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Dosing strategies for conversion of haemodialysis patients from short-acting erythropoiesis stimulating agents to once-monthly C.E.R.A.: experience from the **MIRACEL** study

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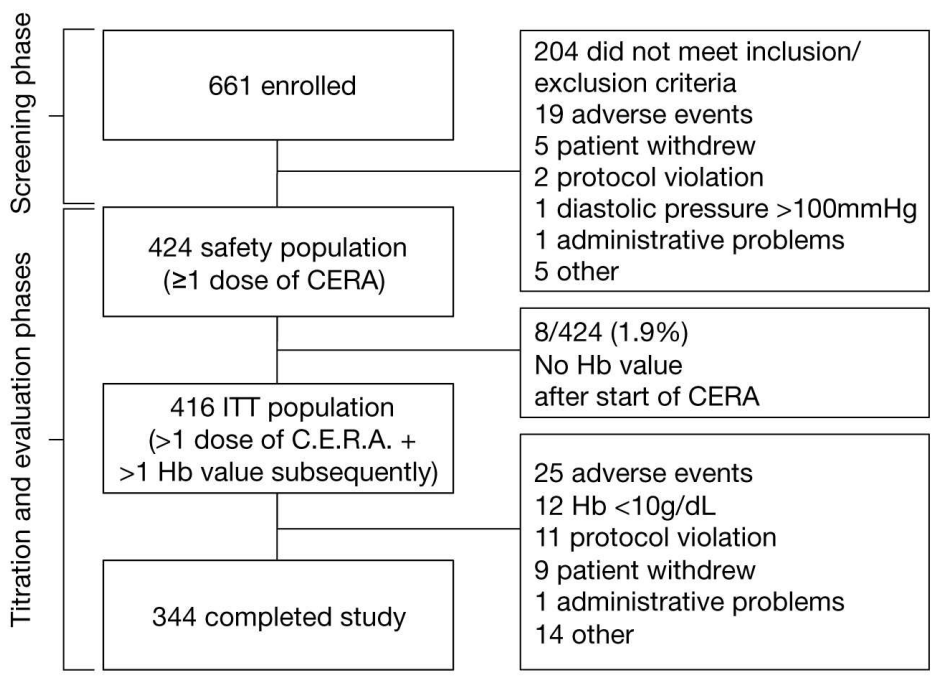
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Dosing strategies for conversion of haemodialysis patients from short-acting erythropoiesis stimulating agents to once-monthly C.E.R.A.: experience from the MIRACEL study

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3 **Dosing strategies for conversion of haemodialysis patients from short-acting**
4 **erythropoiesis stimulating agents to once-monthly C.E.R.A.: experience from the**
5 **MIRACEL study**
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12 behalf of the MIRACEL Study Group
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59 Amgen. All other authors have no conflicts of interest to declare.
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Key words: C.E.R.A., continuous erythropoietin receptor activator, Mircera, ESA, erythropoiesis stimulating agents, MIRACEL, dosing

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Abstract (250 words maximum)

Aims. To analyse the impact of dosing decisions for C.E.R.A., a continuous erythropoietin receptor activator.

Methods. This was a prospective, multicentre, single-arm study in haemodialysis patients receiving epoetin alfa/beta or darbepoetin alfa. After a two-month screening phase, patients were converted to monthly C.E.R.A. using pre-filled syringes during a five-month titration phase and a two-month evaluation phase.

Results. 424 eligible patients were converted to C.E.R.A. Mean Hb was 11.7 ± 0.7 , 11.7 ± 0.8 and 11.5 ± 0.8 g/dL during screening, titration and evaluation, respectively. C.E.R.A. starting dose was $125\mu\text{g}$ (n=311) or $200\mu\text{g}$ (n=106), with corresponding final doses of $129\pm 61\mu\text{g}$ and $203\pm 58\mu\text{g}$. The mean number of C.E.R.A. dose decreases and increases was 0.9 ± 1.0 and 1.1 ± 1.0 per patient, respectively. Hb rarely exceeded 12.5g/dL after a C.E.R.A. dose increase (<8%) and remained ≥ 11 g/dL after a dose reduction on approximately three-quarters of occasions. Among the 53 occasions where Hb decreased ≥ 2 g/dL between two consecutive visits, the previous dose had been withheld (n=9), concomitant blood loss, coagulopathy or infection was present (n=13), or iron parameters were low (n=17). There were 104 adverse events/month during screening, and 45/month during the titration/evaluation phases. Serious adverse events occurred in 18.0 and 21.0 patients/month during the screening and titration/evaluation phases, respectively.

Conclusion. Switching haemodialysis patients from shorter-acting ESA to once-monthly C.E.R.A. using pre-filled syringes is straightforward, and Hb levels remain stable. Starting doses recommendations and dose changes correlated well with the clinical setting, although dose decreases may be undertaken too readily. Collateral factors such as infection or aggravating concomitant medical conditions should be taken into account.

What's known?

Fewer than half of all dialysis patients maintain target haemoglobin levels over a six-month period despite widespread use of erythropoiesis stimulating agents (ESA), partly due to haemoglobin cycling in response to short, intermittent bursts of erythropoietic activity following short-acting ESA administration. C.E.R.A., a continuous erythropoietin receptor activator, offers once-monthly dosing without compromising haemoglobin control in maintenance dialysis patients compared to other ESAs.

