Chapter 7

Hemoglobin levels and health-related quality of life in young and elderly patients on specialized pre-dialysis care

Moniek C.M. de Goeij
Yvette Meuleman
Sandra van Dijk
Diana C. Grootendorst
Friedo W. Dekker
Nynke Halbesma
for the PREPARE-2 study group

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Abstract

Background: In pre-dialysis patients, the optimal treatment choices for controlling hemoglobin (Hb) are unknown because targeting high Hb levels has negative effects – poorer survival – but possible positive effects as well – better health-related quality of life (HRQOL). Moreover, these negative and positive effects may be different in specific subgroups, for example young versus elderly patients.

Methods: In the prospective PRE-dialysis PAtient REcord-2 (PREPARE-2) follow-up study, incident patients starting pre-dialysis care were included between 2004 and 2011 when referred to one of the 25 participating Dutch outpatient clinics. HRQOL was assessed each six-month interval with the short form-36 questionnaire (physical/mental summary measure and eight subscales (range 0-100)). A linear mixed model was used to associate Hb (<11, 11-12 (reference), 12-13, ≥13 g/dl) with HRQOL, stratified by anemia-medication (erythropoiesis stimulating agent and/or iron supplement, ESA/iron) and age (young: <65 years, elderly: ≥65 years).

Results: In elderly patients (n=214) only, a natural high Hb (≥13 g/dl versus 11-12 g/dl) was associated with a statistically significant ($p<0.05$) and/or clinically relevant (>3-5 points) higher physical (11.9 [95% confidence interval (CI) 1.7;22.2]) and mental (6.4 [95% CI -1.7;14.6]) summary score. An ESA/iron induced high Hb did not result in a higher HRQOL in elderly patients. However, in young patients (n=157), only an ESA/iron induced high Hb (≥13 versus 11-12 g/dl) showed an association with a higher physical (8.9 [95% CI 2.1;15.8]) and mental (6.2 [95% CI -0.4;12.8]) summary score. This effect was present on all physical and mental subscales, with the exception of mental health.

Conclusion: The association of Hb levels with HRQOL is different between young and elderly patients with or without prescribed ESA/iron on specialized pre-dialysis care. Therefore, medical care should aim for shared-decision making regarding the appropriate Hb target for each patient leading to a more individualized care.

Introduction

Anemia is a common complication in patients with chronic kidney disease (CKD)[1], and associated with increased mortality and morbidity, lower health-related quality of life (HRQOL), and faster progression to end-stage renal disease[2-9]. Therefore, treatment of anemia with erythropoiesis stimulating agents (ESA), iron supplements, or a combination of the two is important, and several studies have shown that treatment with ESA has a beneficial effect on various health outcomes.[10-14]

However, the optimal hemoglobin (Hb) treatment target level for anemic patients with CKD is still unknown. A meta-analysis[15] showed that targeting high Hb levels (≥12 g/dl) with ESA in anemic CKD patients increases their HRQOL. Positive effects were predominantly found on the physical summary measure of the short form-36 (SF-36) questionnaire.[16] These effects are biologically plausible because common symptoms like low energy, fatigue, and weakness can be ameliorated by treating anemic patients with ESA.[11] Moreover, increasing HRQOL may have additional positive effects independently of other factors because it has been shown that starting dialysis with a high HRQOL increases survival.[17;18]

Besides the positive effects on HRQOL, high Hb targets (≥12 g/dl) in CKD patients can also have negative effects, such as an increased risk of mortality and cardiovascular events, and an accelerated progression to end-stage renal disease.[19] These contradictory results on different health outcomes indicate that it is important to make a well-considered treatment decision, taking personal preferences of CKD patients into account. Good clinical practice would be that each patient discusses the possible positive effects on HRQOL and possible negative effects on other clinical outcomes together with their physician to make an informed decision about the appropriate Hb treatment target.

Unfortunately, there is still insufficient evidence regarding the effect of targeting high Hb levels with anemia-medication on HRQOL to make such a well-considered decision. The studies that are available do not report all HRQOL subscales, do not show clinically relevant effects, and only report results about a heterogeneous population, instead of different subgroups of CKD patients. For example, positive effects on HRQOL may vary with age and CKD stage. Elderly patients and late-stage CKD patients experience more morbidities and have a lower HRQOL compared with young[20] and early-stage[21] CKD patients. A lower HRQOL can lead to a larger possible improvement. Or the opposite may take place, in which treatment ameliorates anemia-related symptoms whereas other morbidity-related symptoms among older patients in late CKD stages remain present, and consequently lead to a less increased HRQOL.

