**Erythropoiesis stimulating agent dosing, haemoglobin and ferritin levels in UK haemodialysis patients 2005-2013**

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**Abstract**

**Background**: Erythropoiesis stimulating agents (ESAs), with intravenous iron supplementation, are the main treatment for anaemia in patients with chronic kidney disease. Although observational studies suggest better outcomes for patients who achieve higher haemoglobin (Hb) levels, randomized controlled trials comparing higher and lower Hb targets have led to safety concerns over higher targets, and to changes in treatment guidelines.

**Methods**: Quarterly data from 2005-2013 were obtained on 28,936 haemodialysis patients from the UK Renal Registry. We examined trends in ESA use and average dose, Hb and ferritin values over time, and Hb according to the Renal Association guideline range.

**Results**: Average ESA dose declined over time, with sharper decreases of ~~Erythropoietin~~ epoetin seen towards the end of 2006, and from 2009. Average Hb for patients on ESAs was 114.1 g/L (95% CI 113.7, 114.6) in the first quarter of 2005, which decreased to 109.6 g/L (95% CI 109.3, 109.9) by the end of 2013. Average serum ferritin was 353 µg/L (95% CI 345, 360) at the start of 2005, increasing to 386 µg/L (95% CI 380, 392) in the final quarter of 2013. The percentage of patients with Hb in the range of 100-120 g/L increased from 46.1% at the start of 2005, to 57.6% at the end of 2013.

**Conclusions**: Anaemia management patterns for haemodialysis patients have changed in the UK between 2005 and 2013. These patterns most likely reflect clinician response to emerging trial evidence and practice guidelines. Registries play an important role in continued observation of anaemia management and will monitor further change as new evidence on optimal care emerges.

**Key words**: Anaemia management, Erythropoiesis stimulating agents, ESA, Haemodialysis, Haemoglobin

**Short summary:** Recent evidence from major clinical trials of erythropoiesis stimulating agents (ESA) raised safety concerns. We examined trends in ESA dosing, haemoglobin and ferritin levels in over 28,000 UK haemodialysis patients between 2005 and 2013. Average haemoglobin decreased over time, ferritin levels increased sharply from 2008-2011, coinciding with decreases in ESA use. These patterns most likely reflect clinician response to emerging trial evidence and resulting clinical practice guidelines.

**Word counts**: Abstract 261, Main text 3180, Total 3441

**Introduction**

Nearly 57,000 adult patients were receiving renal replacement therapy (RRT) in the UK at the end of 2013 (prevalence 888/million), and demand for RRT is rising.(1) Anaemia is a common complication for patients with chronic kidney disease (CKD), resulting in reduced quality of life, fatigue, decreased exercise capacity and shortness of breath. Erythropoiesis stimulating agents (ESAs) are the main treatment for CKD patients with anaemia (2) and are effective in correcting and maintaining haemoglobin (Hb) levels and decreasing the need for blood transfusions. Intravenous iron supplements are an important adjunct in the treatment of anaemia in patients on haemodialysis.

Even partial treatment of anaemia with ESAs is expensive, and full correction of Hb requires much higher doses than partial correction. When ESAs were first introduced into clinical practice, randomised controlled trials were not performed, as it was thought unnecessary and even unethical to leave a control group with untreated anaemia. However, the question of whether full correction of anaemia is preferable to partial correction has now been tested in several randomized controlled trials (RCTs). Besarab et al. randomized haemodialysis patients with cardiovascular co-morbidity to full or partial correction of anaemia: this trial was terminated early when it became clear that benefit from full correction was highly improbable.(3) The Food and Drug Administration (FDA) later classified the trial results as showing increased risk of all-cause mortality for the group randomized to the higher Hb target (4) and a later re-analysis of the full trial report showed no improvement in quality of life (5). Three large RCTs in patients with CKD not yet on dialysis have been completed (6-8) and found no evidence of benefits of a higher (compared with lower) Hb target on cardiovascular events or a composite outcome of death, myocardial infarction, hospitalisation for congestive heart failure and stroke, or they found increased risk of adverse events. These conclusions are difficult to reconcile with data from numerous observational studies which demonstrate that the best outcomes are in patients who have high Hb concentrations but require only low doses of ESAs (130-140 g/L).(9-11) One interpretation is that ESA-sensitive patients derive survival benefit from full correction of anaemia, but that patients with ESA-resistance (which is a predictor of poor survival) may be harmed by the high doses of ESAs prescribed under the trial protocols in the (often unsuccessful) attempt to normalise haemoglobin concentration.