What's new?

Previous large-scale trials of C.E.R.A. in dialysis patients have employed dose adjustments from vials, and were completed before pre-filled syringes for C.E.R.A. became available. Results of the current MIRACEL study may help to guide C.E.R.A. dosing decisions based on a large population of dialysis patients converted from short-acting ESA to once-monthly C.E.R.A. therapy using pre-filled syringes.

Introduction

Erythropoiesis stimulating agents (ESA) are widely used to correct renal anaemia in the dialysis population (1), yet it is estimated that fewer than half of all patients on dialysis maintain haemoglobin (Hb) levels within the desired range of 11-12g/dL over a six-month period (2). One major barrier to establishing effective control is that fluctuations in Hb concentration are almost universal in haemodialysis patients under contemporary ESA therapy (3, 4). Various factors contribute to this 'cycling' (3), including administration of intravenous iron (5), concomitant illnesses or infections, and chronic inflammation (6-8). The underlying cause, however, is the short, intermittent bursts of erythropoietic activity that are triggered by frequent ESA dosing, in contrast to the endogenous, more continuous release of erythropoietin that occurs in response to physiologic requirements in the healthy individual (3, 5).

Use of longer-acting ESA therapy may help to reduce Hb cycling (3). However, extended dosing intervals using conventional ESAs can be problematic in clinical practice (9), and the National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) guidelines state that the efficacy of epoetin alfa and beta decreases if administered only once a week (10). C.E.R.A., a continuous erythropoietin receptor activator, has a half-life of approximately 130 hours (11) compared to ≤ 9 hours for epoetin alfa and beta (12) and ~ 25 hours for darbepoetin alfa (13). Additionally, C.E.R.A. has a relatively low binding affinity for the erythropoietin receptor and slow systemic clearance, such that it provides continuous stimulation of erythropoiesis with a delayed peak reticulocyte count (at approximately day 8 post-dosing) (11). As a result, efficacy is similar using C.E.R.A. once a month or multiple administrations of shorter-acting ESA agents in maintenance dialysis patients (14-16).

There are currently few published data regarding the practicalities of making monthly dose adjustments, for example in a patient with a rising Hb level. Furthermore, pre-filled syringes for C.E.R.A. have become available that were not used in the registration trials. The MIRACEL study was undertaken to examine the conversion of dialysis patients with chronic

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3 kidney disease (CKD) stage from short-acting ESAs to once-monthly C.E.R.A. therapy using
4 pre-filled syringes. The experience from this large national trial may help to facilitate dosing
5 decisions and management of haemodialysis patients receiving C.E.R.A. Here we describe
6 C.E.R.A. doses and dose modifications, and individual responses to therapy, in the
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MIRACEL study population.

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Methods

This was a prospective, single-arm study performed at 90 nephrology centres in Germany during March 2007 to October 2008. The methodology has been described in detail previously (17). In brief, the study population comprised CKD patients ≥ 18 years old receiving continuous haemodialysis three times a week for at least 12 weeks prior to study entry with $Kt/V \geq 1.2$ (single pool) or urea reduction $>65\%$. Patients were required to have Hb level $\geq 10\text{g/dL}$ and $\leq 13\text{g/dL}$ at study entry and to have been receiving intravenous or subcutaneous maintenance epoetin alfa or beta or darbepoetin alfa at a constant dose interval during the previous four months (epoetin 4,000-10,000 IE weekly or 8,000-20,000 IE if administered every two weeks; darbepoetin alfa 20-50 μg weekly or 40-100 μg if administered every two weeks). Serum ferritin concentration was required to be $\geq 100\text{ng/mL}$ and transferrin saturation (TSAT) $\geq 20\%$ during the four weeks prior to study entry and during the screening phase. Key exclusion criteria were erythrocyte transfusion or treatment for relevant acute or chronic bleeding within the preceding eight weeks, diastolic blood pressure $>100\text{mmHg}$, acute or chronic systemic inflammatory disease and/or C-reactive protein (CRP) $>30\text{mg/L}$ and Hb concentration outside the range 10-13g/dL during screening or with a change in Hb level of $\geq 2\text{g/dL}$ during screening.

Patients continued to receive their current ESA regimen, with no change to the dosing interval during a two-month screening phase. At the end of the screening phase, all patients who continued to meet the inclusion/exclusion criteria were converted to monthly administration of C.E.R.A. (Mircera[®] [methoxy polyethylene glycol-epoetin beta], F. Hoffmann-La Roche Ltd., Basel, Switzerland), which was provided as pre-filled syringes containing 50 μg , 75 μg , 100 μg , 125 μg , 150 μg , 200 μg or 250 μg . The starting dose of C.E.R.A. was 125 μg if the patient had previously received $<8,000$ IE epoetin weekly or $<40\mu\text{g}$ darbepoetin weekly, or at a dose of 200 μg if the patient had previously received 8,000-16,000 IE epoetin weekly or 40-80 μg darbepoetin weekly. C.E.R.A. was then administered monthly during a five-month titration phase and a two-month evaluation phase i.e. seven

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3 doses of C.E.R.A. in total. After the first application, C.E.R.A. doses were administered,
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5 aiming at a Hb level in the range 11-12.5g/dL. Intravenous or oral iron supplementation was
6
7 permitted, targeting a serum ferritin concentration in the range 100-800ng/mL or TSAT in the
8
9 range 20-50%.