The aim of the current study was to gain more knowledge about the combined association of Hb levels and the prescription of anemia-medication on all HRQOL subscales, in elderly compared with young CKD patients starting specialized pre-dialysis care.

Methods

Study design

The PRE-dialysis PAtient REcord-2 (PREPARE-2) study is an ongoing, prospective follow-up study of incident pre-dialysis patients treated in 25 nephrology outpatient clinics in The Netherlands. Patients were included between July 2004 and June 2011, at the start of specialized pre-dialysis care. They were treated by their nephrologist in their regular scheme according to the treatment guideline of the Dutch Federation of Nephrology[22], a guideline partly based on the K/DOQI[23] and KDIGO[24] guidelines. Patients were followed until the start of dialysis, receiving a kidney transplant, death, or censoring. Censoring was defined as: moving to an outpatient clinic not participating in the PREPARE-2 study, recovery of kidney function, refusal of further study participation, lost to follow-up, or August 1, 2012 (end of follow-up), whichever came first. The study was approved by the Medical Ethics Committee or the Institutional Review Board (as appropriate) of all participating centers.

Patients

To be eligible for inclusion, patients had to be at least eighteen years of age and the inclusion should take place at the moment of referral to a specialized pre-dialysis outpatient clinic. In practice, this refers to incident pre-dialysis patients with an estimated glomerular filtration rate (eGFR) of less than 20-30 ml/min/1.73 m^2, in whom renal function loss is progressive. Patients with a failing kidney transplant were also included in the study, if the transplantation was at least one year ago. All participants gave their written informed consent prior to study inclusion.

Data collection

Data on demography, biometry, primary kidney disease, co-morbidities, medication prescriptions, and HRQOL were collected at the start of specialized pre-dialysis care and in subsequent six-month intervals. Corresponding laboratory data were extracted from the electronic hospital information systems or medical records. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[25]

Measurements and definitions

HRQOL was assessed with the generic validated SF-36 questionnaire[16], which consists of 36 items that can be divided into eight subscales. The scores on the items within each subscale are summed and transformed to a 0-100 scale, with higher scores indicating a better HRQOL. Two summary measures can be composed of the eight subscales: physical summary score (consisting of the four subscales physical functioning, role-physical, bodily pain, and general health) and mental summary score (consisting of the four subscales vitality, social functioning, role-emotional, and mental health). GFR was estimated using the four-variable Modification

of Diet in Renal Disease (MDRD) formula[26]. The Hb levels (mmol/l) were measured according to the standard procedure in each participating outpatient clinic. We converted the Hb level in mmol/l to g/dl with the conversion factor 1.6113 and categorized it into four groups (<11, ≥11-<12, ≥12-<13, and ≥13 g/dl). The chosen categories were based on the current treatment guideline for anemic CKD patients (target is ≥11-<12 g/dl, and ≥13 g/dl should not be targeted[27]).