The target Hb for patients with CKD in the UK Renal Association Clinical Practice Guidelines was >100 g/L with no suggested maximum in 2002-2007 (3rd edition).(12) These were altered to 105-125 g/L (4th edition 2007-2009) (13) and lowered to 100-120 g/L in the latest version (5th edition published in 2010) (2) following publication of the RCTs in 2006 (6, 8) and 2009.(7) The impact of these guideline changes on ESA dosing and hence on achieved Hb levels remains unclear. We therefore examined trends in ESA dosing in UK haemodialysis patients between 2005 and 2013 and corresponding trends in achieved Hb levels. We related these trends to changes in the national guidelines for management of anaemia.

**Methods**

We identified RCTs and treatment guidelines with the potential to affect anaemia management for patients on haemodialysis during the period 2005-13. These were used to construct a timeline depicting when changes in management were expected.

The UK Renal Registry (UKRR) collects clinical and biochemical data from all patients aged 18 years or over receiving renal replacement therapy (RRT) in the UK. Data are extracted electronically, on a quarterly basis, and are validated and cleaned prior to analysis.(14) Some centres submit data extracts that include ESA doses. All patients who received haemodialysis in 2005-2013 in centres submitting ESA doses were included in analyses. Centres reporting fewer than 60% of haemodialysis patients being treated with ESAs were considered to have incomplete data and their data for that quarter were excluded. Patients from 37 centres across England, Wales and Northern Ireland were included in the analyses (from a total of 62 centres in these regions). A patient was considered to be incident during their first year of haemodialysis.

Patients were defined as being on an ESA if a drug type (Darboepoietin, ~~Erythropoietin~~ epoetin-alpha, -beta, or -not otherwise specified, or Methoxy polyethylene glycol-epoetin beta) and/or a dose was recorded. ESA dose is presented as weekly ~~Erythropoietin~~ epoetin dose in our analysis. Doses of ≤ 150 IU/week (likely to be Darbepoietin) were harmonised with ~~Erythropoietin~~ epoetin data by multiplying by 200. No adjustments were made with respect to route or frequency of administration. The measurement of Hb (g/L) that was closest to the end of the quarter was extracted. Serum ferritin was measured in µg/L. Data were also extracted on age, sex, race (White, South Asian, Black, Chinese, other, or missing), year of starting renal replacement therapy and primary renal disease (diabetes, glomerulonephritis, hypertension, polycystic kidneys, pyelonephritis, renal vascular disease, other or uncertain (15)).

*Statistical methods*

For each calendar year, we derived descriptive statistics summarising the demographic and clinical characteristics of the cohort. ESA dose and ferritin were log transformed as they had positively skewed distributions. The percentage of patients on the different ESA drug types were calculated for each quarter. To examine trends in anaemia management over time, we calculated geometric mean of ESA dose (with 95% confidence interval (CI)) per quarter, stratified by drug type ((1)Darboepoietin and (2) ~~Erythropoietin~~ epoetin-alpha, -beta, or -not otherwise specified; there were not enough numbers to also include a Methoxy polyethylene glycol-epoetin beta group). The doses were also examined restricting to incident patients. Mean achieved Hb levels were calculated separately for ESA treated and non-treated patients. We calculated the proportion of all patients on ESA treatment over time, and the proportion of patients with Hb in the categories: <100, 100-120 and >120 g/L. Patients were also put into categories according to their ESA status: those always receiving ESAs over the time period, patients changing on/off ESAs over the time, and those never receiving ESAs. Trends in these statistics over time were compared with the timeline of events with the potential to affect anaemia management. All means and proportions were standardized by year using direct standardization, according to the age, sex, race and primary renal disease distribution for all years of data combined. The numbers with missing values for these factors were reported and people with missing values were excluded from analyses. ~~We carried out a sensitivity analysis including only the 21 centres that contributed data for all years.~~ All analyses were carried out using StataTM version 13.

