance were the only HD-related variables positively associated with CV death. Among blood chemistry values, ferritin deficiency (<100 ng/ml) predicted a fatal CV event, whereas intermediate-high creatinine (7.1–8.7 mg/dl) and high hemoglobin (>13 g/dl) levels protected against this outcome. Erythropoiesis-stimulating agent (ESA) doses between 4,000 and 8,000 IU/week were significantly related to a higher risk of CV death compared to <4,000 IU/week and non-treated patients.

**Independent Predictors of All-Cause Mortality**

The model predicting all-cause mortality (table 4) was quite similar to the model predicting only deaths of CV origin. The main differences were the appearance of 4 new predictors: interdialysis weight gain, dialysis time, iPTH levels, and antihypertensive use. On the contrary, the following variables lost the predictive effect observed with CV deaths: HD intolerance and hemoglobin or ferritin levels.

**Independent Predictors of CV Events**

A few of the variables associated with CV death were also significantly related to the presence of a CV event (age comorbidity Charlson score, Karnofsky score, albumin levels, and anticoagulant use; table 5). In addition, former smokers presented fewer CV events than non-smokers; and a history of cardiac arrhythmia, left ven-

| Number of events | Rate per 100 patient-years (95% CI) |
|------------------|-----------------------------------|
| Death            | 484                               | 13.8 (12.6–15.1) |
| CV death         | 221                               | 6.3 (5.5–7.2)    |
| CV event         | 1,580<sup>a</sup> (in 713 patients) | 45.2 (43.0–47.5) |
| Hospitalization for CV reasons | 660 (in 378 patients) | 18.9 (17.5–20.4) |

<sup>a</sup> Including fatal events.
tricular hypertrophy, standard heparin type use, antihypertensive or CV drug use, and iron doses of ≥75 mg/week predicted more CV events.

### Independent Predictors of Hospitalization due to CV Cause

With respect to CV hospitalization, the results (table 6) were quite similar to those obtained for CV events. The main differences were observed with hemoglobin (levels of <10 g/dl predicted more hospitalizations), and antithrombotic or hypolipidemic drug use. In this model, a previous history of cardiac arrhythmia or left ventricular hypertrophy were not significant.

### Discussion

Approximately one third of patients initiating HD in Spain in 2003–2004 suffered a CV event during the first 2 years. Those events were more frequent and more often lethal in patients who had already suffered a previous CV event. The presence of other comorbidities (such as diabetes, which was included as a component of the Charlson score), advanced age or impaired functional status (low Karnofsky score) were also important risk factors in our population, in addition to low albumin or ferritin levels and low BMI. Among factors related to HD, the use of a catheter as vascular access and HD intolerance predicted earlier CV mortality.

The CV death rate was 6.3/100 patient-years, accounting for almost 50% of all deaths (13.8/100 patient-years). A recent analysis of the European Renal Association-European Dialysis and Transplantation Association Registry revealed that, despite the increased risk of death associated with HD, no excess of CV mortality is observed [26]. The incidence found in our study is very similar to those reported by the majority of previous studies in European populations, but lower than those observed in US populations [21, 23, 27]. Additionally, in our study the all-cause and CV mortality rates during the first year were constant, which differs with results from the DOPPS (higher mortality rate during the first 120 days) [27]. The discrepancy can be partially explained by differences in the method of analysis, since in the DOPPS cohort deaths that occurred within 60 days after HD withdrawal were taken into account, and when these deaths were excluded, the overall mortality rate decreased to a level comparable to ours (15.1/100 patient-years between days 121 and 365) [27]. In addition, some differences in the baseline characteristics between the ANSWER and the DOPPS cohorts