Statistical analyses

Continuous baseline characteristics were presented as mean ± standard deviation (SD) or median (boundaries of interquartile range, IQR) and dichotomous baseline characteristics were presented as percentages. A linear mixed model was used to associate the Hb categories (11-12 g/dl as reference) with HRQOL during the first two years of pre-dialysis care. We chose to restrict the time of follow-up until two years to prevent selection bias, as the healthy and stable patients, whom are still on pre-dialysis care after two years, would have a relatively large contribution to the overall association. In the model we included the four Hb categories as a fixed independent variable and the continuous HRQOL as a dependent variable, both updated each six months, and the variable time as a random variable. The results from this model indicate the difference in HRQOL score between the different Hb categories (compared with the reference category ≥11-<12 g/dl) on each time point during the first two years of pre-dialysis care. In other words, the results indicate the 'average' HRQOL difference between Hb categories. This linear mixed model was also performed after stratification by (1) the prescription of anemia-medication (erythropoiesis stimulating agent and/or iron supplement, ESA/iron) at the start of pre-dialysis care (yes/no) and (2) age (young: <65 years, and elderly: ≥65 years). To avoid power problems we also performed a continuous (per 1 g/dl increase) analysis in patients with Hb levels ≥11 g/dl (i.e. patients with optimal and high Hb levels). Patients with Hb levels <11 g/dl were excluded because categorical analyses before stratification showed a different effect size on HRQOL in these patients. We adjusted for the potential baseline confounders age, sex, primary kidney disease, cardiovascular disease, diabetes mellitus, eGFR, proteinuria, albumin, and systolic blood pressure. Associations of Hb with HRQOL were interpreted both statistically ($p<0.05$) and clinically (categorical analyses: >3-5 points[28], and for the continuous analyses: >1.5-2.5 points per each 1 g/dl increase). When information on stratification variables – age and ESA/iron prescription - or confounders were missing at the start of pre-dialysis care, data were imputed with the method of multiple imputation in PASW/SPSS (using ten repetitions). Multiple imputation is a technique where missing data for a patient are imputed by a value that is predicted by other known characteristics of this patient.[29;30] The imputation model included all characteristics described in Table 1, plus the outcome reached and follow-up time because missing baseline characteristics are often related to the outcome.[31] Skewed distributed continuous variables, including follow-up time, were logarithmically transformed before entering into the model. All statistical analyses were performed with PASW/SPSS version 20.0.

Sensitivity analyses

We performed five sensitivity analyses to test the robustness of our results. First, we repeated all analyses after imputation of the missing baseline characteristics of all 502 included patients. Second, after defining young patients as <70 years and elderly patients as ≥70 years, analyses were repeated. Third, we repeated all linear mixed model analyses with an additional interaction term in the model: Hb categories*time. By including this term we investigated whether the association between Hb and HRQOL is different over time. In other words, whether the pattern of HRQOL over time differs between the Hb categories. Fourth, during pre-dialysis care some patients discontinue and others start using ESA/iron and patients can switch from the category <65 to ≥65 years. Therefore, we included the time-dependent variables ESA/iron prescription and age (young: <65 years, elderly: ≥65 years), updated each six months, in the linear mixed model instead of stratifying the analyses by ESA/iron prescription and age at the start of pre-dialysis care. Thereafter, we performed an additional analysis with the potential confounders systolic blood pressure, eGFR, proteinuria, and albumin also included as time-dependent variables.

Results

Baseline characteristics

Of the 502 patients included in the PREPARE-2 study, 371 patients were included in our primary statistical analyses. Patients were excluded if a Hb measurement and physical or mental summary score in the same six-month interval during the first two years of pre-dialysis care were not available. Table 1 shows the baseline clinical characteristics of these patients. Respectively 19%, 30%, and 51% had Hb levels below, on, or above the current treatment target (11-12 g/dl, Table 1). The majority had renal vascular disease as primary kidney disease and often diabetes mellitus as co-morbidity. Patients with Hb levels ≥13 g/dl had a higher eGFR, lower body mass index, less often diabetes mellitus, and more often cardiovascular disease compared with patients on target (≥11-<12 g/dl). Moreover, the higher prevalence of cardiovascular disease was present in elderly patients (≥65 years; 62% for ≥13 g/dl and 45% for 11-12 g/dl) and not in young patients (<65 years; 32% and 28%, respectively). Information regarding prescription of medication at the start of pre-dialysis care was only available for 323 (87%) patients. Of these, 54% were prescribed ESA/iron therapy, which was similar across all Hb levels. Darbepoetin and iron supplements were prescribed more often than epoetin, especially in patients with high Hb levels (≥12 g/dl).

Association of Hb levels with HRQOL

Patients with high Hb levels (≥13 g/dl) had a statistically ($p<0.05$) and clinically (>3-5 points) higher physical summary score (56.7 versus 51.8, Table 2) compared with patients on target (11-12 g/dl). Adjustment for confounders did not essentially change the results. On all physical subscales, with the exception of bodily pain, this difference was clinically relevant. Furthermore, patients with low Hb levels (<11 g/dl) had a lower mental summary score

compared with patients on target (60.4 versus 66.1, p<0.05). On all subscales of the mental summary measure, with the exception of mental health, this difference was clinically relevant.