**Results**

*Timeline of events that may have impacted on anaemia management*

Events that may have impacted on anaemia management in the UK are summarized in Figure 1. The CHOIR trial, published in 2006 (8), randomized 1,432 patients with CKD not on RRT to a Hb target of 135 g/L or 113 g/L. There was evidence of increased risk of the primary outcome (a composite of death, MI and hospitalization for heart failure or stroke) in the high- compared with the low-haemoglobin group (hazard ratio [HR] 1.34; 95% CI 1.03, 1.74). In the CREATE trial, also published in 2006 (6), 603 patients with CKD not on RRT were randomized to a target Hb of 130-150 or 105-115 g/L. Early complete correction of anaemia did not reduce the risk of cardiovascular events. In the TREAT trial, which was the largest RCT and was published in 2009 (7), 4,038 patients with diabetes, CKD and anaemia were randomly assigned to achieve a haemoglobin level of approximately 130 g/L with the use of Darbepoetin alfa or placebo (patients in the placebo group received Darbepoetin alfa as a rescue agent if Hb <90 g/L). The risk of a composite outcome of death or cardiovascular event was similar in the two groups (HR for Darbepoetin alfa vs. placebo 1.05; 95% CI 0.94, 1.17), but there was a higher incidence of stroke in the Darbepoetin alfa arm (HR 1.92; 95% CI, 1.38 to 2.68). Following publication of these RCTs, the target Hb for patients with CKD was lowered to 100-120 g/L in UK Renal Association and NICE treatment guidelines.(2, 16) The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines suggest that ESA therapy should be started when Hb is between 90-100 g/L for adult dialysis patients and that ESAs should not be used to maintain Hb concentration above 115 g/L in adult patients with CKD, but that individualisation of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 115 g/L and will be prepared to accept the risks. (17)

*Characteristics of study cohort*

A total of 28,936 haemodialysis patients were included in the cohort. 1,695 (5.9%) never received ESAs within the study period 2005-2013, 6,648 (23.0%) changed on/off ESAs over the time period and 20,593 (71.2%) always received ESA therapy. Darboepoietin was the drug used most frequently (51.3%), followed by ~~Erythropoietin~~ epoetin-beta (21.8%), ~~Erythropoietin~~ epoetin-alpha (17.3%), ~~Erythropoietin~~ epoetin-not otherwise specified (7.4%) and Methoxy polyethylene glycol-epoetin beta (2.3%). Demographic characteristics of the yearly cohorts are shown in Table 1. The number of patients included in the cohort almost doubled over time, but the age, sex and race distributions changed very little. In 2013 the median age of patients was 66.9 years (interquartile range 54.1 to 76.8 years), with 7,726 (61.3%) male, and 10,095 (80.7%) of White race. The proportion of patients with diabetes as the primary renal disease increased over time, from 16.9% of patients in 2005 to 21.7% in 2013. The number of incident patients included increased steadily over time from N=1,457 in 2005 to N=2,234 in 2013.

