# Mineral Metabolism and Anaemia Correction in Haemodialysed Patients

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**Abstract**

**Background**. Calcium-phosphorus metabolism disturbances have been involved in renal anaemia correction. Recent data suggest a better anaemia control in haemodialysed (HD) patients with serum calcium and phosphorus levels above the targets and in those with iPTH below recommended target. The study aimed to evaluate the influence of calcium-phosphorus metabolism parameters on renal anaemia correction in HD patients.

**Methods**. One hundred and sixty-six patients undergoing chronic HD for at least 3 months in a single centre were enrolled in a prospective, longitudinal, observational trial for 6 months. Parameters of anaemia management (percentage of patients with Hb >11g/dL, haemoglobin - Hb, cumulative epoetinum dose, cumulative intravenous iron dose, iron status) and of calcium-phosphorus metabolism were assessed. The European and National Best Practice Guidelines recommendations were used for therapeutical intervention and monitoring.

**Results**. 85% of patients reached the target Hb at the end of the study versus only 43% at the beginning. Hb significantly and progresively increased from 10.8 to 11.9 g/dL. Serum calcium and phosphorus levels did not significantly change. After 6 months, a significantly greater percentage of patients achieved the target serum phosphorus (51.2 vs 35.5%) and calcium-phosphorus product significantly decreased (49.0 vs 54.6 $mg^2/dL^2$). Only 20% of patients were initially at target iPTH. There were no differences in any of the calcium-phosphorus metabolism parameters between the patients who reached target Hb and those with Hb<11 g/dL. The percentage of patients receiving epoetinum and the cummulative doses did not changed. A significantly greater percentage of patients achieving optimum anaemia correction reached target iron status (90% vs 62% at initiation). Mean cumulative iron dose was significantly greater in patients with initial Hb below target. Patients with initial Hb>11 g/dL had a significantly higher HD vintage (10.7 vs 6.5 years).

**Conclusions.** Anaemia correction was ameliorated in HD patients, without significant changes in epoetinum therapy. Calcium-phosphorus product significantly decreased. The results do not support the relationship between calcium-phosphorus metabolism parameters and anaemia correction. Iron metabolism significantly improved. Patients with target Hb had a greater HD vintage.

**Key words.** Renal anaemia, calcium-phosphorus metabolism, haemodialysis, epoetinum, iron balance

## Introduction

Renal anaemia and calcium-phosphorus metabolism disturbances are frequently found in chronic kidney disease (CKD) and are interrelated (1). Correction of both anaemia and calcium-phosphorus metabolism results in a decreased in morbidity and mortality, an improvement in the quality of life and an increase survival in CKD patients (2, 3).

A recent analysis of data from Dialysis Outcomes and Practice Patterns Study (DOPPS) revealed a paradox: serum calcium and phosphorus above the levels recommended by the currently used Best Practice Guidelines (6, 15), although imply an increased mortality risk, especially from cardiovascular causes, seem to positively influence anaemia management (4). The purpose of this study was to assess the influence of calcium-phosphorus metabolism parameters on anaemia correction.

## Patients and Methods

We performed a prospective, longitudinal, observational trial, with a total duration of 6 months. The subjects were followed between March 1 - August 31, 2006. The study had the approval of the local Hospital Ethics Committee and was conducted according to the Declaration of Helsinki and Tokyo as amended in Venice (1983).

*Patients*

All the 166 patients undergoing chronic haemodialysis for least 3 months in a single centre ("Dr Carol Davila" Fresenius Nephrocare Dialysis Centre, Bucharest) not enrolled in other trials were included. All subjects gave a written informed consent.

*Parameters*

The percentage of patients reaching the target haemoglobin (Hb) recommended by the Romanian Best Practice Guidelines for the treatment of renal anaemia (5) at the end of the study was used as the primary efficacy parameter.

Anaemia treatment was also evaluated using: Hb level, mean cumulative epoetinum dose, mean cumulative intravenous iron dose and the parameters of iron metabolism (serum ferritin, transferrin saturation).

Calcium-phosphorus metabolism was assessed by serum calcium corrected for serum albumin level, serum phosphorus and intact PTH (iPTH). Because of financial reasons, the serum level of 25(OH) D3 couldn't be determined.

