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VDRA therapy is associated with improved survival in dialysis patients with serum intact PTH ≤150 pg/mL: results of the Italian FARO Survey

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Abstract

Background. Chronic kidney disease (CKD) patients affected by mineral bone disorders (MBD) have higher rates of all-cause and cardiovascular-related mortality. Approximately, one-third of dialysis patients have low serum parathyroid hormone (PTH) levels (≤150 pg/mL). However, the reason why these patients have higher mortality compared to patients with normal PTH levels has not yet been fully elucidated.

Methods. The FARO study was performed on 2453 Italian patients followed prospectively from 28 dialysis centres over a 2-year period. Data were collected every 6 months and end points included time-to-death cumulative probability in patients with serum intact PTH (iPTH) ≤150 pg/mL and the effect of vitamin D receptor activation (VDRA) therapy. Kaplan–Meier curves and proportional hazards regression models stratified by PTH levels (i.e. ≤150 and >150 pg/mL) were used to determine cumulative probability of time-to-death and adjusted hazard ratios (HRs) for demographic, clinical and CKD-MBD treatment characteristics.

Results. The cumulative probability of death was higher ($P < 0.01$) for patients with serum iPTH levels ≤150 pg/mL [25.1%, 95% confidence interval (CI): 22.1–28.5 at 18 months] versus those with serum iPTH levels within the normal range (18.0%, 95% CI: 16.1–20.1). In a model with time-dependent covariates restricted to time periods when patients had iPTH levels ≤150 pg/mL, lower mortality was observed in patients treated with VDRA [i.e. HR = 0.62, 95% CI: 0.42–0.92 for oral or intravenous (IV) calcitriol; HR = 0.18, 95% CI: 0.04–0.8 for IV paricalcitol] versus those not receiving any VDRA ($P < 0.01$) independently of other variables. Patients who received IV paricalcitol, compared with either oral or IV calcitriol, showed reduced mortality, but this was not statistically significant (HR = 0.3, 95% CI: 0.07–1.31, $P = 0.11$).

Conclusion. Results from this observational study suggest that VDRA therapy was associated with improved survival in dialysis patients, even with low serum iPTH levels.

Keywords: calcitriol; CKD-MBD; haemodialysis; paricalcitol; PTH

Introduction

Patients with chronic kidney disease (CKD) who are affected by mineral bone disorders (MBD) have been shown to have higher rates for both all-cause and cardiovascular-related mortality. In fact, CKD is associated with lower circulating levels of 1α,25-dihydroxyvitamin D_3 (1,25-D) [1, 2], inducing serious clinical implications, such as reduction in intestinal calcium (Ca) absorption, impairment of skeletal density, increase in parathyroid hormone (PTH) production and dysregulation of phosphorus (P) metabolism [3, 4]. Thus, maintaining sufficient levels of vitamin D is important for maintaining mainly bone health. On the contrary, excessive exogenous treatment with active 1,25-D (i.e. calcitriol) may result in abnormally elevated mineral levels, which are associated with increased risk of morbidity (e.g. vascular calcification) and mortality [5, 6]. In order to maximize the beneficial effects of 1,25-D, while reducing the risks associated with excessive calcitriol treatment, several synthetic vitamin D receptor activators (VDRAs) have been developed, which are efficacious in treating CKD-MBD [3, 7, 8, 9].

For several decades, VDRA therapy has been used as the mainstay therapy for CKD-MBD in patients receiving

haemodialysis (HD) [10, 11]. This therapy has been significantly associated with a reduction in all-cause [12, 13, 14] and cardiovascular-related mortality rates [13, 15, 16]. Inadequate or late treatment of CKD-MBD is associated with enhanced bone and cardiovascular disease [17]. Reduced 1,25-D levels and, thus, limited vitamin D receptor activation (VDRA) in CKD patients result in elevated serum PTH levels, which may play a role in the high prevalence of cardiovascular disease observed in this population [18]. Surprisingly, a high proportion of dialysis patients have low serum PTH levels, but why they have higher mortality compared to patients with serum PTH levels in the normal range has not yet been fully elucidated [19, 20, 21]. Usually, dialysis patients with low serum PTH levels do not receive any form of active vitamin D to avoid a further reduction of PTH and increase the risk of adynamic bone disease [22, 23, 24].