*Use of ESAs 2005-2013*

Prior to 2007, when existing guidelines had no upper limit to Hb levels, the geometric mean dose of ESA remained stable for ~~Erythropoietin~~ epoetin-drugs and showed a steady increase for Darbepoetin (Figure 2) whilst the proportion of patients on ESAs remained relatively constant (Figure 3). Near the end of 2006 and in early 2007 there appears to be a decline in the proportion of patients on ESA with a modest dose reduction, most likely in response to the joint publication of the NICE guideline (39) and the CHOIR and CREATE trials (4, 6) (see Figure 1). The decline in patients treated with ESAs continues until 2013 (percentage of patients receiving ESAs decreases from 92.4% (95% CI 91.7%, 93.1%) in the first quarter of 2005 to 87.3% (95% CI 86.7%, 87.9%) in the final quarter of 2013). There is an overall decline in average Darbepoetin dose from mid-2006. Average doses of ~~Erythropoietin~~ epoetin-drugs declined from 2006, followed by a rise in 2008-2009, followed by a second decline from around 2010 after the publication of the TREAT trial (7) and further published guidelines. The average Darbepoetin dose declined from 64~~2~~31 IU/week (95% CI 6221, 6649 IU/week) in the first quarter of 2005 to 5921 IU/week (95% CI 5780, 6066 IU/week) in the last quarter of 2013. The average ~~Erythropoietin~~ epoetin dose declined from ~~6421~~ 8107 IU/week (95% CI ~~6221~~ 7884, ~~6649~~ 8336 IU/week) in the first quarter of 2005 to ~~5921~~ 7310 IU/week (95% CI ~~5780~~ 7133, ~~6066~~ 7491 IU/week) in the last quarter of 2013. The percentage of patients on the different ESA drug types is shown in the online supplement. Similar ESA dose patterns were observed in incident patients (online supplement).

*Achieved haemoglobin and ferritin 2005-2013*

The Hb patterns for patients on ESAs mirror what is seen with ESA dosage so that we observe an initial small increase in mean Hb until end of 2006 followed by a steady decline (Figure 4). Mean Hb for patients on ESA in the first quarter of 2005 was 114.1 g/L (95% CI 113.7, 114.6 g/L) and was 109.6 g/L (95% CI 109.3, 109.9) by the end of 2013. The decline in mean Hb appears to start in 2007, following NICE guidelines (18) and the publication of the CHOIR (8) and CREATE (6) trials in 2006. The decrease in average Hb levels is then observed for many years – when further guidelines and the TREAT trial (7), were published - until a settling of Hb levels in 2012 and 2013. The lowering in Hb was seen for patients who were receiving ESAs, those not on treatment, and across treatment groups (always on ESAs, changing on/off ESAs, never on ESAs; Figure 5), although the numbers never receiving ESAs were small and the pattern showed large fluctuations. The percentage of patients with Hb >120 g/L has decreased over time from 36.3% at the start of 2005, to 22.4% at the end of 2013 (Figure 6). The percentage of patients with Hb in the range of 100-120 g/L has increased from 46.1% at the start of 2005, to 57.6% at the end of 2013. From the second quarter of 2011 onwards, over 55% of haemodialysis patients have had Hb in the range of 100-120 g/L. In contrast to average Hb levels, there has been a sharp increase in ferritin levels from 2008-2011 (Figure 7), with a decline at around the beginning of 2011 after which levels appear to have stabilised. Average serum ferritin was 353 µg/L (95% CI 345, 360 µg/L) in the first quarter of 2005, and 386 µg/L (95% CI 380, 392 µg/L) in the final quarter of 2013.

**Discussion**

*Summary of findings*

We examined ESA dose and Hb levels in haemodialysis patients from 2005 to 2013 in the UK. This period included publications of major clinical trials and changes to treatment practice guidelines. The use of ESAs has decreased over time, but it is not possible to unpick which events had most influence on dosing, as results from RCTs and anaemia management guidelines were published in close proximity. Average Hb decreased over time, with levels after 2011 largely compliant with the Renal Association 2010 target range of 100-120 g/L. A decrease in Hb levels over time was observed for both patients that were treated by ESAs and those not receiving ESAs, suggesting that after the reduction in the Hb target thresholds, patients were started on ESAs at lower levels of Hb. A small, but sharp increase in ferritin levels was seen from 2008-2011, coinciding with decreases in ESA use. This pattern cannot be directly explained by adherence to revised anaemia management guidelines. Serum ferritin is a marker of iron balance i.e. iron loss from occult bleeding, blood sampling and loss of blood in the dialysis machine, versus dietary absorption plus intravenous supplementation. The observed pattern of ferritin may have been driven by coincident economic pressures to improve the cost-effectiveness of ESA use as well as by emerging evidence that intravenous iron was safe and effective.(19) Alternatively, it could be that clinicians are administrating the same amount of iron to patients, but it is not being used up so quickly because of reduced ESA doses. Interestingly, the last two years have seen a stable pattern with no increase or decrease in levels.