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12 Monthly study visits took place during the screening phase (months -2 and -1), the titration
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14 phase (months 1-5) and the evaluation phase (months 6-8). The primary efficacy variable
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16 was the number of patients with Hb values in the range 11-12.5g/dL or 10-13g/dL at all visits
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18 during the evaluation phase among evaluable patients, defined as those in whom two or
19
20 more valid Hb levels were recorded during the evaluation phase. Safety variables included
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22 adverse events, vital signs, laboratory measurements and serum iron parameters. A
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24 decrease in Hb \geq 2g/dL between two consecutive visits was recorded as an adverse event of
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26 special interest. All data are presented descriptively with no formal statistical analyses, as
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28 planned in the study protocol.
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34 The study was undertaken in accordance with the Declaration of Helsinki and Good Clinical
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36 Practice. All patients provided written consent following approval of the study protocol from
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38 the German federal health authority and the ethics committee at each participating centre.
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Results

Patient population

Six hundred and sixty-one patients were enrolled to the trial and underwent screening. Of these, 424 (64.1%) were eligible to enter the evaluation phase and formed the safety population (Figure 1). In the majority of cases (204/237, 86.1%), non-eligibility for the evaluation phase was due to violation of inclusion/exclusion criteria, most frequently cycling beyond the specified Hb range of 10-13g/dL or showing a Hb decrease of ≥ 2 g/dL (n=93), a change in previous ESA or dosing interval (n=61), or receiving a dose of previous ESA outside the specified range (n=58) (Figure 1). The intent-to-treat (ITT) population included 416/424 patients (98.1%). Eight patients were excluded from the ITT population because no Hb value was available after switch to C.E.R.A. The evaluation and titration phases were completed by 344/424 patients (81.1%).

The majority of patients were male (60.8%), with a mean age of 63.1 years (Table 1).

Approximately three-quarters of patients were treated with epoetin at study entry (306/424, 72.2%), with the remainder receiving darbepoetin. Almost all patients (391/424, 92.2%) were receiving at least once-weekly ESA application at study entry, with 48.6% (206/424) requiring two or more doses per week (Table 2). Most patients (336/424, 79.2%) were given intravenous iron, and a further 14 patients (3.3%) were receiving oral iron supplementation.

Hb concentration

Across the total study population, the mean Hb level remained stable throughout the trial, at 11.7 ± 0.7 , 11.7 ± 0.8 and 11.5 ± 0.8 g/dL during the screening, titration and evaluation phases, respectively (ITT population). During screening, 36.8% (153/416) of patients were within the 11-12.5g/dL range at each of the two screening visits, compared to 30.8% (109/354) at all three visits during the evaluation phase; 91.6% (381/416) and 74.9% (265/354) of patients remained inside the wider range of 10-13g/dL at each of the screening and evaluation visits,

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3 respectively. The proportion of patients within the target Hb ranges during the evaluation
4 phase was similar regardless of whether they had previously received epoetin (11-12.5g/dL:
5 75/258 [29.1%]; 10-13g/dL: 196/258 [76.0%]) or darbepoetin (34/96 [35.4%]; 10-13g/dL:
6 69/96 [71.9%]).
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10 11 12 *Initial C.E.R.A. dose*

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15 The initial monthly dose of C.E.R.A. was 125µg in 311 patients (73.3%) and 200µg in 106
16 patients (25.0%). For patients with a previous ESA dose of <8,000 IE epoetin or <40µg/week
17 darbepoetin, 95.6% (284/294) were correctly allocated to the 125µg starting dose group
18 (Table 2). Among patients in the higher ESA dose category (≥8,000 IE epoetin or
19 ≥40µg/week darbepoetin), 22.0% (27/123) were started on the lower C.E.R.A. dose of 125µg
20 instead of the recommended dose of 200µg. The remaining seven patients received starting
21 doses other than 125µg or 200µg, against protocol. The final mean dose was 129±61µg and
22 203±58µg among patients who started on 125µg and 200µg, respectively. The proportion of
23 patients requiring dose modifications of any type was similar for the cohorts who started on
24 125µg or 200µg, although the mean number of dose decreases was lower in patients with an
25 initial dose of 200µg (0.7±0.9 versus 1.0±1.0 for patients with a starting dose of 125µg)
26 (Table 2). Fewer patients who began on a dose of 200µg received all seven C.E.R.A. doses
27 (70.8% versus 85.2% in the 125µg starting-dose group).
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46 The proportion of patients within the narrow Hb target range (11-12.5g/dL) at the end of the
47 screening phase was 63.9% (195/305) among those given the 125µg starting dose and
48 56.7% (59/104) for patients initiated on 200µg C.E.R.A., a difference that was maintained at
49 the final visit of the evaluation phase (54.4% versus 52.9%). Across all three evaluation
50 visits, the proportion of patients within the 11-12.5g/dL target range or the 10-13g/dL range
51 compared to the proportion above or below target was significantly higher for the 125µg
52 versus the 200µg starting dose (Table 3).
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C.E.R.A. dose adjustments