### Table 3. Independent predictors of CV death within the 2 years after HD initiation in the multivariate Cox regression model

| Predictors of CV death | Hazard ratio | 95% CI for HR | p value |
|------------------------|-------------|--------------|--------|
| Age comorbidity Charlson score (ref. ≤4) | <0.001*<sup>a</sup> | | |
| 5–56                   | 1.74        | 0.85–3.55    | 0.131  |
| 7–8                    | 3.25        | 1.60–6.60    | 0.001  |
| ≥9                     | 3.60        | 1.73–7.49    | 0.001  |
| Gender, female         | 1.43        | 1.06–1.93    | 0.019  |
| BMI (ref. 20–25)       | <0.001*<sup>a</sup> | | |
| <20                    | 1.88        | 1.16–3.04    | 0.010  |
| 25–30                  | 0.88        | 0.63–1.23    | 0.472  |
| ≥30                    | 0.59        | 0.38–0.90    | 0.014  |
| Karnofsky score (ref. >70–100) | <0.001*<sup>a</sup> | | |
| >50–70                 | 2.07        | 1.47–2.91    | <0.001 |
| 0–50                   | 2.19        | 1.47–3.27    | <0.001 |
| Vascular access, catheter | 1.36      | 1.00–1.86    | 0.049  |
| HD intolerance, yes<sup>b</sup> | 1.69      | 1.06–2.69    | 0.026  |
| Albumin <3.5 g/dl      | 2.47        | 1.84–3.34    | <0.001 |
| Creatinine, mg/dl (ref. >8.7) | 0.116<sup>a</sup> | | |
| <4.9                   | 0.76        | 0.52–1.12    | 0.162  |
| 4.9–5.9                | 0.65        | 0.43–0.98    | 0.042  |
| 6.0–7.0                | 0.74        | 0.48–1.13    | 0.167  |
| 7.1–8.7                | 0.52        | 0.31–0.89    | 0.018  |
| Hemoglobin, g/dl (ref. >11–11.9) | 0.207<sup>a</sup> | | |
| ≥13                    | 0.34        | 0.14–0.83    | 0.018  |
| 12–12.9                | 1.01        | 0.60–1.69    | 0.973  |
| 10–10.9                | 0.91        | 0.60–1.39    | 0.677  |
| <10                    | 0.93        | 0.62–1.38    | 0.715  |
| Ferritin, ng/ml (ref. 100–500) | 0.010<sup>a</sup> | | |
| <100                   | 1.58        | 1.16–2.16    | 0.003  |
| >500                   | 0.97        | 0.57–1.66    | 0.918  |
| AST, U/l (ref. <11)    | 0.010<sup>a</sup> | | |
| 11–14.9                | 1.11        | 0.68–1.82    | 0.665  |
| 15–17.9                | 1.69        | 1.04–2.76    | 0.033  |
| 18–22.9                | 0.83        | 0.52–1.34    | 0.448  |
| ≥23                    | 0.92        | 0.55–1.54    | 0.746  |
| Anticoagulants, yes    | 2.41        | 1.58–3.67    | <0.001 |
| Erythropoiesis-stimulating agent dose, IU/week (ref. not treated) | 0.013<sup>a</sup> | | |
| <4,000                  | 0.77        | 0.47–1.26    | 0.295  |
| 4,000–8,000            | 1.61        | 1.12–2.31    | 0.010  |
| 8,000–16,000           | 1.56        | 0.99–2.46    | 0.054  |
| >16,000                | 1.72        | 0.68–4.34    | 0.247  |

<sup>a</sup> p value indicates the overall effect of the variable in the model.

<sup>b</sup> Defined as hypotension recorded at >50% of dialyses performed during the past month. The model was also adjusted by: alcohol consumption; CKD etiology, dyslipidemia, previous cardiac arrhythmia, left ventricular hypertrophy, SBP before HD session; hemodialysis technique, dialysis time, glucose; potassium; iPTH; phosphorus- binder drugs, cardiovascular drugs, hypolipidemic drugs.
may explain the increased early mortality rate in the second one: a higher use of a catheter as vascular access (67 versus 46% in our sample) and a higher frequency of inadequate predialysis nephrology care, the strongest predictor of early mortality in their cohort (23% saw a nephrologist 1 month before initiation of dialysis versus 17% saw one 3 months before in the ANSWER study).