*Comparison with other studies*

Results from RCTs and clinical practice patterns in the USA have influenced anaemia management in recent years. A study of US non-dialysis chronic kidney disease patients found that the emergence of safety concerns following RCTs and the subsequent changes in product labelling, restrictions to reimbursement for ESAs and changes to clinical practice guidelines all appeared to influence physician dosing practices resulting in less frequent use of ESAs, lower ESA doses and lower achieved Hb levels.(20) A study of US haemodialysis patients from the United States Renal Data System (USRDS) found that ESA dosing decreased from 2007, and that Hb levels mirrored ESA dosing trends.(21) The Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor (DPM) was developed to detect and report on trends in dialysis care before, during, and after implementation of the end-stage renal disease prospective payment system (PPS), which was initiated by the US Centers for Medicare and Medicaid Services in January 2011. The percentage of patients with Hb > 120 g/L declined from 32% in August 2010 to 14% in December 2012. The mean prescribed dose of patients receiving IV Epoetin decreased from 20,500 U/week in August 2010 to 13,300 U/week in December 2012, with the greatest decline occurring during June to August 2011. An increase of iron use was observed in 2011 and serum measures of iron stores increased.(22) However, the rise in average IV iron dose did not persist beyond 2011. The sustained rise in ferritin levels in United States dialysis patients after policy changes in 2011 appeared to be partly due to reductions in ESA dosing and not solely IV iron dosing practices.(23) In Germany, dialysis procedure rates were changed in 2002 from per-session to weekly flat rate payments, and quality assurance was introduced in 2009 with defined treatment targets for different indices including haemoglobin. DOPPS phases 1–4, (1998–2011) found that haemoglobin levels increased since 1998 and remained consistent since 2005, with only 8–10% of patients below 100 g/L. Around 90% of patients were prescribed ESAs, with the dose declining since peaking in 2006. Intravenous iron use was highest in 2011.(24)

*Strengths and weaknesses*

The UK Renal Registry is a large and highly representative database allowing trends in clinical practice patterns to be captured.(11) This study gives an indication that clinicians are responding to changes in guidelines important for patient safety. The analysis of ESA usage is however limited by incomplete data returns, as some renal centres do not routinely record computerised data on ESA dose or drug type. Centres reporting fewer than 60% of haemodialysis patients being treated with ESAs were considered to have incomplete data and were excluded from the analysis. These exclusion criteria are relatively arbitrary but they are in part based upon the frequency distribution graph of centres’ ESA use as it appears in the data. The percentage of patients on ESAs is calculated from these data and incomplete data returns risk impacting on any conclusions drawn. The dose conversion used for Darbepoetin may not accurately estimate weekly ~~Erythropoietin~~ epoetin dose. There is no information on how much iron therapy was being used to treat anaemia in this population, however data were available on ferritin levels giving an indication of achieved iron stores over the period. Data were only obtained from haemodialysis patients and are not generalizable to peritoneal dialysis patients or other CKD populations.