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3 The mean C.E.R.A. dose was $142\pm 48\mu\text{g}$ during the titration and evaluation phases, with little
4 change between the first dose ($143\pm 34\mu\text{g}$) and the final dose ($148\pm 68\mu\text{g}$). C.E.R.A. dose
5 changes across the titration and evaluation phases are summarised in Table 2. During the
6 titration phase, the C.E.R.A. dose was adjusted in 310 patients (73.1%), of whom 153
7 (36.1%) required only one dose modification, 120 patients (28.3%) required two dose
8 modifications and 37 (8.7%) required three dose modifications. During the evaluation phase,
9 171 patients (40.3%) needed further dose modification: 130 had one dose change (30.7%)
10 and 41 (9.7%) needed two dose changes. The number of patients requiring either dose
11 decreases or increases was similar during the titration phase (decreases, $n=192$; increases,
12 $n=179$), while more patients required a dose increase during the evaluation phase
13 (decreases, $n=76$; increases, $n=112$). The mean number of dose decreases and increases
14 per patient was 0.62 and 0.57, respectively, during the titration phase and 0.23 and 0.34
15 during the evaluation phase (Table 2). Overall the mean number of dose changes per patient
16 was 1.19 and 0.57 during the titration and evaluation phases, respectively. Achievement of
17 Hb target ranges at month 6, 7 and 8 was analysed according to C.E.R.A. dose changes at
18 the previous visit (i.e. months 5, 6 and 7, respectively) (Table 4). Among patients who
19 received a dose increase at the preceding visit, only a small proportion (<8%) exceeded
20 12.5g/dL at the next visit while approximately 40% were below 11g/dL; 80-90% of patients
21 were within the wider range of 10-13g/dL after a dose increase. Following a dose decrease,
22 between 19% and 28% of patients were below 11g/L at the next visit (a smaller proportion
23 than in the population overall), and only <4% were below 10g/dL (Table 4).
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50 *Characteristics of patients experiencing Hb decrease*

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53 In total, nine patients experienced a decrease of $\geq 2\text{g/dL}$ Hb between two consecutive
54 screening visits, and 51 experienced this decrease during the titration or evaluation phases.
55 Altogether, 53 reports of Hb decrease $\geq 2\text{g/dL}$ were filed, since two patients experienced this
56 event twice during treatment. Forty-three (81.1%) of these events were classified as mild or
57 moderate, with ten (18.9%) graded as severe (three with a suspected relation to study drug).
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3 In eleven (21.6%) of the 51 patients a relationship to study drug was suspected, and four
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5 (7.8%) participants discontinued the trial for this reason (one additional patient discontinued
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7 the trial on day 215 after a Hb drop from 14.1 to 12.0 g/dL without an attempt to increase the
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9 previous monthly dose of 50µg C.E.R.A.). There were no differences between the
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11 subpopulation who experienced ≥ 2 g/dL decrease in Hb and the rest of the population in
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13 terms of demographics, concomitant illness or time since start of dialysis (data not shown).

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15 In 9/53 (17.0%) cases, the drop in Hb level reflected an elective decision to withhold a
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17 monthly application of C.E.R.A. In seventeen patients (32.1%), laboratory parameters
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19 indicating varying degrees of iron deficiency (based on serum ferritin, serum iron and/or
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21 TSAT) were reported at least once during the titration or evaluation phases. In thirteen
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23 (24.5%) of the 53 cases a Hb decrease of ≥ 2 g/dL was associated with active bleeding,
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25 coagulopathy or infection. A drop in Hb of ≥ 2 g/dL was reported in twenty patients in the
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27 absence of obvious clinical reasons. Increasing the monthly dose of C.E.R.A. led to a
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29 satisfactory increase in Hb in 17/20 (85%) of these patients.
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35 There were no marked differences in mean Hb across the titration and treatment phases in
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37 patients with or without ≥ 2 g/dL Hb decrease, or in the mean or starting dose of C.E.R.A
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39 (Table 5).
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42 *Safety*

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45 In total, 208 patients (49.1%) reported adverse events during the two-month screening phase
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47 versus 359 patients (84.7%) during the combined seven-month titration and evaluation
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49 phases. This represented an adverse event rate of 104 events per month during the two-
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51 month screening phase while receiving short-acting ESA and 45 events per month during the
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53 seven-month titration/evaluation phases, after being switched to C.E.R.A. The incidence of
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55 adverse events among patients receiving an initial C.E.R.A. dose of 125µg was 83.6%
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57 (260/311), and 88.7% (94/106) for those given a starting dose of 200µg. Adverse events
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59 suspected to be related to study medication were reported in 96 patients (22.6%). Thirty-six
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patients (8.5%) experienced serious adverse events during the two-month screening phase,

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3 compared to 168 patients (39.6%) during the combined seven-month titration/evaluation
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5 phases, equivalent to 18.0 and 21.0 patients with serious adverse events per month,
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Discussion

Our results indicate that conversion of haemodialysis patients to once-monthly C.E.R.A. using pre-filled syringes maintains stable levels of Hb in a population previously receiving at least once-weekly dosing of epoetin or darbepoetin in over 90% of cases. Conversion was simple to perform, with a mean of 2.0 dose changes per patient, based on local clinical judgment over the seven-month period of C.E.R.A. administration.