*Therapeutic Intervention*

The therapeutic interventions for both renal anaemia and secondary hyperparathyroidism followed the

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recommendations of the Romanian Best Practice Guidelines (5, 6).

All patients requiring iron supplementation received intravenous iron sucrose (Venofer®; Vifor Intl, St. Galen, Switzerland), administered in a slow infusion diluted in 250 mL saline solution, in the last 30 minutes of the HD session.

The treatment with erythropoesis stimulating agents (ESAs) was initiated when haemoglobin levels were below 11g/dL on two consecutive measurements at minimum two weeks apart and achieving the optimum iron status. The complete evaluation according to the recommendations of Best Practice Guidelines (5, 8, 9) did not reveal any other cause of anaemia except but the renal one. Depending on the co-morbidities and the clinical impact of anaemia, the treatment with ESAs was considered also in patients with Hb above 11 g/dL. All the patients included in this study received epoetinum beta (NeoRecormon®; F. Hoffmann-La Roche, Basel, Switzerland) administered subcutaneously, once a week, according to the recommendations of Best Practice Guidelines (5, 8, 9, 10).

Considering the abnormalities of calcium-phosphorus metabolism, patients with hypocalcaemia received daily 1-1,5 g of elemental calcium (calcium carbonate, *per os*, between meals). The patients with hyperphosphataemia received dietary recommendations aiming to reduce the phosphates intake and calcium carbonate 3-6 g daily with meals, as a phosphate binder. Aluminium based phosphate binders have not been prescribed in any patient during the observation period.

The patients with high iPTH level (>300pg/mL) were treated with calcium carbonate. If iPTH was persistently above the recommended target for the CKD stage and if the serum calcium and phosphorus were within the normal range (spontaneously or after therapeutic intervention), the patients received calcitriol 0,125- 0,25µg or an equivalent dose of oral alfa-calcidol daily. The treatment was discontinued in case of hypercalcaemia or hyperphosphataemia, and restarted after the correction of these abnormalities, with half of the previous dose.

Monitoring schedule

Clinical examination and all the laboratory determinations, including haematological status, iron balance and calcium-phosphorus metabolism parameters were monitored according to Best Practice Guidelines for renal anaemia (5), and secondary hyperparathyroidism respectively (6). All the blood samples were withdrawn before the midweek HD session (7).

Estimated Kt/V using Daugirdas II formula was used to assess dialysis dose. The inflammatory status was evaluated by C reactive protein (CRP).

*Statistical analysis*

Statistical analysis was performed using an SPSS 10 package. Data were analysed using descriptive methods: mean and standard deviation for parameters with normal distribution, or median and interquartile range for skewed data. ANOVA, Mann-Whitney and t-Student tests were used to compare the results. A p value of less than 0.05 was considered to be statistical significant.

## Results

*Patients and haemodialysis treatment characteristics*

The studied cohort (SCD cohort) included 56% men, with a mean age of 52.6 years. The mean HD vintage was of 8.3 years. Thirty-four percent of patients had more than 10 years on HD and 10% of them even more than 20 years. Primary glomerular nephropathies were the leading cause of the chronic kidney disease (CKD) (Table 1).

**Table 1.** Patient's characteristics

| | **SCD Cohort (n=166)** | **ESAM-2 [11] (n=8100)** |
|---|---|---|
| Demographic data | | |
| Age (years) | 52.6 ± 13.1 | 62.5 ±14.6 |
| Gender (males, %) | 56 | 57 |
| HD vintage (years) | 8.0 ± 6.8 | 3.9 ± 4.5 |
| over 10 years (%) | 34 | |
| over 20 years (%) | 10 | |
| Body mass index (BMI, kg/m$^2$) | 24.6 ± 4.7 | 23.8 ± 5.4 |
| Causes of ESRD: | | |
| Primary glomerular nephropathies (%) | 52 | 21 |
| Tubulo-interstitial nephropathies (%) | 16 | 10 |
| Hereditary/Congenital/ diseases (%) | 13 | 10 |
| Vascular diseases (%) | 9 | 16 |
| Systemic diseases (%) | 6 | 24 |
| Other/Unknown (%) | 4 | 19 |

All the enrolled patients followed the standard HD treatment of the unit: 3 sessions per week, with 4.5 hours per session. Native arterio-venous fistula was used as vascular access in the majority of subjects (92.2%). Only 7.8% of patients used a central venous catheter. In all patients polysulfone membranes and bicarbonate dialysate were used. The blood and dialysate flow were 250mL/min, and 500mL/min respectively.