*Conclusions*

Anaemia management patterns for haemodialysis patients have changed in the UK between 2005 and 2013, with these changes likely to have been in response to results from RCTs and changing clinical practice guidelines. There has been a decrease in ESA use, dose and average achieved Hb levels in recent years, with fewer patients having Hb levels >120 g/L and more patients having Hb within the 100-120 g/L target range. Average serum ferritin levels have increased in the same time period. Previous research suggests clinicians are responsive to clinical guidelines though the degree that new practice is adopted can vary considerably depending on the context.(25, 26) It is likely that in this case, economic considerations due to the price of ESAs further facilitated adoption of the guidelines as clinicians could reduce unit expenditure by reducing ESA dosage and treating fewer patients. The continued monitoring of anaemia management through Registry data is important for patient safety and enhancing patient quality of life and enables us to ensure that any new evidence on the optimal use of ESA therapy for haemodialysis patients is translated into every day clinical care.

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**Conflict of interest statement**

None to declare

**References**

1. Rao A, Casula A, Castledine C. UK Renal Registry 17th Annual Report: Chapter 2 UK Renal Replacement Therapy Prevalence in 2013: National and Centre-specific Analyses. Nephron. 2015;129 Suppl 1:31-56.

2. Mikhail A, Shrivastava R, Richardson D. Clinical Pracitice Guidelines. Anaemia of CKD. 5th 2009-2012 ed. [www.renal.org/guidelines:](http://www.renal.org/guidelines%3A) UK Renal Association; 2010.

3. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339(9):584-90.

4. FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease <http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm2011> [11/08/2015].

5. Coyne DW. The health-related quality of life was not improved by targeting higher hemoglobin in the Normal Hematocrit Trial. Kidney Int. 2012;82(2):235-41.

6. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006;355(20):2071-84.

7. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de ZD, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019-32.

8. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355(20):2085-98.

9. Levin A, Djurdjev O, Duncan J, Rosenbaum D, Werb R. Haemoglobin at time of referral prior to dialysis predicts survival: an association of haemoglobin with long-term outcomes. Nephrol Dial Transplant. 2006;21(2):370-7.

10. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol. 2006;17(4):1181-91.

11. Macdougall IC, Tomson CR, Steenkamp M, Ansell D. Relative risk of death in UK haemodialysis patients in relation to achieved haemoglobin from 1999 to 2005: an observational study using UK Renal Registry data incorporating 30,040 patient-years of follow-up. Nephrol Dial Transplant. 2010;25(3):914-9.

12. The Standards and Audit Subcommittee of the Renal Association. Treatment of adults and children with renal failure. Standards and audit measures. 3rd ed: The Renal Association; 2002.

13. Cassidy M, Richardson D, Jones C. Cinical Practice Guidelines. Module 2: Complications. 4th 2007 ed. [www.renal.org/guidelines:](http://www.renal.org/guidelines%3A) UK Renal Association; 2007.

14. Ansell D, Tomson CR. UK Renal Registry 11th Annual Report (December 2008): Chapter 15 The UK Renal Registry, UKRR database, validation and methodology. Nephron Clin Pract. 2009;111 Suppl 1:c277-85.

15. UK Renal Registry 17th Annual Report: Appendices. Nephron. 2015;129 Suppl 1:267-322.

16. National Institute for Health and Clinical Excellence. Anaemia management in people with chronic kidney disease. NICE clinical guideline 114. <http://www.nice.org.uk/guidance/cg114>. 2011.

17. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney International Supplements. 2012;2(5):279-335.

18. National Institute for Health and Clinical Excellence. Anaemia management in people with chronic kidney disease. NICE clinical guideline 39. <https://www.nice.org.uk/guidance/cg39>. 2006.

19. Susantitaphong P, Alqahtani F, Jaber BL. Efficacy and safety of intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients: a meta-analysis. American journal of nephrology. 2014;39(2):130-41.

20. Regidor D, McClellan WM, Kewalramani R, Sharma A, Bradbury BD. Changes in erythropoiesis-stimulating agent (ESA) dosing and haemoglobin levels in US non-dialysis chronic kidney disease patients between 2005 and 2009. Nephrol Dial Transplant. 2011;26(5):1583-91.