The current analysis focussed on C.E.R.A. dosing, both in terms of the initial dose at the point of conversion and the effect of subsequent dosing decisions. Guidance relating to the initial C.E.R.A. dose stated that a monthly dose of 125µg C.E.R.A. was to be used if the patient had received <8,000 IE epoetin weekly or <40µg darbepoetin weekly, with a 200µg dose if the patient had previously received 8,000-16,000 IE epoetin weekly or 40-80µg darbepoetin weekly. While this guidance was not followed in all patients (notably, approximately one in five patients on high previous ESA doses were started on the lower C.E.R.A. dose of 125µg), the mean value of previous ESA exposure was correct for each initial C.E.R.A. dose group. There was little change in the mean dose from baseline in both the 125µg and 200µg starting dose groups, with mean final dose of 129µg and 203µg, respectively, across the titration and evaluation period. The apparent anomaly that more patients with a starting dose of 125µg were above the upper limit of both target ranges than those who started with the higher dose of 200µg likely reflects the variation in responsiveness to ESA therapy between patients that necessitated higher dosing of the previous ESA agent. Thus, patients receiving higher doses of ESA at study entry may have been less responsive to treatment. Overall, patients who received a starting dose of 125µg were significantly more likely to be within target range for both the 11-12.5g/dL and 10-13g/dL ranges (Table 2). This did not lead to a greater number of dose changes in the 200µg starting group compared to the 125µg starting group although there were fewer dose decreases in the 200µg group during the evaluation phase. Overall, patients received a

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3 similar number of dose increases or dose decreases during C.E.R.A. administration. The
4 current recommendations for initial C.E.R.A. starting dose would appear to be appropriate.
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8 Following a C.E.R.A. dose increase it was unusual to observe a Hb level above 12.5g/dL
9 (<8% of patients) or 13g/dL ($\leq 3\%$). After a dose decrease, the frequency of Hb levels below
10 11g/dL was 19-28%, suggesting that dose decreases should perhaps be undertaken more
11 cautiously. With 90% of patients within the 10-13g/dL range following a dose decrease,
12 withholding a dose rarely seemed necessary. The rarity of Hb levels greater than 12.5g/dL in
13 this population is reassuring in the light of results from the TREAT study that showed an
14 increased risk of stroke and thromboembolic events in non-dialysis CKD patients with Type 2
15 diabetes when a Hb level of 13g/dL was targeted during darbepoetin treatment (19). These
16 findings from TREAT and from the CHOIR trial, in which the same high hemoglobin target of
17 13.5g/dL was associated with adverse outcomes in non-dialysis patients (20), have
18 engendered caution about aggressive Hb targets and high-dose ESA therapy. Interestingly,
19 however, discussion around these current target-based strategies is fueled by emerging
20 evidence from the TREAT study, indicating that it was not the high Hb level *per se* that was
21 associated with cardiovascular risk, but rather the inadequate hematopoietic response
22 toward darbepoetin therapy (21).
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42 We examined in depth any potential underlying clinical factors for the observed Hb decrease
43 of $\geq 2\text{g/dL}$ between two monthly visits that was observed in $\sim 12\%$ of patients during the
44 titration and evaluation phases. In a quarter of the 53 cases that occurred during C.E.R.A.
45 therapy, the decrease was associated with comorbidities that would be expected to influence
46 Hb level (bleeding, coagulopathy or infection) while a third of patients were experiencing
47 some degree of absolute or functional iron deficiency during the course of the study.
48
49 Furthermore, for a fifth of patients with a decrease of $\geq 2\text{g/dL}$ the previous C.E.R.A. dose had
50 been withheld. Thus, unexplained decreases in Hb of 2g/dL or more appear to be relatively
51 uncommon and most likely reflect the cycling of Hb levels. The high proportion of patients
52 with comorbidity or low iron levels in this subpopulation, however, underscores the need to
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3 monitor and anticipate the patient's general medical status, including (sub-clinical) infection,
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5 surgical intervention, (occult) bleeding, coagulopathy and iron status. Therapeutic targeting
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7 of these comorbidities may stabilise and improve Hb level without the need for C.E.R.A. dose
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9 increases, while timely dose reductions may be required upon their resolution.
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13 There was no meaningful pattern of difference in serum ferritin between patients within,
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15 above or below Hb target ranges. The lowest mean TSAT value was seen in patients below
16
17 target, a difference that reached significance for the 10-13g/dL target range. However, mean
18
19 TSAT levels comfortably exceeded the recommended minimum of 20% for CKD patients
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21 receiving ESA therapy (10) and almost 80% of patients were receiving intravenous iron
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23 therapy as recommended (18). While this offers a reminder of the importance of achieving an
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25 adequate iron supply to decrease the risk of relative ESA hyporesponsiveness (22) it seems
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27 unlikely that iron deficiency exerted a marked effect on the attainment of Hb levels in this
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29 population.
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34 C.E.R.A. administration was based on the use of pre-filled syringes, allowing an assessment
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36 of the impact of routine management. We recognise, however, that extrapolation of these
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38 findings to the clinical setting is partially restricted by the exclusion criteria that were applied,
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40 which with hindsight were over-restrictive. During screening an unexpectedly high proportion
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42 of patients cycled outside 10-13g/dL, experienced a Hb change of ≥ 2 g/dL or required a dose
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44 change, such that 36% of screened patients were excluded. Learning from this, a follow-up
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46 study (SESAM: Non-interventional **S**tudy to analyze **E**fficacy, **S**afety and **A**pplicability of
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48 **M**ircera in hemodialysis patients in daily routine) has been undertaken using a similar study
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50 design but without the inclusion and exclusion criteria used in the current trial.
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54 In conclusion, data from this large, multicentre study demonstrate that switching
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56 haemodialysis patients from shorter-acting ESA to once-monthly C.E.R.A. using pre-filled
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58 syringes can be undertaken simply and easily, with most patients requiring no more than two
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60 dose modifications over the five-month treatment period, based on local clinical judgement.
The switch to once-monthly dosing could be expected to reduce staffing time and the