Correction of anaemia and calcium-phosphorus metabolism disturbances

*Anaemia correction*

The percentage of patients with target Hb as recommended by the Romanian Best Practice Guidelines (5 ) increased significantly during the observation period: 84.9% vs. 43.4% at the beginning (p<0.0001) (Figure 1). 39.2 % of patients maintained the target Hb level all over the study.

Hb level increased progressively and significantly during the study, from 10.8±1.7 g/dL to 11.9±1.5 at the end of observation period. .

Serum calcium levels corrected for serum albumin did not significantly change: 8.8±0.8 at the end versus 9.1 ± 0.9 mg/dL initially, both values being below the target range (9.2-9.6 mg/dL (6)) (Table 2).

At the end of the study 28.3% of patients had serum calcium within the target range, as compared to 21.1% at the beginning; the difference did not reach statistical significance (Table 2).

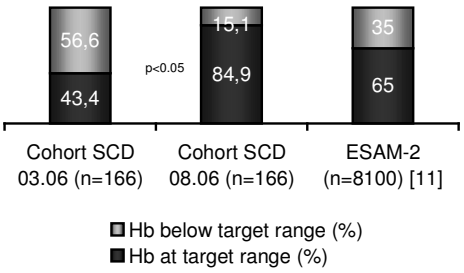


**Figure 2.** Percentage of patients achieving the target haemoglobin

*Correction of the calcium-phosphorus metabolism*

Serum calcium levels corrected for serum albumin did not change significantly during the study, with 28% of patients within the target range at the end of the study (Table 2). No significant differences have been noted in the percentage of patients with target serum calcium, during the observation period.

At the end of the study the mean serum phosphates level was of 5.5 ± 1.5 mg/dL, lower than at initiation (6.0 ± 1.8 mg/dL), but the difference was not statistically significant (Table 2). Similarly, the percentage of patients with target serum phosphates was greater after 6 months of follow-up (51.2 versus 35.5% at baseline, p>0.05).

The calcium-phosphorus product was significantly lower at the end of the study (49.0 ± 14.2 versus 54.6 ± 17.3 $mg^2/dL^2$ initially) (Table 2).

Because of financial reasons, iPTH was determined only at baseline. Serum iPTH level was 192.0 (75.0, 514.3) pg/mL. Only 19.9% of patients had serum iPTH within the target range.

The time course changes in the calcium-phosphorus metabolism parameters are presented in Table 2.

**Table 2.** Haematologic, iron status and calcium-phosphorus metabolism parameters during the study

| Parameter | March 2006 (n=166) | August 2006 (n=166) | p |
|---|---|---|---|
| **Calcium-phosphorus metabolism** | | | |
| Albumin-corrected serum calcium (mg/dL)* | 9.1±0.9 | 8.8±0.8 | 0.06 |
| Patients with corrected serum calcium within target range (%) | 28.3 | 21.1 | 0.8 |
| Serum phosphates (mg/dL) * | 6.0±1.8 | 5.5±1.5 | 0.06 |
| Patients with serum phosphates within target range (%) | 35.5 | 51.2 | 0.02 |
| Calcium-phosphorus product ($mg^2/dL^2$) * | 54.6 ± 17.3 | 49.0 ± 14.2 | 0.03 |
| Patients with Ca-P product at target (%) | 32.6 | 50.2 | 0.01 |
| iPTH (pg/mL) # | 192.0 (75.0, 514.3) | | |
| Patients with target iPTH (%) | 19.9 | | |
| **Need for epoetinum treatment** | | | |
| Patients treated with epoetinum (%) | 72.9 | 69.3 | 0.46 |
| Epoetinum dose (UI/kg per week and per patient treated) | 79.1 | 68.9 | 0.06 |
| Erythropoietin Resistance Index * (UI/kg per week and per g/dL Hb) | 7.9±4.9 | 6.4±4.8 | 0.02 |
| **Iron metabolism** | | | |
| Serum ferritin (ng/mL) # | 382.5 (266.8, 477.8) | 478.0 (335.0, 558.0) | <0.0001 |
| Patients with optimum serum ferritin (%) | 89.2 | 93.9 | 0.13 |
| Transferrin saturation (%)* | 24.8±8.4 | 31.6±9.2 | 0.03 |
| Patients with optimum TSAT (%) | 64.0 | 90.4 | <0.0001 |
| Patients with optimum iron status (%) | 62.0 | 90.4 | 0.01 |
| **Need for iron treatment** | | | |
| Patients treated with iron (%) | 53.0 | 59.0 | 0.27 |
| IV Iron dose (mg/month per patient treated) # | 50 (50, 100) | 50 (25, 50) | 0.4 |
| **Dialysis dose and inflammatory status** | | | |
| Kt/V* | 1.4±0.1 | 1.4±0.2 | 0.9 |
| C reactive protein (mg/L) # | 4.0 (2.0, 8.0) | 4.0 (3.0, 7.0) | 0.9 |
| Patients with CRP > 5 mg/L (%) | 38% | 34% | 0.8 |