21. Freburger JK, Ng LJ, Bradbury BD, Kshirsagar AV, Brookhart MA. Changing Patterns of Anemia Management in US Hemodialysis Patients. Am J Med. 2012;125(9):906-U204.

22. Fuller DS, Pisoni RL, Bieber BA, Port FK, Robinson BM. The DOPPS practice monitor for U.S. dialysis care: update on trends in anemia management 2 years into the bundle. Am J Kidney Dis. 2013;62(6):1213-6.

23. Karaboyas A, Zee J, Morgenstern H, Nolen JG, Hakim R, Kalantar-Zadeh K, et al. Understanding the Recent Increase in Ferritin Levels in United States Dialysis Patients: Potential Impact of Changes in Intravenous Iron and Erythropoiesis-Stimulating Agent Dosing. Clinical journal of the American Society of Nephrology : CJASN. 2015.

24. Kleophas W, Karaboyas A, Li Y, Bommer J, Reichel H, Walter A, et al. Changes in dialysis treatment modalities during institution of flat rate reimbursement and quality assurance programs. Kidney Int. 2013;84(3):578-84.

25. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet. 1993;342(8883):1317-22.

26. Grol R, Dalhuijsen J, Thomas S, Veld C, Rutten G, Mokkink H. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. Bmj. 1998;317(7162):858-61.

**Table 1 Characteristics of the cohort by year**

|  | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Number of patients |  |  |  |  |  |  |  |  |  |
|  Incident | 1457 | 1694 | 1736 | 1895 | 1946 | 1921 | 1864 | 2006 | 2234 |
|  Total (including incident) | 6930 | 7896 | 8637 | 9419 | 10326 | 10648 | 10824 | 11462 | 12609 |
| Age, years: median (IQR) | 65.5(51.5, 75) | 66.0(52.1, 75.4) | 65.9(52.4,75.5) | 66.1(52.9,75.7) | 66.4(53.2, 5.9) | 66.7(53.7, 6.2) | 66.8(53.5,76.5) | 67.0(53.9, 76.6) | 66.9(54.1, 76.8) |
| Sex, N (%) |  |  |  |  |  |  |  |  |  |
|  Male | 4,216 (60.8%) | 4,880 (61.8%) | 5,346 (61.9%) | 5,784 (61.4%) | 6,262 (60.6%) | 6,471 (60.8%) | 6,579 (60.8%) | 7,037 (61.4%) | 7,726 (61.3%) |
|  Female | 2,714 (39.2%) | 3,016 (38.2%) | 3,291 (38.1%) | 3,635 (38.6%) | 4,064 (39.4%) | 4,177 (39.2%) | 4,245 (39.2%) | 4,425 (38.6%) | 4,883 (38.7%) |
| Race, N |  |  |  |  |  |  |  |  |  |
|  White | 5,477 (83.6%) | 6,286 (84.1%) | 6,884 (83.4%) | 7,580 (83.4%) | 8,419 (83.2%) | 8,783 (83.2%) | 8,822 (81.9) | 9,489 (82.9%) | 10,095 (80.7%) |
|  Black | 295 (4.5%) | 328 (4.4%) | 367 (4.5%) | 400 (4.4%) | 467 (4.6%) | 457 (4.3%) | 514 (4.8%) | 499 (4.4%) | 779 (6.2%) |
|  Asian | 677 (10.3%) | 751 (10.1%) | 882 (10.7%) | 983 (10.8%) | 1,073 (10.6%) | 1,143 (10.8%) | 1,263 (11.7%) | 1,266 (11.1%) | 1,403 (11.2%) |
|  Chinese | 39 (0.6%) | 41 (0.6%) | 46 (0.6%) | 45 (0.5%) | 50 (0.5%) | 55 (0.5%) | 51 (0.5%) | 49 (0.4%) | 68 (0.5%) |
|  Other | 64 (1.0%) | 70 (0.9%) | 75 (0.9%) | 81 (0.9%) | 105 (1.0%) | 125 (1.2%) | 128 (1.2%) | 138 (1.2%) | 160 (1.3%) |
|  Missing | 378 | 420 | 383 | 330 | 212 | 85 | 46 | 21 | 104 |
| Primary renal disease:N (%) |  |  |  |  |  |  |  |  |  |
|  Diabetes | 3684 (16.9) | 4417 (17.5) | 4948 (18.1) | 5678 (19.2) | 6541 (19.5) | 6701 (19.3) | 7102 (20.1) | 7778 (20.5) | 8832 (21.7) |
|  Glomerulonephritis | 3330 (15.3) | 3933 (15.6) | 4223 (15.5) | 4509 (15.2) | 5005 (15.0) | 5242 (15.1) | 5219 (14.8) | 5735 (15.1) | 6186 (15.2) |
|  Hypertension | 1239 (5.7) | 1339 (5.3) | 1458 (5.3) | 1666 (5.6) | 1999 (6.0) | 2154 (6.2) | 2139 (6.1) | 2533 (6.7) | 2856 (7.0) |
|  Polycystic kidneys  | 1646 (7.6) | 1881 (7.5) | 1999 (7.3) | 2101 (7.1) | 2335 (7.0) | 2415 (7.0) | 2382 (6.7) | 2596 (6.9) | 2737 (6.7) |
|  Pyelonephritis | 2389 (11.0) | 2766 (11.0) | 3075 (11.3) | 3271 (11.1) | 3537 (10.6) | 3518 (10.2) | 3473 (9.8) | 3601 (9.5) | 3794 (9.3) |
|  Renal vascular disease | 1768 (8.1) | 2095 (8.3) | 2201 (8.1) | 2247 (7.6) | 2436 (7.3) | 2515 (7.3) | 2517 (7.1) | 2586 (6.8) | 2532 (6.2) |
|  Other | 2988 (13.7) | 3519 (13.9) | 3766 (13.8) | 4139 (14) | 4776 (14.3) | 5137 (14.8) | 5405 (15.3) | 5755 (15.2) | 6116 (15.0) |
|  Uncertain | 4712 (21.7) | 5309 (21.0) | 5658 (20.7) | 5981 (20.2) | 6847 (20.5) | 6979 (20.1) | 7110 (20.1) | 7321 (19.3) | 7657 (18.8) |
|  Missing | 241 | 305 | 375 | 434 | 424 | 287 | 257 | 267 | 388 |