Data from the prospective Accelerated Mortality on Renal Replacement (ArMORR) study in HD patients correlated low circulating levels of 25-dihydroxyvitamin D3 and 1,25-D with increased all-cause and cardiovascular mortality [25] and indicated that survival was significantly improved in patients receiving VDRA therapy compared with untreated patients [25, 26]. Even in patients with less severe stages of CKD (i.e. Stages 3–5) who have yet to begin HD, calcitriol was associated with a significant survival benefit [27, 28].

The Kidney Disease Outcomes Quality Initiative (K/DOQI) updated their international guidelines in 2003 with regard to target levels for serum intact PTH (iPTH), Ca and P in an effort to help lower secondary hyperparathyroidism (SHPT)-related mortality [22]. Studies examining the long-term safety of VDRAs in CKD patients with SHPT who achieve these K/DOQI target ranges are currently lacking. Therefore, using data from FARO, an Italian survey of dialysis patients with SHPT that assessed their position within or outside of KDOQI target ranges [29], the clinical outcome of VDRA therapy on mortality was examined in the present study.

Materials and methods

Study design

The FARO study was a prospective multicentre survey of treatment practices undertaken from April 2006–October 2007 in 28 dialysis centres in Italy [29]. Briefly, patient questionnaires were completed at each centre in four 1-week sessions, evenly distributed over an 18-month period (baseline, Month 6, Month 12 and Month 18) and subsequently reviewed and approved by the physician in charge. This survey was designed, so patients could enter or exit a given dialysis centre over the course of the 18-month period, resulting in variation in sample sizes for each of the four surveys (e.g. new patient, death or transfer to another centre). Further details of the study design have been published elsewhere [29]. All patients provided written informed consent and the study was in compliance with the Italian Legislative Decree 196/2003.

Mortality risk assessments

For patients with Stage 5 CKD on HD, we used the 2003 guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation that recommend specific targets, including serum iPTH levels from 150 to 300 pg/mL [22]. A recent European observational study showed the lowest risk of mortality among patients with iPTH values within the KDOQI target range, further supporting the use of this iPTH range [30]. In fact, the 2009 Kidney Disease–Improving Global Outcomes (KDIGO) guidelines were not yet available at the time this study was designed [31]. iPTH was measured by second-generation commercially available kits. The commercially available kits used were not identical across all dialysis centres. Risk of all-cause mortality by iPTH levels (≤150 versus >150 pg/mL) was assessed using a time-dependent model in all patients at each post-baseline session (i.e. Months 6, 12 and 18). A model of time-dependent covariates restricted to periods when patients had iPTH ≤150 pg/mL was also used to assess the effect of VDRA therapy [untreated, oral/intravenous (IV) calcitriol or IV paricalcitol] on survival (all-cause mortality).

Time to all-cause mortality hazard ratios (HRs) were assessed for patients with iPTH ≤150 pg/mL and adjusted for various demographic and clinical values, including dialysis vintage (per 10-year increase), age (per 10-year increase), sex, comorbidities and history of diabetes. Time-dependent variables included serum albumin (per 1-unit increase), serum haemoglobin (per 1-unit increase), serum phosphorus (≤3.5 versus >3.5 to ≤5.5 and >5.5 versus >3.5 to ≤5.5 mg/dL), serum calcium (≤8.4 versus >8.4 to ≤9.5, >9.5 to ≤10.5 versus >8.4 to ≤9.5 and >10.5 versus >8.4 to ≤9.5 mg/dL). Patients who moved or were transferred to other dialysis centres or who were lost to follow-up (168 in total) were censored as alive at the last visit performed.