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2
3 potential for dosing errors (23). Hb level remained stable after the switch. Following an
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5 increase in C.E.R.A. dose, it was infrequent to observe a Hb level above 12.5g/dL, 1 and
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7 dose decreases did not lead to an increased rate of Hb values below 11g/dL, indicating that
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9 dose changes were performed appropriately and without unexpectedly pronounced changes
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11 in Hb level. Recommendations for the starting dose of C.E.R.A. were suitable, with the mean
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13 dose remaining almost unchanged during the following seven months. Altogether, the safety
14
15 profile of C.E.R.A. was not different to other ESA.
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35

36 37 **Authors' contributions**

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40 All authors performed the study, undertook data collection, and critically reviewed and
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42 approved the manuscript.
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Table 1. Patient demographics

Parameter	Safety population (n=424)
Male gender, n (%)	258 (60.8%)
Age (years)	
Mean±SD	63.1±14.7
Median (range)	66.0 (24 – 93)
Body mass index (kg/m ²)	
Mean±SD	27.0±5.2
Median (range)	26.3 (16.0 – 54.5)
Hb (g/dL) ^a	
Mean±SD	11.7±0.8
Median (range)	11.8 (9.7 – 13.9)
Serum ferritin (ng/mL) ^a	
Mean±SD	685±594
Median (range)	564 (1.0 - 8720)
Transferrin saturation (TSAT) (%) ^a	
Mean±SD	28.5±12.9
Median (range)	26.0 (9.8-112.5)
C-reactive protein (mg/L) ^a	
Mean±SD	0.9±1.6
Median (range)	0.5 (0 – 16.8)
Serum albumin (g/L) ^a	
Mean±SD	40.1±15.7
Median (range)	39.9 (25 – 52)
Time since start of haemodialysis (years)	
Mean±SD	4.3±4.3
Median (range)	3.3 (0.3 – 35.6)
Kt/V (single pool) ^a	
Mean±SD	1.58±0.32
Median (range)	1.52 (1.06 – 3.78)
Diabetes mellitus, n (%)	90 (21.2%)
Hypertension, n (%)	311 (73.3%)

^a Baseline visit (month 1)

Table 2. ESA therapy at study entry and C.E.R.A. dose modifications during the titration and evaluation phases, according to initial C.E.R.A. dose (safety population)

	All patients (n=424)	C.E.R.A. starting dose ^a	
		125µg (n=311)	200µg (n=106)
Previous ESA treatment, n (%)			
Epoetin alfa	113 (26.7)	84 (27.0)	26 (24.5)
Epoetin beta	188 (44.3)	139 (44.7)	47 (44.3)
Epoetin delta	5 (1.2)	4 (1.3)	1 (0.9)
Darbepoetin alfa	118 (27.8)	84 (27.0)	32 (30.2)
Previous ESA dose ^a			
Epoetin (IE/week), mean±SD	6170±1814	5504±1381	8337±1198
Darbepoetin (µg/week), mean±SD	30.1±9.5	26.2±6.6	40.6±7.9
Previous ESA dose ^a			
<8,000 IE/week or <40µg/week	-	284/294 (95.6)	10/294 (3.4)
≥8,000 IE/week or ≥40µg/week	-	27/123 (22.0)	96/123 (78.0)
Previous administrations/week, n (%)			
<1.0	33 (7.8)	26 (8.4)	7 (6.6)
1.0 to <2.0	185 (43.6)	133 (42.8)	47 (44.3)
2.0 to <3.0	108 (25.5)	81 (26.0)	25 (23.6)
3.0 to <4.0	98 (23.1)	71 (22.8)	27 (25.5)
Previous ESA route of administration			
Intravenous	336 (79.2)	251 (80.7)	82 (77.4)
Subcutaneous	88 (20.8)	60 (19.3)	24 (22.6)
C.E.R.A. dose (µg/month)			
All doses			
Mean±SD	142±48	125±37	193±42
Median (range)	132 (18-275)	125 (18-225)	200 (86-275)
First dose (month 1), mean±SD	143±34	125±0	200±0
Final dose (month 7), mean±SD	148±68	129±61	203±58
C.E.R.A. dose changes			
Any change			
n, %	352 (83.0)	261 (83.9)	87 (82.1)
Mean±SD	2.0±1.4	2.1±1.4	1.7±1.3
Median (range)	2 (0-5)	2 (0-5)	1 (0-5)
Any dose decrease, mean±SD	0.9±1.0	1.0±1.0	0.7±0.9
Any dose increase, mean±SD	1.1±1.0	1.1±1.1	1.0±0.8
C.E.R.A. doses administered			
Mean±SD	6.4±1.5	6.5±1.4	6.0±1.8
7, n (%)	345 (81.4)	265 (85.2)	75 (70.8)
6, n (%)	11 (2.6)	5 (1.6)	6 (5.7)
5, n (%)	15 (3.5)	9 (2.9)	6 (5.7)
4, n (%)	13 (3.1)	9 (2.9)	4 (3.8)
3, n (%)	14 (3.3)	8 (2.6)	6 (5.7)
2, n (%)	15 (3.5)	9 (2.9)	6 (5.7)
1, n (%)	11 (2.6)	6 (1.9)	3 (2.8)