The independent risk factors more strongly associated with CV events were higher Charlson age comorbidity score, previous history of cardiac arrhythmia or left ventricular hypertrophy, poor functional status and low albumin levels. Other European studies have also observed that prior comorbidities are the most powerful predictors of a CV event [28–30]. In the USRDS cohort analyzed by Trivedi et al. [21] (with a lower prevalence of CV history [27.4%] and different ethnic origin [64% Caucasians]), prior coronary disease and lower albumin values conferred a higher risk of cardiac death, but black ethnicity, a history of hypertension, and higher hemoglobin levels were protective factors.

Hemoglobin levels of >13 g/dl protected against CV mortality, which agrees with some previous studies [31–34]. Patients with ferritin deficiency (<100 ng/ml) presented increased CV death with respect to patients within the European Best Practice Guidelines targets (100–500 ng/ml), whereas patients with levels of >500 ng/ml...
Table 6. Independent predictors of hospitalization for CV reasons within the 2 years after HD initiation in the multivariate Cox regression model

| Predictors of hospitalization for CV reasons | Hazard ratio | 95% CI for HR | p value |
|---------------------------------------------|-------------|---------------|---------|
| Age comorbidity Charlson score (ref. ≤4)    | 1.00        |               | 0.002a  |
| 5–6                                         | 1.52        | 1.00–2.29     | 0.048   |
| 7–8                                         | 2.05        | 1.34–3.15     | 0.001   |
| ≥9                                          | 2.23        | 1.44–3.54     | <0.001  |
| Tobacco use (ref. non-smoker)               | 1.00        |               | 0.021a  |
| Current smoker                              | 0.98        | 0.69–1.40     | 0.983   |
| Former smoker                               | 0.73        | 0.58–0.91     | 0.006   |
| Karnofsky score (ref. >70–100)              | 1.00        |               | 0.001a  |
| >50–70                                      | 1.31        | 1.03–1.67     | 0.029   |
| 0–50                                        | 1.74        | 1.28–2.37     | <0.001  |
| Albumin <3.5 g/dl                           | 1.33        | 1.07–1.65     | 0.009   |
| Hemoglobin, g/dl (ref. >11–11.9)            | 1.00        |               | 0.132a  |
| ≥13                                         | 1.03        | 0.61–1.76     | 0.910   |
| 12–12.9                                     | 1.39        | 0.93–2.08     | 0.103   |
| 10–10.9                                     | 1.09        | 0.78–1.54     | 0.608   |
| <10                                         | 1.40        | 1.02–1.93     | 0.039   |
| Antihypertension drugs, yes                 | 1.42        | 1.01–2.00     | 0.046   |
| Cardiovascular drugs, yes                   | 1.36        | 1.08–1.73     | 0.010   |
| Anticoagulants, yes                         | 1.91        | 1.31–2.79     | 0.001   |
| Antithrombotics, yes                        | 1.64        | 1.13–2.37     | 0.009   |
| Iron dose, mg/week (ref. not treated)       | 1.00        |               | 0.041a  |
| <40                                         | 0.63        | 0.33–1.19     | 0.154   |
| 40–74.9                                     | 1.45        | 1.05–2.01     | 0.026   |
| ≥75                                         | 1.16        | 0.91–1.48     | 0.225   |
| Hypolipidemic drugs, yes                    | 1.32        | 1.02–1.71     | 0.033   |

*a p value indicates the overall effect of the variable in the model. The model was also adjusted by: BMI, nephrologist follow-up time, CKD etiology, dyslipidemia, hypertension, previous cardiac arrhythmia, left ventricular hypertrophy, vascular access type, dialysis time, heparin type, HD intolerance, glucose, creatinine, alkaline phosphatase.