Table 1: Baseline clinical characteristics of the total study population and stratified by categories of hemoglobin levels

	Total n=371	**<11[1] n=68**	**≥11-<12[1] n=104**	**≥12-<13[1] n=75**	**≥13[1] n=106**
Age (years)	69 (55-76)	70 (51-78)	69 (57-75)	69 (57-76)	65 (53-76)
Sex (%, male)	67	60	67	65	73
Body mass index (kg/m^2)[2]	26.4 ± 4.9	27.0 ± 5.4	26.3 ± 5.0	26.4 ± 4.6	26.1 ± 4.8
Smokers / quitters <1 year before inclusion (%)	24	18	24	24	27
Primary kidney disease (%)					
Diabetes mellitus	13	18	11	12	13
Glomerulonephritis	14	10	14	17	12
Renal vascular disease	30	41	28	29	29
Other	43	31	47	42	46
eGFR (ml/min/1.73 m^2)[3]	16.9 ± 6.0	15.5 ± 4.9	15.9 ± 5.9	17.6 ± 5.2	18.4 ± 6.8
Urinary protein excretion (g/24h)[4]	1.0 (0.3-2.1)	1.1 (0.3-2.0)	1.0 (0.4-2.4)	0.7 (0.2-2.0)	1.1 (0.4-2.2)
Urea (mmol/l)[5]	22.1 ± 7.0	23.7 ± 7.1	22.6 ± 6.9	21.1 ± 6.4	21.4 ± 7.5
Albumin (g/l)[6]	40.7 ± 4.6	39.1 ± 5.0	40.5 ± 4.4	41.3 ± 4.7	41.5 ± 4.5
Systolic blood pressure (mmHg)[7]	142 ± 22	142 ± 23	144 ± 24	139 ± 19	141 ± 23
Hemoglobin (g/dl)[1]	12.3 ± 1.5	10.3 ± 0.5	11.6 ± 0.3	12.5 ± 0.3	14.0 ± 0.9
Diabetes mellitus (%)[8]	26	38	25	21	22
Cardiovascular disease (%)[9]	43	40	39	41	47

Continuous variables are presented as mean ± standard deviation for normally distributed variables and as median (boundaries of interquartile range) for skewed variables. [1] Hemoglobin level is given in g/dl and available for 353 patients. Available for: [2] 366, [4] 210, [5] 338, [6] 324, [7] 368 patients. [3] Estimated glomerular filtration rate (eGFR) is calculated with the four-variable Modification of Diet in Renal Disease formula and available for 351 patients. [8] Defined as the presence of a cerebrovascular accident, vascular problems, angina pectoris, myocardial infarction, or decompensatio cordis. [9] Present as primary kidney disease or co-morbidity.

Table 2: Association of hemoglobin levels with health-related quality of life during pre-dialysis care

	<11 Mean [95% CI]	**≥11-<12 Mean [95% CI]**	**≥12-<13 Mean [95% CI]**	**≥13 Mean [95% CI]**
Physical functioning	54.3 [50.6;58.0]	56.5 [53.1;59.9]	59.6 [56.3;63.0][1]	60.7 [57.2;64.2][1,2]
Role-physical	39.7 [32.9;46.6]	43.0 [37.1;48.9]	43.1 [37.2;49.1]	50.3 [44.2;56.4]
Bodily pain	65.1 [61.1;69.2][1,2]	70.8 [67.3;74.3]	71.6 [68.1;75.1]	73.6 [70.0;77.1]
General health	38.5 [35.8;41.1]	38.7 [36.4;41.0]	40.0 [37.7;42.3]	41.8 [39.4;44.1][1,2]
Physical summary	49.9 [46.5;53.2]	51.8 [48.9;54.8]	53.9 [50.9;56.9]	56.7 [53.6;59.8][1,2]
Vitality	47.9 [44.9;50.9][1,2]	52.8 [50.2;55.5]	52.6 [49.9;55.2]	52.9 [50.2;55.7]
Social functioning	65.3 [61.5;69.1][1,2]	73.0 [69.7;76.3]	71.7 [68.3;75.0]	75.3 [71.9;78.7]
Role-emotional	62.1 [55.4;68.7]	68.6 [63.1;74.1]	69.1 [63.4;74.7]	71.9 [66.6;77.2]
Mental health	70.1 [67.3;72.8]	72.8 [70.4;75.2]	73.4 [71.0;75.8]	73.5 [71.0;75.9]
Mental summary	60.4 [57.2;63.7][1,2]	66.1 [63.3;68.9]	66.4 [63.6;69.3]	67.7 [64.8;70.6]