^a 7 patients received another initial starting dose of C.E.R.A. (data not shown)

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Table 3. C.E.R.A. dose for patients within or outside target Hb ranges at all three visits during the evaluation phase (ITT population)

	Within range	Above only	Below only	Above & below	Not evaluable or missing	P value
	11-12.5g/dL					
C.E.R.A. dose						
All doses, mean±SD (µg/month) ^a	132±55	109±59	163±61	157±64	216±65	<0.001 ^b
Initial dose 125µg, n (%)	85/305 (27.9)	62/305 (20.3)	115/305(37.7)	8/290 (2.8)	20/290 (6.9)	0.002 ^c
Initial dose 200µg, n (%)	23/104 (22.1)	7/104 (6.7)	48/104 (46.2)	1/97 (1.0)	18/97 (18.6)	
	10-13g/dL					
C.E.R.A. dose						
All doses, mean±SD (µg/month) ^a	140±60	109±66	178±58	n.a.	216±65	<0.001 ^b
Initial dose 125µg, n (%)	201/290(69.3)	31/290 (10.7)	38/290 (13.0)		20/290 (6.9)	0.007 ^c
Initial dose 200µg, n (%)	60/97 (61.9)	4/97 (4.1)	15/97 (15.5)		18/97 (18.6)	

^a During evaluation phase^b Chi square test^c Kruskal-Wallis test for difference between 125µg versus 200µg starting dose

Table 4. C.E.R.A. dose changes at the previous visit and iron markers for patients within or outside target Hb ranges at all three visits during the evaluation phase (ITT population)

	11-12.5g/dL				10-13g/dL			
	Within range	Above only	Below only	P value	Within range	Above only	Below only	P value
Previous C.E.R.A. dose ^a								
<i>Month 6 visit</i>								
Increased, n (%)	58/131 (44.3)	10/131 (7.6)	52/131 (39.7)	0.002 ^b	105/131 (80.2)	4/131 (3.1)	11/131 (8.4)	0.020 ^b
Decreased, n (%)	69/131 (52.7)	24/131 (18.3)	36/131 (27.5)		115/131 (87.8)	9/131 (6.9)	5/131 (3.8)	
Equal, n (%)	68/104 (65.4)	11/104 (10.6)	24/104 (23.1)		92/104 (88.5)	1/104 (1.0)	10/104 (9.6)	
Withheld, n (%)	2/3 (66.7)	1/3 (33.3)	0/3		2/3 (66.7)	1/3 (33.3)	0/3	
<i>Month 7 visit</i>								
Increased, n (%)	70/132 (53.0)	5/132 (3.8)	54/132 (40.9)	<0.00 ^b	112/132 (84.8)	3/132 (2.3)	14/132 (10.6)	0.038 ^b
Decreased, n (%)	81/129 (62.8)	22/129 (17.1)	24/129 (18.6)		112/129 (86.8)	10/129 (7.8)	5/129 (2.9%)	
Equal, n (%)	63/91 (69.2)	14/91 (15.4)	12/91 (13.2)		80/91 (87.9)	6/91 (6.6)	3/91 (3.3)	
Withheld, n (%)	3/4 (75.0)	1/4 (25.0)	0/4		3/4 (75.0)	1/4 (25.0)	0/4	
<i>Month 8 visit</i>								
Increased, n (%)	74/133 (55.6)	9/133 (6.8)	49/133 (36.8)	0.004 ^b	112/133 (84.2)	3/133 (2.3)	17/133 (12.8)	<0.001 ^b
Decreased, n (%)	81/127 (63.8)	19/127 (15.0)	25/127 (19.7)		115/127 (90.6)	7/127 (5.5)	3/127 (2.4)	
Equal, n (%)	57/81 (70.4)	7/81 (8.6)	17/81 (21.0)		79/81 (97.5)	0/81	2/81 (2.5)	
Withheld, n (%)	4/7 (57.1)	2/7 (28.6)	0/7		5/7 (71.4)	1/7 (14.3)	0/7	
Serum ferritin ^c								
Mean±SD (ng/mL)	690±427	887±847	693±483	0.66 ^c	688±480	1006±774	806±565	0.11 ^c
<200ng/mL, n (%)	10/22 (45.5)	2/22 (9.1)	10/22 (45.5)	0.27 ^b	22/22 (100)	0/22	0/22	0.17 ^b
Transferrin saturation (TSAT) ^c								
Mean±SD (%)	35.3±15.0	37.2±19.3	32.7±13.3	0.41 ^c	35.5±15.3	32.3±14.7	27.9±10.9	0.01 ^c
<20%, n (%)	24/46 (52.2)	5/46 (10.9)	17/46 (37.0)	0.58 ^b	37/46 (80.4)	2/46 (4.3)	7/46 (15.2)	0.33 ^b