Statistical analysis

The Kaplan–Meier (KM) method was used to estimate the cumulative probability of all-cause mortality in all patients and stratified by iPTH level (i.e. ≤150 versus >150 pg/mL). KM survival estimates were also performed for patients who had iPTH ≤150 pg/mL to assess the effect of VDRA therapy on all-cause mortality in this patient subgroup. Stratified (by iPTH level) Cox proportional hazard regression models were used to estimate time to all-cause mortality HRs. For each HR, the 95% confidence interval (CI) was computed. This analysis was adjusted for all potential confounders and variables that changed during the follow-up were included as time-dependent covariates. In the few cases, when a measurement had missing information, the last available value was used. All Cox proportional hazard regression models were stratified by each participating clinical centre. A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS (version 8.2 for WindowsTM, Cary, NC) and STATA (version 8.0; College Station, TX) software.

Results

Disposition, demographic and clinical characteristics

Disposition, demographic and clinical characteristics for patients who participated in this survey are previously described [29]. Briefly, of 2637 patients initially included in the study, 2453 were included in the current analysis. A total of 184 patients were excluded for the following reasons: 146 (5.54%) were lost to follow-up after participating in a single survey period, 29 (1.1%) received treatment other than oral or IV calcitriol or IV paricalcitol and 9 (0.34%) were deceased prior to the first study session. Sample sizes for each of the four 1-week sessions varied due to changes in patient exit and entry over the 18-month period (baseline, $n = 2453$; Month 6, $n = 2437$; Month 12, $n = 2079$ and Month 18, $n = 1736$). All further analysis was based on the following patient subgroups: serum iPTH levels of ≤150 and/or >150 pg/mL. Baseline demographic and clinical characteristics for the two patient groups are presented in Table 1. Demographic characteristics were similar between the two groups. Although the majority of comorbid conditions remained unchanged between patient subgroups, the number of patients with left ventricular hypertrophy was significantly higher in patients with elevated iPTH (>150 pg/mL; 57.5 versus 52.9%, $P < 0.014$). In contrast, a higher proportion of patients with iPTH ≤150 pg/mL had cerebrovascular disease (14.8 versus 10.9%, $P = 0.011$).

Mineral metabolism-related treatment

Subgroup analysis of the number of HD patients with either low or high levels of iPTH (≤150 or >150 pg/mL) receiving VDRA or phosphate-binding therapy for the four visits is summarized in Table 2. At baseline, the majority of patients were treated with oral calcitriol (87% in the 'low' iPTH group and 55.8% in the 'high' iPTH group). The percentage of patients (for both iPTH groups) treated with oral calcitriol also decreased gradually over the four visits. In contrast, few patients from either iPTH subgroups were administered calcitriol intravenously (5.5 versus 18.5% at baseline) and no change was observed over the course of the survey period. The number of patients administered paricalcitol (IV) increased gradually over the four visits in both patient subgroups, a greater proportion of patients with iPTH >150 pg/mL receiving this medication compared to patients with iPTH levels ≤150 pg/mL. Approximately half of patients (in either iPTH subgroup) received phosphate-binding therapy and the proportion of these patients did not change over the four visits.

Table 1. Demographic and clinical characteristics of the study population[a]

Clinical characteristics	PTH ≤150 pg/mL, *n* = 823	PTH >150 pg/mL, *n* = 1630	P-value
Demographics			
Men, *n* (%)	506 (61.5)	1025 (62.9)	
Women, *n* (%)	317 (38.5)	605 (37.1)	0.48
Age, years (range)	68 (58–77)	68 (56–75)	0.067
Dialysis vintage, months (range)	30 (10–72)	39 (12–81)	0.053
Comorbid conditions			
Hypertension, *n* (%)	540 (65.6)	1104 (67.7)	0.31
Dyslipidaemia, *n* (%)	144 (17.5)	325 (19.9)	0.15
Diabetes, *n* (%)	132 (16)	240 (14.7)	0.37
Left ventricular hypertrophy, *n* (%)	435 (52.9)	937 (57.5)	0.014
CAD, *n* (%)	182 (22.1)	378 (23.2)	0.37
PAD, *n* (%)	191 (23.2)	323 (19.8)	0.089
Cerebrovascular disease, *n* (%)	122 (14.8)	178 (10.9)	0.011
Laboratory			
iPTH (pg/mL)	78 (40–113)	345 (235–502)	<0.001
Serum phosphorus (mg/dL)	4.7 (3.9–5.6)	5.1 (4.4–5.9)	<0.001
Serum calcium (mg/dL)	9.1 (8.6–9.5)	9 (8.5–9.6)	0.79
Haemoglobin (g/dL)	11.3 (10.5–12)	11.4 (10.5–12.1)	0.22
Serum albumin (g/dL)	3.7 (3.4–4)	3.8 (3.4–4.1)	0.005