* - mean ± standard deviation; # - median (interquartile interval)

The influence of calcium-phosphorus metabolism parameters on the erythropoietic response

To evaluate the presumed influence of calcium-phosphorus metabolism disturbances on anaemia correction, we comparatively analysed the parameters of calcium-phosphorus metabolism at baseline among patients who reached an optimum control of anaemia at the end of the study and those with Hb lower than 11 g/dL after 6 months of follow-up.

The baseline value of corrected serum calcium was higher in patients achieving the target Hb by the end of the study, but the difference was not statistically significant (Table 3).

Patients who failed to achieve the target for anaemia treatment during the study had higher serum phosphates at baseline, but the difference did not reach statistical significance (Table 3).

There were no differences between patients who reached the target and those with a poor control of renal anaemia, neither in the calcium-phosphorus product nor in serum iPTH (Table 3).

**Table 3.** Baseline calcium-phosphorus metabolism parameters in patients with optimum anaemia correction and in comparison with in patients with Hb <11g/dL at the end of the study

| Patient's category | Parameter | p |
|---|---|---|
| | **Corrected serum calcium (mg/dL)*** | 0.78 |
| With Hb at target (n=139) | 9.23±0.89 | |
| With Hb<11 g/dL (n=25) | 9.17±0.88 | |
| | **Serum phosphates (mg/dL)*** | 0.59 |
| With Hb at target (n=141) | 5.96±1.77 | |
| With Hb<11 g/dL (n=25) | 6.17±1.93 | |
| | **Calcium-phosphorus product ($mg^2/dL^2$)*** | 0.58 |
| With Hb at target (n=139) | 54.99±16.83 | |
| With Hb<11 g/dL (n=25) | 57.08±20.95 | |
| | **iPTH (pg/mL) #** | 0.53 |
| With Hb at target (n=141) | 192.0 (72.0, 474.0) | |
| With Hb<11 g/dL (n=25) | 184.0 (92.0, 538.0) | |

* - mean ± standard deviation; # - median (interquartile interval)

Nevertheless, a consistent improvement in anaemia management was noticed during the study, suggesting essential beneficial intervention in renal anaemia treatment,

not related to the calcium-phosphorus metabolism parameters.

Other factors involved in the responsiveness of anaemia to treatment

*The need for ESAs treatment*

Epoetinum (Epo) treatment requirements were estimated by the percentage of patients who received ESAs during the study, as well as by the epoetinum dose per treated patient at each census point and by the median cumulative epoetinum dose per treated patient.

The percentage of patient who received Epo during the study did not significantly change (Table 2). 73.2% of patients received Epo for at least one month.

The Epo dose decreased, but the difference was not statistically significant (Table 2).

The erythropoietin resistance index (ERI), defined as the Epo dose used for each g/dL Hb, considerably decreased during the study: 6.4 at the end of the 6-month period versus 7.9 UI/kg per week and per g/dL Hb at baseline (Table 2).

The mean cumulative Epo dose used during the study was of 74.2±43.7 UI/kg per week and per patient treated. No significant difference was found in the mean cumulative Epo dose between the patients initially at target Hb and those with baseline Hb below the target level (76.4±31.2 versus 69.5.4±42.1 UI/kg per week and per patient treated).