For each hemoglobin (Hb, g/dl) category the mean [95% confidence interval (CI)] score on the two summary measures and eight subscales is given. The p-values are from a linear mixed model investigating whether the scores were significantly different compared with the reference category (Hb level of ≥11-<12 g/dl). [1] Crude p<0.05. [2] Adjusted p<0.05: sex, age, primary kidney disease, estimated glomerular filtration rate, proteinuria, albumin, systolic blood pressure, cardiovascular disease, and diabetes mellitus.

Association of Hb levels with HRQOL, stratified by ESA/iron prescription and age

In young patients (<65 years) not prescribed ESA/iron at the start of pre-dialysis care, the physical and mental summary scores were similar across all Hb levels (Tables 3 and 4). When young patients were prescribed ESA/iron, high Hb levels (≥13 g/dl) resulted in a statistically significant and clinically relevant higher physical (8.9 [95% confidence interval (CI) 2.1;15.8]) and clinically relevant mental summary score (6.2 [95% CI -0.4;12.8]) compared with young patients on target (≥11-<12 g/dl, Table 3). Comparable results were found when analyzing Hb levels continuously; per 1 g/dl increase of Hb, the physical summary score increased with 4.0 [95% CI 1.2;6.7] and the mental summary score with 2.4 [95% CI -0.1;4.9] points in patients with Hb levels ≥11 g/dl (Table 4). On all physical and mental subscales, with the exception of mental health, this difference was clinically relevant (>1.5-2.5 points increase with each 1 g/dl Hb increase, Figures 1A and 1B).

In elderly patients (≥65 years) not prescribed ESA/iron at the start of pre-dialysis care, natural high Hb levels were associated with a statistically significant and clinically relevant higher physical and clinically relevant mental summary score compared with elderly patients with natural Hb levels ≥11 and <12 g/dl (11.9 [95% CI 1.7;22.2] and 6.4 [95% CI -1.7;14.6], respectively, Table 3). Continuous analyses showed similar results; per 1 g/dl increase of Hb, the physical summary score increases with 3.6 [95% CI -0.1;7.2] and the mental summary score with 2.5 [95% CI -0.6;5.6] points in patients with a Hb level ≥11 g/dl (Table 4). On all physical subscales and the mental subscales role emotional and mental health, this difference was clinically relevant (Figures 1C and 1D).

In contrast, in elderly patients who were prescribed ESA/iron higher Hb levels were not associated with HRQOL. However, low Hb levels (<11 g/dl) were associated with a lower physical (-7.4 [95% CI -13.7;-1.0]) and mental summary score (-14.2 [95% CI -20.7;-7.6]) compared with target Hb levels (Table 3). Adjustment for confounders did not essentially change the results (Table 3).

Sensitivity analyses

Our first sensitivity analysis showed that results were essentially the same when repeating analyses after imputation or after defining young patients as <70 instead of <65 years. None of the linear mixed models showed a significant interaction term between Hb categories and time, indicating that the association of Hb with HRQOL did not change during pre-dialysis care. Using time-dependent variables of ESA/iron prescription, age, and the potential confounders during pre-dialysis care also did not change the results.