[a]CAD, coronary artery disease; PAD, peripheral artery disease.

Survival estimates in HD patients: effect of PTH levels and VDRA therapy

The cumulative risk of all-cause mortality was significantly lower over the course of the survey for patients with serum iPTH >150 pg/mL compared to patients with serum iPTH levels of ≤150 pg/mL ($P < 0.01$, Figure 1). The time course presented in Figure 1 shows that the event curves for iPTH >150 pg/mL patients compared with the iPTH ≤150 pg/mL group had already separated at 6 months and continued to further diverge for the duration of the study. Examining the effect of VDRA treatment in the subgroup of patients with serum iPTH levels of ≤150 pg/mL revealed that VDRA-treated patients (calcitriol or paricalcitol) had lower mortality rates compared to untreated patients ($P < 0.01$, Figure 2). Furthermore, patients treated with paricalcitol (IV) were observed to have improved survival rates (as early as 10 months) compared to calcitriol-treated patients, but this was not statistically significant ($P = 0.11$, Figure 2).

The effect of demographic and clinical variables on survival

Table 3 shows time to death in HD patients after stratifying by major clinical variables. In patients with serum iPTH ≤150 pg/mL, clinical variables that significantly

Table 2. Mineral metabolism related treatments by visit[a]

	Baseline		Month 6		Month 12		Month 18	
	iPTH ≤150 pg/mL, *n* = 823	iPTH >150 pg/mL, *n* = 1630	iPTH ≤150 pg/mL, *n* = 799	PTH >150 pg/mL, *n* = 1638	iPTH ≤150 pg/mL, *n* = 664	iPTH >150 pg/mL, *n* = 1415	iPTH ≤150 pg/mL, *n* = 578	iPTH >150 pg/mL, *n* = 1158
VDRAs, *n* (%)	253 (30.7)	977 (59.9)	239 (29.9)	1025 (62.6)	231 (34.8)	933 (65.9)	231 (40)	799 (69)
Calcitriol, PO (%)	87	55.8	75.7	48.4	72.3	39.5	63.2	36.9
Calcitriol, IV (%)	5.5	18.5	3.8	17.2	6.5	15.8	5.6	14.5
Paricalcitol, IV (%)	4	24.4	12.6	28	10.4	38.7	20.8	41.9
Other (%)	4.3	1.4	1.3	0.5	1.7	0.5	3.5	0.9
Phosphate binder								
Calcium-based (%)	55.2	43.9	50.2	42.6	48.6	43.5	48.8	41.6
Calcium-free (%)	47.3	58.9	45.1	57.9	41.4	60.8	41.9	60.4

[a]*N* refers to the frequency of patients; the per cent of VDRAs and phosphate binders also includes combination use. IV, intravenous; PO, oral.

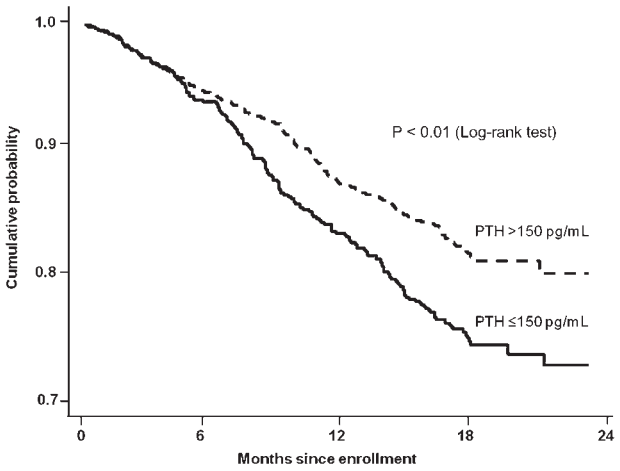

Fig. 1. KM plot of survival estimates by iPTH levels. Survival estimates (all-cause mortality) for FARO patients with levels of serum iPTH >150 pg/mL (dotted line) versus patients with levels of serum iPTH ≤150 pg/mL (solid line; $P < 0.01$).