**Figure 1 Timeline of events**



**Figure 2 Geometric mean ESA weekly dose and 95% confidence interval**





The dashed vertical lines indicate the publication of the CHOIR and CREATE RCTs (2006) and TREAT (2009)

**Figure 3 Percentage use of ESAs with 95% confidence intervals, in all haemodialysis patients**

The dashed vertical lines indicate the publication of the CHOIR and CREATE RCTs (2006) and TREAT (2009)

**Figure 4 Mean haemoglobin levels over time with 95% confidence intervals, in all haemodialysis patients**



Circles represent patients not receiving ESAs; triangles represent patients receiving ESAs

The dashed vertical lines indicate the publication of the CHOIR and CREATE RCTs (2006) and TREAT (2009)

**Figure 5 Mean haemoglobin levels over time in all haemodialysis patients, by ESA status**



Crosses represent patients always receiving ESAs; triangles represent patients changing on/off ESAs over the time period; circles represent patients never receiving ESAs. The dashed vertical lines indicate the publication of the CHOIR and CREATE RCTs (2006) and TREAT (2009)

**Figure 6 Percentages in the haemoglobin in groups (<100, 100-120, >120 g/L), in all haemodialysis patients**



Dark-grey represents Hb<100 g/L; mid-grey represents Hb 100-120 g/L; light grey represents Hb>120 g/L

**Figure 7 Geometric mean ferritin with 95% confidence interval, in all haemodialysis patients**



The dashed vertical lines indicate the publication of the CHOIR and CREATE RCTs (2006) and TREAT (2009)