*Iron balance*

Serum ferritin level increased significantly. On the other hand, the percentage of patients with optimum serum ferritin level for erythropoesis (100-800 ng/mL (5)) remained unchanged during the study (Table 2).

There were no cases of iron overload during the observation period.

Transferrin saturation (TSAT), a marker of iron available for erythropoesis, raised significantly. At the end of the study, significantly more patients were within the target range of 20-50% (5, 8, 9) (Table 2).

90% of patients reached an optimum iron status balance (serum ferritin level 100-800 ng/mL and transferrin saturation 20-50% (5, 6, 7)) at the end of the study, a significantly greater percentage than at initiation (Figure 2).

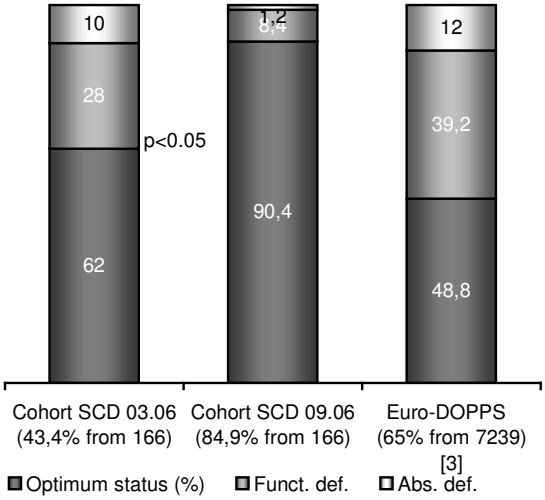


**Figure 2.** Iron status during the study

*The need for intravenous iron*

Neither the percentage of patients receiving intravenous iron nor the mean dose per treated patient did not significantly change (Table 2). 84% patients received at least one intravenous iron dose during observation period.

Nevertheless, the mean cumulative iron dose given to patients with an initial poor control of anaemia was significantly higher than that received by the patients with Hb above target at baseline (176.7 versus 130.0 mg/month per patient ever treated with iron, p<0.02) (Figure 3).

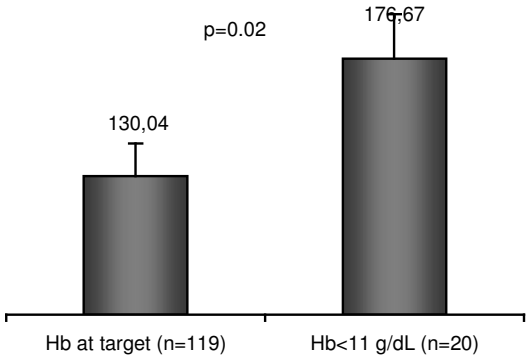


**Figure 3.** Mean cumulative iron dose (mg/month per patient ever treated with iron) in patients with optimum anaemia control and in those with Hb < 11g/dL at the end of the study

*Haemodialysis procedure*

At the enrolment, the patients already at target Hb had a significantly higher HD vintage than those with the Hb below 11g/dL (10.7±7.1 versus 6.5±6.1 years).

There were no significant changes in the HD treatment characteristics, in the efficacy of the HD procedure evaluated by the Kt/V (Daugirdas II formula) or in the inflammatory status assessed by C reactive protein (CRP) level. The percentage of patients with CRP level higher than 5 mg/L did not significantly change (Table 2).

## Discussion

Calcium-phosphorus metabolism disturbances of CKD and renal anaemia are interrelated (1, 12). Correction of the mineral metabolism disturbances could improve renal anaemia response to treatment (12, 13). A recent analysis of data from the DOPPS study suggested that a better control of renal anaemia in HD patients could be associated with levels of the calcium-phosphorus parameters outside of recommended range (6,14,15): above the target range for albumin-corrected serum calcium and serum phosphates, and below target range for serum iPTH, respectively (4). The present study aimed to evaluate the influence of calcium-phosphorus metabolism parameters on renal anaemia correction in HD patients.