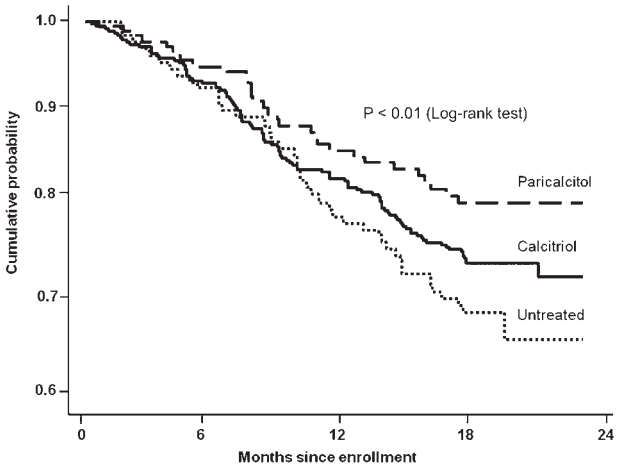

Fig. 2. KM plot of survival estimates by VDRA treatment type. Survival estimates (all-cause mortality) for FARO patients with levels of serum iPTH ≤150 pg/mL treated with paricalcitol (semi-solid line; HR: 0.13, 95% CI: 0.03–0.54, $P < 0.01$) or calcitriol (solid line; HR: 0.62, 95% CI: 0.43–0.89, $P < 0.01$) versus untreated patients (dotted line).

increased time to death were age, presence of cerebrovascular disease, increased albumin or haemoglobin. VDRA treatment was associated with lower all-cause mortality HRs. Oral or IV calcitriol (HR = 0.62, 95% CI: 0.42–0.92, P = 0.02) or IV paricalcitol (HR = 0.18, 95% CI: 0.04–0.8, P = 0.02) was associated with statistically significant reductions in time to death compared to patients who did not receive VDRA therapy (Table 3).

Discussion

Results from this analysis of the FARO survey suggest that VDRA treatment is associated with reduced overall mortality as well as factor-adjusted mortality risks among Italian dialysis patients with SHPT, even when serum iPTH levels are ≤150 pg/mL. In addition, patients who did not receive treatment had a poorer prognosis. Survival data from the present study also suggest that paricalcitol is associated with an improvement over calcitriol for lowering the risk of all-cause mortality [32]. Our findings are confirmed by Teng *et al.* who performed a large ($N = 67\,399$) retrospective analysis that showed a significantly lower mortality rate among HD patients receiving IV paricalcitol compared with those receiving IV calcitriol [33]. Furthermore, patients receiving paricalcitol who switched to calcitriol had significantly higher mortality rates than those receiving calcitriol who switched to paricalcitol; the overall survival advantage attributed to paricalcitol over calcitriol was 16% [33]. Another retrospective database analysis by Tentori *et al.* ($N = 7731$) observed that mortality rates were also significantly lower in HD patients treated with paricalcitol (or doxercalciferol) compared with those treated with calcitriol ($P < 0.05$) [14]. Although these findings favour the use of vitamin D, differences between the different compounds were not statistically significant following adjustment for patient characteristics.