HD initiation with previous ESA administration at moderate or high doses was related to increased CV mortality and all-cause death. These findings differ from the protective effect of ESA administration at low or moderate doses in a time-dependent analysis from the same cohort [43], which suggests that ESA treatment evolution with time provides distinct information from one-point data.

Oral anticoagulants were associated with more CV events and deaths. Only a few studies have evaluated these drugs in patients with CKD, in whom fibrin clots are much tighter than those from healthy individuals [44]. One study found a higher rate of stroke in HD patients on oral anticoagulation or on salicylates regardless of whether they had atrial fibrillation [45], but retrospective analyses from the USRDS found a significantly lower mortality in HD patients with atrial fibrillation taking Coumadin [46]. The use of oral anticoagulation in this population should be carefully weighed on a case-by-case basis because the antithrombotic effect can be counterbalanced by an increased risk of hemorrhagic complications.

Female gender was associated with an increased risk of CV death, which agrees with some previous results [29]. An elevated prevalence of vascular calcifications has been reported in women undergoing dialysis (60% in a Spanish cohort), with more CV events in this female subgroup [47].

Greater interdialysis weight gain was related to increased all-cause mortality. This finding reinforces the need for appropriate management and monitoring of blood volume and pressure between dialysis sessions. Studies have previously suggested that higher diastolic blood pressure in HD patients offers a survival advantage (‘reverse epidemiology’) [48]. However, a review of worldwide studies on incident HD cohorts [49] attributed the reverse epidemiology to a statistical artifact.

Obesity and creatinine levels displayed a reverse association with CV morbidity and mortality, as previously reported [50–52].
No relevant influences of non-traditional risk factors, such as high C-reactive protein, high fibrinogen levels, hyperhomocysteinemia or elevated lipoprotein(a) were found. These findings disagree with some previous results [23].

The results presented above must be interpreted with caution. The observational design does not allow establishment of causal relationships, as we cannot rule out possible unmeasured confounders. For example, the protective effect found for a short dialysis time is probably due to an indirect association with a higher residual renal function: the variable ‘24-hour diuresis’ was not entered in the model due to a high number of missing values, but was inversely associated with mortality in the univariate analysis. The associations with the covariates originate in a unique baseline measure. For the parameters that display an important variation over time, adjusting for longitudinal changes could have led to different conclusions.

However, the predictive usefulness of a single measure at HD initiation is of clinical interest as it is easily understandable. Another limitation is the possible information bias of nephrologists in ascertaining causes of death. With regard to the external validity, the fact that many of the described associations had been previously reported supports the applicability of our findings to patients initiating HD under similar conditions.

In conclusion, the CV morbidity and mortality in Spanish incident HD patients remains very high, especially in patients with a previous history of CV disease, and in older, high comorbidity, low BMI, low albumin or iron-deficient patients. A catheter as vascular access is associated with CV death. Our results suggest that nephrologists may play an important role in improving patient outcome by working on modifiable CV risk factors. First, they should intensify pre-dialysis care in order to increase the number of patients starting hemodialysis with an arteriovenous fistula for vascular access and with an adequate control of hypertension, anemia, mineral metabolism and nutrition. Second, they should try to reduce inflammation and improve the nutritional status of patients on hemodialysis to increase serum albumin [53, 54].

Third, they should prevent iron deficiency by repleting iron stores in patients with either absolute (serum ferritin concentration <100 ng) or functional iron deficiency (transferrin saturation <20%) [37]. Fourth, they should avoid the use of catheters as vascular access and replace them with arteriovenous fistulas. Recent data from Spain suggest that catheters are increasingly used [55, 56]. Thus, a strategic plan with concrete actions as in the US is urgently needed. Finally, they should try to improve tolerance to HD and reduce weight gain between dialysis sessions. Although these recommendations are based on the results of the present and other observational studies and have a weak level of evidence, it seems wise to implement them while waiting for stronger evidence from randomized and controlled trials.

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Appendix

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