Table 3: Association of categorical hemoglobin levels with the physical and mental summary score on each time point during pre-dialysis care, stratified by ESA/iron prescription and age

	n at baseline	<11 Crude Δ score [95% CI]	≥11-<12	≥12-<13 Crude Δ score [95% CI]	≥13 Crude Δ score [95% CI]
Physical summary					
Young – No ESA/iron	79	-1.1 [-9.4;7.1]	0	-3.1 [-9.5;3.2]	-0.9 [-8.2;6.4]
Elderly – No ESA/iron	88	1.5 [-7.0;10.1]	0	4.1 [-4.4;12.6]	11.9 [1.7;22.2][1,2]
Young – ESA/iron	78	1.7 [-6.1;9.4]	0	2.2 [-4.5;8.9]	8.9 [2.1;15.8][1,2]
Elderly – ESA/iron	126	-7.4 [-13.7;-1.0][1]	0	3.7 [-1.7;9.0]	1.1 [-5.0;7.2]
Mental summary					
Young – No ESA/iron	79	1.8 [-6.5;10.1]	0	0.4 [-6.1;6.9]	0.0 [-7.4;7.3]
Elderly – No ESA/iron	88	-3.0 [-10.0;3.9]	0	1.1 [-5.7;7.9]	6.4 [-1.7;14.6][2]
Young – ESA/iron	78	-1.5 [-8.5;5.6]	0	2.7 [-3.7;9.2]	6.2 [-0.4;12.8]
Elderly – ESA/iron	126	-14.2 [-20.7;-7.6][1,2]	0	-1.2 [-6.7;4.3]	-2.6 [-8.8;3.6]

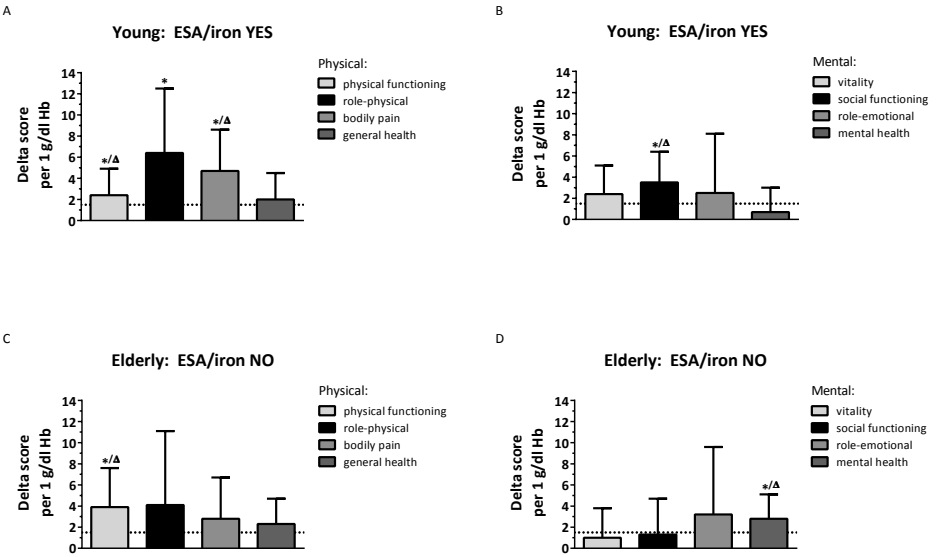
For each hemoglobin (Hb, g/dl) category the difference (Δ score) [95% confidence interval (CI)] in the physical and mental summary score is given, compared with the reference category (Hb level of ≥11-<12 g/dl). All analyses were stratified by ESA/iron prescription at the start of pre-dialysis care and age (<65 years, young, and ≥65 years, elderly). The p-values are from a linear mixed model investigating whether the scores were significantly different between the Hb categories. [1] Crude p<0.05. [2] Adjusted p<0.05: adjusted for sex, age, primary kidney disease, estimated glomerular filtration rate, proteinuria, albumin, systolic blood pressure, cardiovascular disease, and diabetes mellitus.

Table 4: Association of continuous hemoglobin levels with the physical and mental summary score on each time point during pre-dialysis care, stratified by ESA/iron prescription and age

	n at baseline	Hb ≥11: optimal and high Per 1 g/dl increase Crude Δ score [95% CI]
Physical summary		
Young – No ESA/iron	79	1.0 [-1.5;3.6]
Elderly – No ESA/iron	88	3.6 [-0.1;7.2][2]
Young – ESA/iron	78	4.0 [1.2;6.7][1,2]
Elderly – ESA/iron	126	1.0 [-1.6;3.6]
Mental summary		
Young – No ESA/iron	79	0.9 [-1.7;3.4]
Elderly – No ESA/iron	88	2.5 [-0.6;5.6][2]
Young – ESA/iron	78	2.4 [-0.1;4.9]
Elderly – ESA/iron	126	-0.4 [-2.8;2.0]