More recently, Tentori *et al.* [34] compared different methods for evaluating the clinical impact of vitamin D and observed that previously published Dialysis Outcomes and Practice Patterns Study data [35] may have been distorted by potential confounders that could not be measured, even if in this study there were HD patients treated with oral vitamin D that included the native form. Therefore, the benefit afforded by VDRA treatment on survival in patients on HD remains to be verified in a prospective randomized clinical trial even if we consider that in this analysis, the overall unadjusted mortality rate was 16 deaths per 100 patient-years. Furthermore, among patients prescribed and not prescribed vitamin D, death rates were 14 and 17.9 per 100 patient-years, respectively, and this difference persisted even when data were adjusted for demographic confounders. Although the present study was not designed to assess how specific VDRA dosing regimens affected patient survival, it is important to consider dosage ranges when discussing mortality data to determine clinical relevance. Patients who participated in the FARO study received weekly mean doses of oral calcitriol, IV calcitriol or IV paricalcitol which ranged from 1.9 to 2.2, 3.4 to 3.7 and 11.2 to 15.9 μg, respectively, depending on the study visit [32]. Other evidence suggests that VDRAs at similar or higher doses are capable of providing significant clinical benefit in these patients [12, 15, 34]. A time-dependent, 2-year prospective analysis of patients on maintenance HD therapy ($N = 58\,058$) by Kalantar-Zadeh *et al.* [12] demonstrated that even lower doses of paricalcitol (1–4.99 μg/week) were associated with reductions in all-cause mortality HRs. Further analysis on a subset of patients ($N = 34\,307$) from the same database revealed that HD patients who received an average weekly dose of IV paricalcitol (14.3 μg/week) comparable to that of patients in our study, also experienced significant reductions in the relative risk of death compared with untreated patients [34]. A recent historical cohort study of chronic HD patients in Latin American

Table 3. HRs of time to death in patients with serum iPTH levels ≤150 pg/mL[a]

Clinical characteristics	Hazard criteria	HR	95% CI	P-value
Dialysis vintage	Per 10-year increase	0.94	0.7–1.26	0.67
Age at enrolment	Per 10-year increase	1.34	1.14–1.58	<0.01
Sex	Women versus men	1.01	0.73–1.4	0.95
Hypertension	Yes versus no	0.7	0.48–1.01	0.06
Dyslipidaemia	Yes versus no	1.14	0.75–1.72	0.55
Cardiovascular disease	Yes versus no	0.83	0.56–1.21	0.33
Cerebrovascular disease	Yes versus no	1.58	1.11–2.25	0.01
Diabetes	Yes versus no	1.06	0.7–1.59	0.8
Albumin (g/dL)	Per 1-unit increase	0.55	0.41–0.75	<0.01
Haemoglobin (g/dL)	Per 1-unit increase	0.69	0.6–0.79	<0.01
Serum phosphorus (mg/dL; >5.5 ref.)	<3.5	0.93	0.53–1.62	0.8
	3.5–5.5	0.96	0.61–1.5	0.85
Serum calcium (mg/dL; 8.4–9.5 ref.)	<8.4	1.17	0.78–1.76	0.44
	9.5–10.5	0.88	0.54–1.43	0.61
	>10.5	1.64	0.68–3.99	0.27
VDRA use (no use ref.)	Calcitriol (IV/PO)	0.62	0.42–0.92	0.02
	Paricalcitol	0.18	0.04–0.8	0.02
Phosphate binders (no use ref.)	Calcium-based	0.7	0.49–1	0.05
	Calcium-free	0.69	0.47–1.03	0.07

[a]IV, intravenous; PO, oral; ref., reference value.

dialysis sites demonstrated significant overall survival benefit of oral active VDRA (97% calcitriol) using a mean daily dose as high as 0.51–1 μg and as low as <0.25 μg compared to no VDRA therapy [15]. This study showed that mean daily doses of oral active vitamin D <1 μg showed a significant benefit in survival rate. Interestingly, the reduction in mortality risk was even seen at the lowest PTH tertile, where a higher tendency in mortality risk has previously been described [36] and accompanied with high serum calcium and phosphorus levels [33]. Although these studies do suggest an overall dose-related survival benefit afforded by VDRA therapy, a recent large observational study by Shinaberger *et al.* [37] failed to show any meaningful association between the absolute dosage of paricalcitol and survival among maintenance HD patients. However, increasing levels of the ratio of paricalcitol dosage to serum concentration of PTH were associated with better survival. These findings need to be confirmed in clinical trials.