At baseline only 43% of the enrolled patients had Hb above 11g/dL. At the end of the study, optimum anaemia control was obtained in 85% of subjects, a significantly higher percentage than at the initiation and even higher than the European mean of 65%, reported by the *European Survey on Anaemia Management 2003* (ESAM-2) study (11) (Figure 1). It is important to underline that the National Guidelines recommended a target Hb of above 10.5 g/dL for more than 85% patients from a dialysis unit (an individual level above 11 g/dL for individuals (5)), lower than that mentioned by the European and American Guidelines of 11 g/dL for more than 85% patients of the centre (8, 9). Thus, at the end of the study, the enrolled patients had a good control of anaemia,

with a Hb level above the target not only according to the local recommendations (5), but also to the European and American Guidelines (8,9).
Throughout the study period Hb increased progressively to a mean value of 11.9 g/dL, higher than the European value of 11.4 g/dL (11). In the same time, the erythropoietin resistance index considerably decreased.
The analysis of calcium-phosphorus metabolism parameters evolution during the study revealed an improvement in serum phosphates control, reflected by an increased percentage of patients within the target range (6). The calcium-phosphorus product considerably decreased, suggesting also an improvement in calcium-phosphorus metabolism.
These results do not sustain a relationship between any of the analysed calcium-phosphorus metabolism parameters (albumin-corrected serum calcium, serum phosphorus, calcium-phosphorus product, iPTH) and anaemia correction, but suggest the strong involvement of other factors in renal anaemia management. ESA treatment, iron status and iron supplementation, dialysis efficacy and HD vintage, as well as the inflammatory status were evaluated as possible other factors to explain the reported improvement in anaemia correction.
The need for ESAs treatment, as evaluated by the percentage of patients treated and by the dose had no significant variation during the study.
The iron status significantly improved: 90% patients attained the optimum levels for erythropoesis at the end of the study period, a percentage even higher than that of 49% reported for Europe (11) (Figure 2).
The percentage of patients who received intravenous iron did not significantly change during the study. Even though, the mean cumulative iron dose received by patients with Hb at baseline below 11g/dL was considerably higher than that received by patients with Hb at target from the beginning. These results suggest the role of iron supplementation in renal anaemia management, via an improved iron balance.
The study started in March 2006, one year after the elaboration implementation of the Romanian Best Practice Guidelines for the management of renal anaemia and of secondary hyperparathyroidism. The HD treatment characteristics did not change during the study. Similarly, there were no significant variations neither in the dialysis efficacy assessed by Kt/V, or in the inflammatory status evaluated by C reactive protein. Therefore, the significant improvement in anaemia management and trend of calcium-phosphorus metabolism parameters to reach the targets could be, to a certain extent, the result of an accurate use of the monitoring and treatment schedules settled by the guidelines.
The patients with the Hb in the target range from the beginning of the study had a greater HD vintage. These data suggest a better anaemia control in patients with higher HD duration. Similar data were reported in a study on 226 HD patients, revealing that patients who did not need Epo for anaemia correction had a greater HD vintage (16).
The value of this study in analysing the relationship between calcium-phosphorus metabolism and anaemia correction is limited mainly by the small number of enrolled subjects, but also by the lack of possibilities to determine iPTH and it's time course changes after the therapeutic intervention. Very important as well, the studied cohort is different from the European HD population (4, 11), the patients in our group being younger, with a greater HD vintage and having a greater percentage of primary glomerular nephropathies as underlying kidney disease (Table 1).
On the other hand, since the study was prospective, with an observation period of 6 months, including almost all stable HD patients from the biggest dialysis unit in our country, it could give an insight on the state of renal anaemia and calcium-phosphorus metabolism disturbances management in HD patients. Furthermore, our data suggest that the improvements in iron status and a longer HD vintage treatment are key factors involved in reaching renal anaemia therapeutic targets.

**Conclusion**

Renal anaemia management was significantly improved during the study: the percentage of patients reaching the target Hb significantly increased, while the erythropoietin resistance index decreased. 85% of subjects had Hb above 11 g/dL at the end of the study, thus achieving the levels recommended by the Best Practice Guidelines.
The analysis of calcium-phosphorus metabolism parameters revealed an improvement in serum phosphates control and a significant decrease of calcium-phosphorus product.
The results do not sustain the relationship between the analyzed calcium-phosphorus metabolism parameters (albumin-corrected serum calcium, serum phosphorus, calcium-phosphorus product, iPTH) and anaemia correction.
Erythropoesis stimulating agent's therapy was not changed during the study. Iron status substantially improved, at the end of the study 90% patients reaching the optimum iron balance for erythropoesis.
Patients with target Hb levels at the enrolment had a greater HD vintage.

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