^a Dose at visit prior to month 6, month 7 or month 8 study visit^b Chi square test^c Kuskal-Wallis test

Table 5. Comparison of patients with or without Hb decrease $\geq 2\text{g/dL}$ between two consecutive study visits during the titration or evaluation phase (reported as adverse event of special interest) (safety population)

	Hb decrease $\geq 2\text{g/dL}$ (n=52)	No Hb decrease $\geq 2\text{g/dL}$ (n=372)	P value
Hb (g/dL) ^a			
Mean \pm SD	11.8 \pm 0.85	11.7 \pm 0.84	0.20 ^b
Median (range)	11.9 (10.0 – 13.5)	11.7 (9.7 – 13.9)	
C.E.R.A. dose			
All doses, mean \pm SD ($\mu\text{g/month}$)	143.8 \pm 52.2	142.0 \pm 47.7	0.78 ^b
Starting dose 125 μg , n (%)	39/311 (12.5)	272/311 (87.5)	0.61 ^c
Starting dose 200 μg , n (%)	13/106 (12.3)	93/106 (87.7)	
Serum ferritin ^a			
Mean \pm SD (ng/mL)	820 \pm 595	666 \pm 592	0.014 ^b
<200ng/mL, n (%)	0/25	25/25 (100)	0.058 ^d
Transferrin saturation (TSAT) ^a			
Mean \pm SD (%)	28.8 \pm 14.0	28.5 \pm 12.7	0.86 ^b
<20%, n (%)	11/82 (13.4)	71/82 (86.6)	0.71 ^d

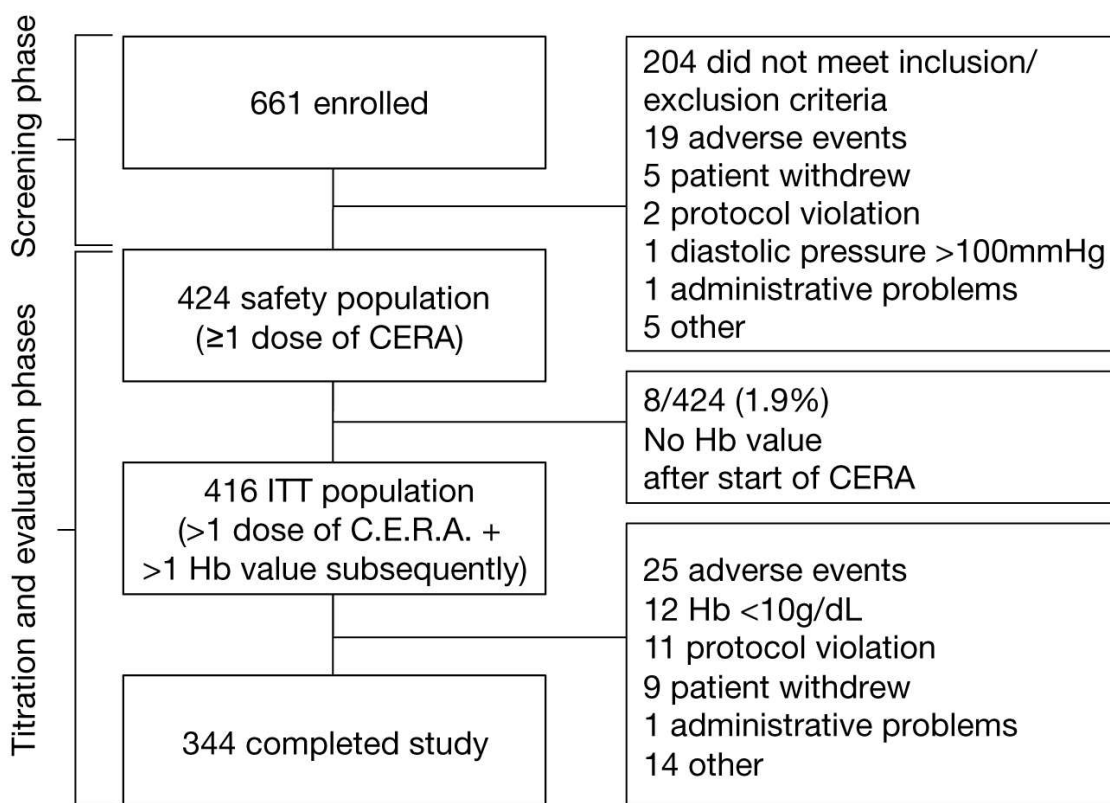
^a Baseline visit (month 1)

^b Wilcoxon rank sum test

^c Chi square test

^d Fishers exact test

Figure 1. Patient disposition



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