For each 1 g/dl increase in hemoglobin (Hb) level the difference (Δ score) [95% confidence interval (CI)] in the physical and mental summary score is given. All analyses were stratified by ESA/iron prescription at the start of pre-dialysis care and age (<65 years, young, and ≥65 years, elderly). The p-values are from a linear mixed model investigating whether the scores significantly changed with each g/dl Hb increase. [1] Crude p<0.05. [2] Adjusted p<0.05: adjusted for sex, age, primary kidney disease, estimated glomerular filtration rate, proteinuria, albumin, systolic blood pressure, cardiovascular disease, and diabetes mellitus.

Figure 1: Association of hemoglobin levels with all physical and mental subscales during pre-dialysis care in patients with a hemoglobin level ≥11 g/dl, stratified by ESA/iron prescription and age



The bars indicate the change and the error bars the 95% confidence interval of the subscale scores (y-axis), with each 1 g/dl increase in hemoglobin (Hb) level. Analyses were stratified by ESA/iron prescription at the start of pre-dialysis care and for age (young: <65 years, and elderly: ≥65 years). A linear mixed model was used to investigate whether the subscale scores changed significantly. The dashed horizontal lines represent an increase in the subscale score of 1.5-2.5 points with each 1 g/dl increase in Hb, which is considered clinically relevant. * Crude $p<0.05$. $^{\Delta}$ Adjusted $p<0.05$: adjusted for sex, age, primary kidney disease, estimated glomerular filtration rate, proteinuria, albumin, systolic blood pressure, cardiovascular disease, and diabetes mellitus.

Discussion

This study in patients on specialized pre-dialysis care found several significant improvements in HRQOL throughout different ranges of Hb levels. The most pronounced difference in HRQOL was present in patients with Hb levels below compared with on target (11-12 g/dl) and this difference was clinically relevant for the mental summary measure and five subscales; role-physical, bodily pain, vitality, social functioning, and role-emotional. In patients with high Hb levels (≥13 g/dl), additional increases of HRQOL were present, which were clinically relevant for the physical summary measure and four subscales; physical functioning, role-physical, general health and role-emotional. These findings are in line with the literature[3], although the study of Finkelstein *et al.* found a stronger effect on the vitality subscale in the upper Hb ranges.

Although these results in the overall heterogeneous pre-dialysis population are interesting, we should focus on specific subgroups because after stratifying by the prescription of ESA/iron and age (young, <65 years, and elderly, ≥65 years), various associations of Hb levels

with HRQOL were found. In elderly patients without ESA/iron prescription, high Hb levels (≥13 g/dl) were associated with a clinically relevant higher physical and mental summary score, except on the subscales vitality and social functioning. No association was found in young patients without ESA/iron prescription. Possibly, elderly patients with high 'natural' Hb levels (≥13 g/dl) are very vital (score on the subscale vitality in our data; 51.6) and have less severe co-morbidities, and thereby experience a high HRQOL. Furthermore, the absent association of low Hb levels (<11 g/dl) with HRQOL in both young and elderly patients without ESA/iron prescription may be explained by the presence of clinical indications to not prescribe ESA/iron despite low Hb levels, for instance the absence of anemia-related symptoms.

Besides this, young patients with high Hb levels (≥13 g/dl) compared with patients on target (11-12 g/dl) who are prescribed ESA/iron experienced a clinically relevant higher physical and mental summary score, except for the subscale mental health, and this difference was most pronounced for the physical summary measure. In contrast, in elderly patients who are prescribed ESA/iron no association was found between high Hb levels and better HRQOL. Only elderly patients with low Hb levels (<11 g/dl) had a lower physical and mental summary score, and this difference was most pronounced on the mental summary measure.