As previously reported, approximately two-thirds of all patients in the FARO study failed to achieve target iPTH levels and nearly 90% failed to achieve combined target iPTH, P and Ca levels as described by the K/DOQI guidelines [22, 29], indicating that the achievement of K/DOQI target ranges may be difficult for many CKD patients with SHPT. Therefore, the reassessment of K/DOQI target ranges may be warranted to determine if they are too strict, also prompted by considering new target values reported in KDIGO guidelines. Regardless, the impact on survival is clear. VDRA therapy was shown to be significantly associated with a reduced risk of all-cause mortality among all the FARO survey patients, even in patients with serum iPTH levels of ≤150 pg/mL.

There are several limitations to the FARO survey that need be addressed. The sample size was smaller than desired, heterogeneous and treatment duration varied between patients. It is likely that this heterogeneity (therapy and population characteristics) was attributed to differences in resources available (treatment resources, medical experience/knowledge and financial resources) between different clinical centres. Thus, further studies in larger and more homogeneous patient populations are warranted. However, despite the relatively short observation period (i.e. 18 months), we were still able to observe significant differences in patient mortality risk between treatment groups. A common weakness with observational studies is the potential for confounding by indication, which may have also been relevant in the present study [38]. Trends suggested that more robust differences may have been evident if a larger sample size and a longer observation period had been evaluated. The lack of a standardized therapy resulted in a relatively heterogeneous non-randomized patient population including both prevalent and incident dialysis patients and thus prevented the possibility of comparing different dosing regimes within treatment groups. iPTH was measured using commercially available kits. Although each centre did not change the usual method of assay during the study period [29], thus maintaining optimized conditions, identical kits were not used across the various centres. This poses a potential limitation since it is recognized that heterogeneity exists between iPTH measurement for different commercially available kits [39, 40].

In conclusion, these data suggest that VDRAs may be crucial in decreasing all-cause and mortality in HD patients. Moreover, paricalcitol may provide an improvement over calcitriol-treated patients even when levels of serum iPTH are ≤150 pg/mL. The benefit of VDRA treatment on survival in HD patients remains to be confirmed in large prospective randomized clinical trials.

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Predictors of haemoglobin levels and resistance to erythropoiesis-stimulating agents in patients treated with low-flux haemodialysis, haemofiltration and haemodiafiltration: results of a multicentre randomized and controlled trial

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Abstract

Background. Predictors of haemoglobin (Hb) levels and resistance to erythropoiesis-stimulating agents (ESAs) in dialysis patients have not yet been clearly defined. Some mainly uncontrolled studies suggest that online haemodiafiltration (HDF) may have a beneficial effect on Hb, whereas no data are available concerning online haemofiltration (HF). The objectives of this study were to evaluate the effects of convective treatments (CTs) on Hb levels and ESA resistance in comparison with low-flux haemodialysis (HD) and to evaluate the predictors of these outcomes.

Methods. Primary multivariate analysis was made of a pre-specified secondary outcome of a multicentre, open-label, randomized controlled study in which 146 chronic HD patients from 27 Italian centres were randomly assigned to HD (70 patients) or CTs: online pre-dilution HF (36 patients) or online pre-dilution HDF (40 patients).

Results. CTs did not affect Hb levels ($P = 0.596$) or ESA resistance ($P = 0.984$). Hb correlated with polycystic kidney disease ($P = 0.001$), C-reactive protein ($P = 0.025$), ferritin ($P = 0.018$), ESA dose ($P < 0.001$) and total cholesterol ($P = 0.021$). The participating centres were the main source of Hb variability (partial eta^2 0.313, $P < 0.001$). ESA resistance directly correlated with serum ferritin ($P = 0.030$) and beta2 microglobulin ($P = 0.065$); participating centres were again a major source of variance (partial eta^2 0.367, $P < 0.001$). Transferrin saturation did not predict either outcome variables ($P = 0.277$ and $P = 0.170$).

Conclusions. In comparison with low-flux HD, CTs did not significantly improve Hb levels or ESA resistance.