Our finding that in young anemic patients high Hb levels were independently associated with a higher physical summary score is in line with the pre-dialysis trials included in the meta-analysis of Clement *et al*.[32-36] However, the effects found in these trials were on average smaller than in our study. This discrepancy can be explained by age (our cohort is younger) and a different classification of Hb categories.[32;34;36] Our finding that high Hb levels in young patients who are prescribed ESA/iron were also independently associated with a higher mental summary score is in line with two trials included in the meta-analysis.[32;33] An explanation for finding an increased HRQOL with higher Hb levels in young and not in elderly patients who are prescribed ESA/iron could be the following. Besides anemia, elderly patients often experience many co-morbidities. By prescribing ESA/iron, elderly patients are only relieved of their anemia-related symptoms and this may lead to a smaller improvement of HRQOL than in young patients. Another explanation could be that, compared with young patients, elderly patients experience less demanding daily activities, such as occupational activities.[37] The effects in young patients were mainly found on the physical subscale role-physical and on the mental subscale social functioning. This finding could be explained by the fact that, generally speaking, daily activities are restored when Hb is targeted to 11-12 g/dl, but that in young patients a higher Hb level may be necessary to perform all daily activities.

Our study furthermore showed that for 68 patients who were prescribed ESA/iron Hb levels were still below target (<11 g/dl). Possible explanations for this low Hb level are ESA resistance (non-responders)[38] and ESA/iron non-compliance. Non-compliance to medication is extremely high (30-60%) in patients with chronic illnesses[39], including CKD patients[40]. In this study, we found that solely in elderly patients low Hb levels, despite ESA/iron prescription, were associated with a lower HRQOL, especially regarding the mental summary measure. A possible explanation for this discrepancy could be that elderly patients often are prescribed

more medications and lifestyle restrictions than young patients. Being non-compliant can thereby affect various aspects of their health and can consequently lead to a lower HRQOL. The stronger effect on the mental summary measure could be explained by the fact that normalization of Hb levels with ESA/iron has the strongest effect on the mental subscale vitality[28] and that non-compliance is often associated with depressive symptoms and poor well-being[41;42].

In contrast to the beneficial effect on HRQOL, targeting high Hb levels may have serious disadvantages as well. Consistent with the studies showing a higher risk of cardiovascular events when targeting high Hb levels[19], we found a higher prevalence of cardiovascular disease in patients with Hb levels ≥13 g/dl compared with 11-12 g/dl (47% versus 39%). Moreover, this higher prevalence of cardiovascular disease was more pronounced in elderly compared with young patients. This finding may implicate that in elderly patients prescribed with ESA/iron, high Hb levels do lead to negative effects but not give rise to positive effects. This may even more advocate the development of age-specific anemia treatment guidelines for patients on pre-dialysis care. Unfortunately, we could not investigate whether the mortality risk increases with increasing Hb levels due to the low event rate before the start of dialysis.

A great strength of the PREPARE-2 study is the longitudinal instead of cross-sectional character, resulting in Hb levels and HRQOL measurements for every six-month interval during pre-dialysis care. Because of these repeated measurements, changes over time, for example HRQOL, can be investigated. Furthermore, our results can be generalized to the complete period of pre-dialysis care in patients with an eGFR below 30 ml/min/1.73 m^2 who are starting specialized pre-dialysis care. A disadvantage of our study is that we have missing data because not all patients visited a pre-dialysis outpatient clinic each six months and most data was routinely collected. Due to the missing data, we could only include 371 of the 502 patients in our statistical analyses, which may lead to selection bias. However, baseline characteristics were similar between the 371 included and 131 excluded patients. Furthermore, results remained similar after imputing missing values at the start of pre-dialysis care for all 502 patients included in the study, which makes it less likely that our analyses suffered from selection bias. In addition, we stratified by ESA/iron therapy solely based on the prescription of these medications at the start of pre-dialysis care. In practice, the prescription of ESA/iron can change over time. However, results did not change when the prescription of these medications was updated over time. Furthermore, we only know whether ESA/iron was prescribed and we do not know what the medication compliance rates are.

Although trials are needed to confirm our findings, our results indicate that targeting high Hb levels in young, and not in elderly, patients on specialized pre-dialysis care increases their HRQOL. Furthermore, more studies are needed to investigate whether the negative effects of targeting high Hb levels on clinical outcomes are more present in elderly compared with young patients. We believe that future research should investigate negative (mortality and morbidity) and positive (better HRQOL and survival on dialysis) effects in subgroups of specific

patients. This scientific evidence is needed to better inform physicians and patients for making an individualized treatment decision regarding the appropriate Hb target, also based on patients' preferences.

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